THE LAST DECADE OF HIV?

Reaching sustainable HIV control through improved epidemiological understanding and health systems innovations

CAROLINE A. BULSTRA

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Het laatste decennium van hiv?
Het bereiken van duurzame hiv-bestrijding door verbeterd epidemiologisch inzicht en innovaties in gezondheidssystemen

Proefschrift

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Promotor:	Prof.dr. S.J. de Vlas
Overige leden:	Prof.dr. J.H.H.M. van de Wijgert Prof.dr. F.G.J. Cobelens Prof.dr. E.C.M. van Gorp
Copromotor:	Dr. J.A.C. Hontelez

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Chapter 1

General introduction

The HIV pandemic has been one of the most devastating public health threats in recent history. After emerging as a new human pathogen during the mid-20th century, the virus spread rapidly, infecting more than 79 million people worldwide, of whom 36 million have died due to its consequences. In the late 1990s, HIV related mortality peaked worldwide, with over 2 million deaths annually. The pandemic was especially severe in sub-Saharan Africa, where over 10% of the population was infected in many countries, and the high mortality rates had altogether reduced overall life expectancies. However, scientific breakthroughs coupled with an unprecedented global effort to control the pandemic have substantially expanded worldwide access to a wide range of biomedical and behavioural interventions to treat and prevent HIV infection, sparking optimism that the end of the pandemic could be in sight. Nowadays, about 75% of all people living with HIV worldwide are receiving life-saving treatment, even in the poorest countries of the world, and the number of new infections has been declining tremendously. In a landmark General Assembly on HIV and AIDS in 2016, the United Nations endorsed the ambitious commitment to end the pandemic by 2030. While progress towards this noble endeavour has been substantial, many obstacles still exist in reaching sustainable control of the pandemic. In this thesis, I present scientific research on the epidemiology of HIV and the potential of health systems innovations, which might contribute to overcoming some of these obstacles, and thereby help to ensure that we are truly living in the last decade of HIV.

1.1 HIV AND AIDS

Pathogenesis

The Human Immunodeficiency Virus (HIV) is a retrovirus that targets and seriously impairs the immune system after infection, increasing a person's vulnerability to other pathogens [1]. HIV is mainly transmitted sexually, but can also be transmitted from mother to child during pregnancy, through sharing needles for medical purposes or injecting drugs, or through blood transfusions [1]. After entering the body, the virus attacks CD4-receptor carrying cells, *i.e.* white blood cells that are crucial in the immune response against infectious pathogens (**Figure 1**) [2]. The virus then replicates in the host cells, releasing new virus particles into the body.

Short flu-like illness, overall malaise, tiredness and a body rash can occur 2-6 weeks after infection. This 'acute phase' is characterised by high viral loads in the body, as the virus is able to replicate and infect CD4 cells unimpeded [3,4]. After this period, HIV may be asymptomatic for years and viral loads are often lower, but virus replication continues. This process gradually decreases circulating CD4 counts in the body; weakening the patients' immune system [5–7]. When left untreated, this gradual weakening eventually leads to acquired im-

munodeficiency syndrome (AIDS), typically after about 10 years post-infection [8–10]. At this stage, symptoms can include weight loss, chronic diarrhoea [1], and a range of opportunistic infections such as tuberculosis, pneumonia, herpes simplex, and mucosal candidiasis [11]. Untreated AIDS leads to death in all cases, often about a year after onset of symptoms [9].

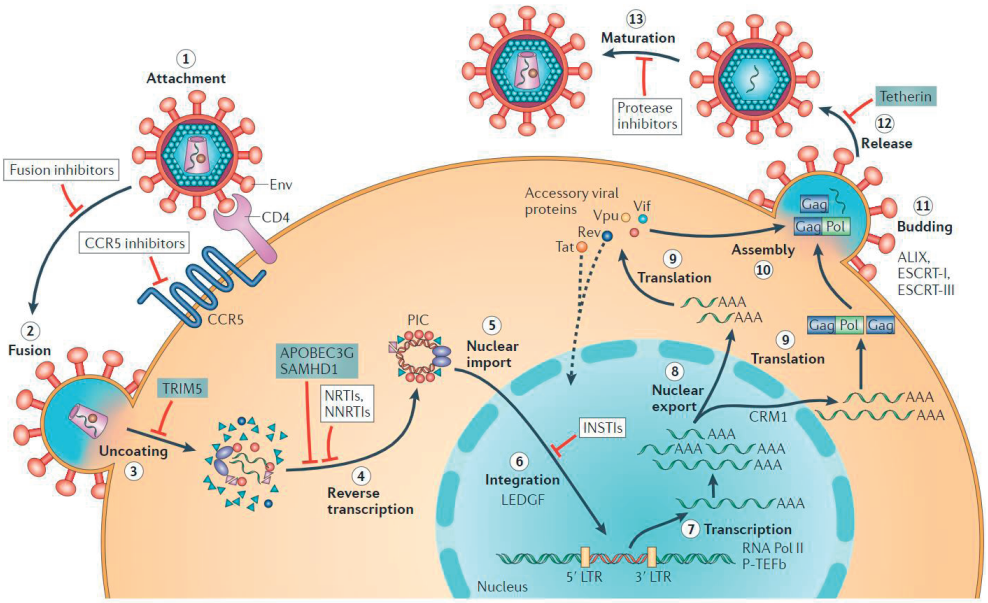

Figure 1. Schematic overview of the HIV replication cycle. Source: Engelman *et al.*, Nature, 2012 (https://www.nature.com/articles/nrmicro2747) [2].

Antiretroviral therapy

HIV is treated with combination antiretroviral therapy (ART), which prevents the development of AIDS and reduces premature mortality [12], but does not cure the infection. ART consists of several antiretroviral pharmaceuticals that prevent HIV from replicating by targeting different parts of the virus replication cycle. As a result, the amount of viral particles circulating in a patient's body (*i.e.* the viral load) is reduced, allowing for immune system recovery [9,12] and an increase in CD4 cells after a few months [13]. Successful treatment improves the overall health of patients and prolongs survival. Nowadays, average life expectancy of individuals living with HIV who receive treatment is comparable to life expectancy among HIV-negative people [14–16]. Adverse effects of treatment reduced substantially with new treatment regimens and are often mild and temporary (*e.g.* nausea, vomiting, skin rash) [17]. Long-term adverse effects present in less than 10% of people living with HIV on treatment and include diabetes and other metabolic complications, atherosclerotic cardiovascular disease, kidney dysfunction, osteoporosis, weight loss or gain and insomnia [17–19].

In addition to a positive effect on survival, the ART-induced reduction in a patient's viral load also significantly decreases their infectivity [20,21]. Different trials and observational studies made evident that ART successfully reduces onward HIV transmission from mother-to-child during pregnancy by around 50% [22,23] and from infected to uninfected adult through unprotected sex acts by more than 90% [24,25]. In turn, modelling studies have shown that under these efficacy assumptions, widespread access to ART in sub-Saharan Africa could substantially reduce overall incidence [26–28], or even eliminate HIV transmission altogether [29,30]. Since then, providing ART to people living with HIV is not only motivated by the benefits for individual patients, but also by its potential to effectively curb the spread of HIV [31,32].

HIV prevention

Next to ART, several other biomedical interventions are effective in protecting against HIV infection. Condoms are highly effective in reducing the risk of contracting HIV during sexual intercourse, reducing HIV incidence in serodiscordant sex acts by about 80% to 90% when used consistently [33,34]. Furthermore, several randomised trials have found that voluntary medical male circumcision (VMMC) reduces the individual-level risk of female-to-male HIV transmission via sexual intercourse by approximately 60% [35–37]. Finally, pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) with antiretroviral medicines are available for HIV prevention for HIV-negative people before or after high-risk exposure, respectively [38,39].

In addition, behavioural and structural interventions can reduce HIV transmission. Behavioural interventions focus on, for instance, reducing the number of sexual (high-risk) partners and promoting consistent condom use during risky sexual intercourse among adolescents and sex workers and their clients, or promoting the use of clean needles and syringes and oral opiate substitution therapy (*e.g.*, methadone) among injecting drug users [40]. More structural interventions focus on improving societal challenges such as reducing poverty, improving education and knowledge about HIV, empowering women, reducing (gender) inequalities, and fighting HIV-related stigma [41,42]. Such interventions could lead to earlier diagnosis and treatment of people living with HIV and increased uptake of interventions to prevent onward transmission of HIV.

1.2 HIV EPIDEMIOLOGY

The HIV virus likely has its origins in the jungle of the Democratic Republic of Congo, where it spilled over from chimpanzees and other apes to local wildlife hunters around the 1920s [43–45]. The virus was first discovered in 1983 [46], when young people, mostly men who

have sex with men, died due to unexplained severe immunodeficiencies in New York [47], San Francisco [48,49], and other large cities in the Unites States [50–52]. Shortly thereafter, cases were identified in Africa, Europe, Asia, and many other parts of the world, where the virus presumably was already present [53]. By the end of 1985, at least one case was identified in every region of the world [54,55]. By 1990, over 2 million people were being diagnosed with HIV annually [56,57], mostly in sub-Saharan Africa. AIDS was the number one cause of death among young men and women (aged 25-44 years) in multiple countries across the world [58,59]. Since the start of the pandemic, more than 79 million people have been infected with HIV globally (**Figure 2**), of whom over a third died due to AIDS [9,60].

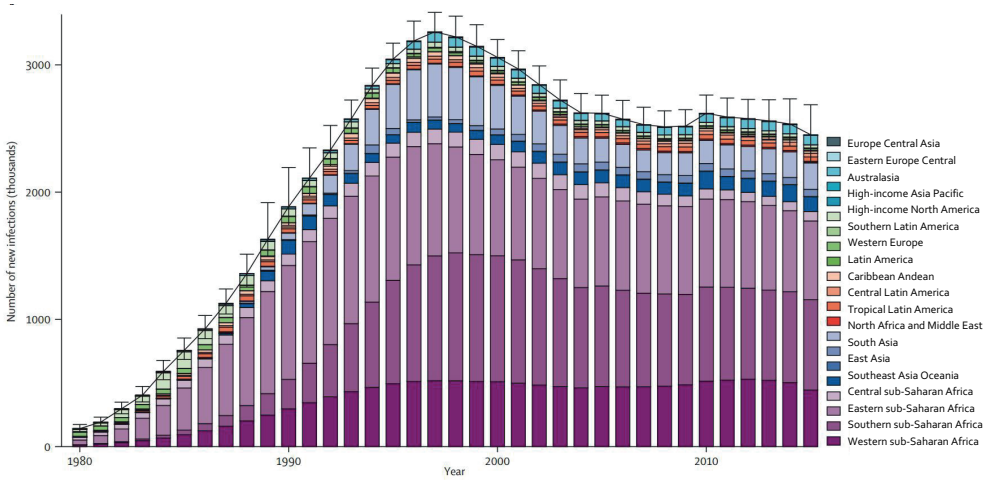

Figure 2. Incidence of new HIV infections from 1980 to 2015. Source: Global Burden of Disease HIV Collaborators, Lancet HIV, 2015 [56].

At present, around 37 million people are living with HIV globally, with sub-Saharan Africa still being the most affected area. Roughly 70% of all people currently living with HIV reside on the subcontinent [61]. Especially countries in Eastern and Southern Africa are the worst affected by the pandemic, where over 10% or even 20% of the general adult population is living with HIV in some of the countries (**Figure 3**). Whereas epidemics in sub-Saharan Africa are aging—meaning that the population living with HIV gets older, while less new infections occur—HIV transmission continues to be high in some areas and populations. In this thesis, I present studies on two key features of HIV epidemiology on the subcontinent, for which better knowledge could substantially improve our efforts to control transmission: geospatial heterogeneity of HIV transmission, and the role of so-called "key populations".

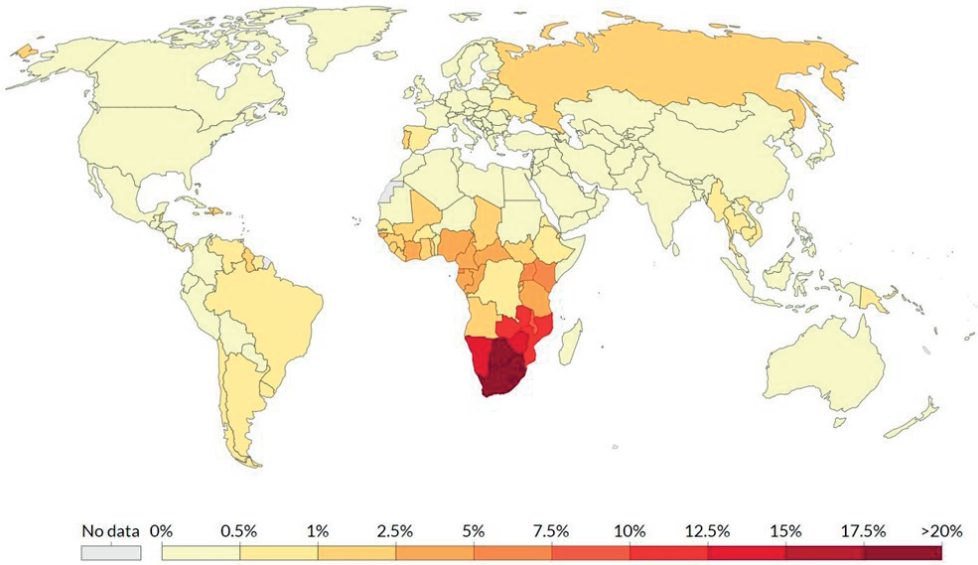

Figure 3. Share of the adult population (15-49 years) infected with HIV by country, 2017 (latest estimates). Source: Institute for Health Metrics and Evaluation (IHME) through Our World in Data (https://ourworldindata.org/hiv-aids).

Geospatial heterogeneity in HIV prevalence and transmission

The HIV prevalence in sub-Saharan Africa is not uniformly distributed across and within countries, but highly geographically heterogeneous: high-risk foci (also called 'hotspots') alternate with lower risk areas leading to large fluctuations in disease occurrence within countries. **Figure 4** illustrates that, while national-level HIV prevalence estimates (Figure 4a) can give some indication of the HIV burden, provincial (Figure 4b), district (Figure 4c) or 5-km grid level (Figure 4d) level prevalence estimates show that this burden is hardly ever evenly distributed within countries. [62]. This geographic variation in disease occurrence is not unique to HIV, and is observed in many other infectious and non-communicable diseases. It can be the result of underlying spatial variation in risk and protective factors, for instance environmental factors (*e.g.*, climate conditions that affect the density of mosquitos transmitting malaria [63] and sandflies transmitting leishmaniasis [64], or air quality variations that are related to asthma [65]) or the availability and uptake of preventive interventions (*e.g.*, vaccination coverage for measles [66] or presence of mass drug administration programmes in schools to treat and prevent soil transmitted helminths [67]).

While some knowledge exists on the determinants of geospatial heterogeneity for HIV (*e.g.* variations in sexual behaviour or the presence of high-risk populations [68,69]), it is not fully understood which factors are most important in driving heterogeneity in HIV transmission in sub-Saharan Africa and how these factors differ from location to location. Filling this gap in knowledge could help targeting the right interventions at the right people at the right

places, thereby enhancing the effectiveness of control policies, and also improving their efficiency.

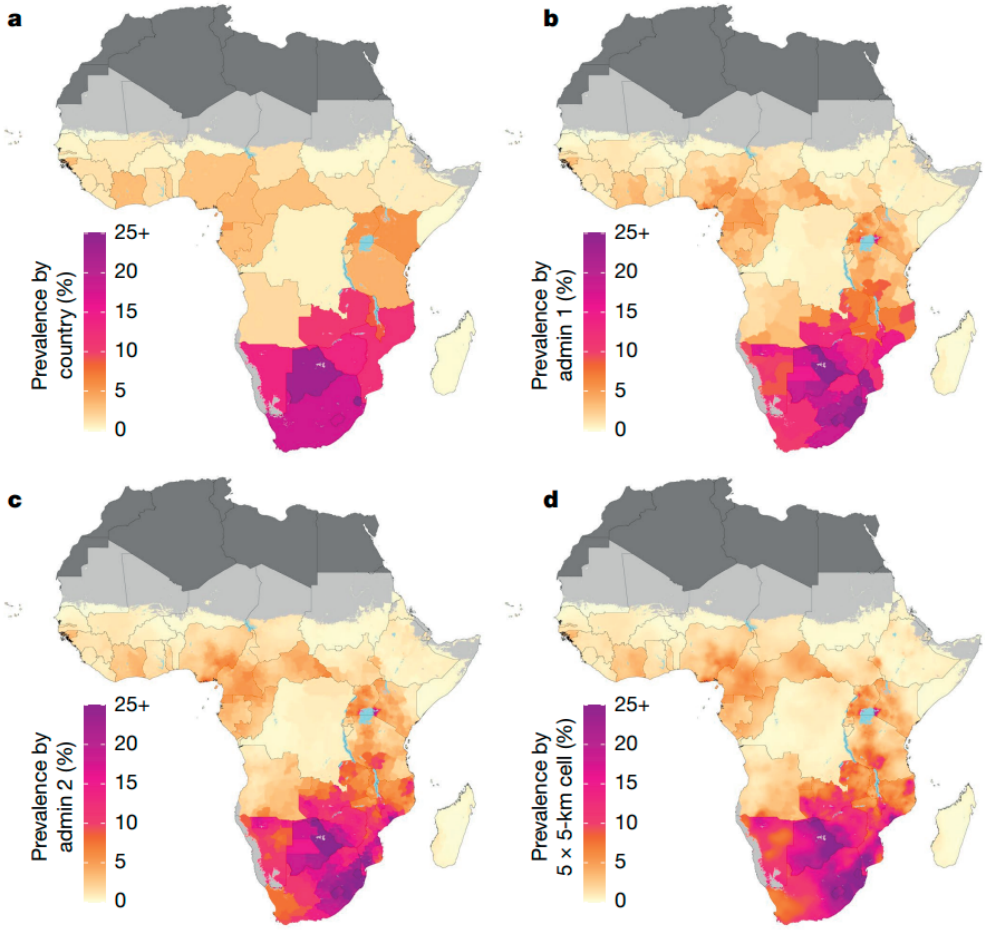

Figure 4. Estimated HIV prevalence in 2017 at the (a) national level, (b) administrative subdivision 1 level, (c) administrative level 2, and (d) by 5 km^2 [62].

In this thesis, I employ geographical information systems (GIS) technologies to study geospatial heterogeneity in HIV transmission and prevalence using open-source population surveys from Eastern and Southern Africa.

Geographical information systems (GIS) technologies are computer systems that allow for analysing and displaying geographically referenced information [70]. Geospatial modelling uses GIS to represent and analyse spatial associations and patterns of georeferenced information on diverse topics [70]. Geospatial modelling is increasingly being used in public

health and medicine, and can help to better understand the spatial variation of disease and its relationship to environmental factors and the health care system [70,71]. The most important GIS applications in public health are: (1) models to map the distribution of clusters (or 'hotspots') of disease and adverse health events, much like the famous analysis by John Snow in 1854 when a cholera outbreak hit the city of London, England [72]); (2) models to examine potential associations with risk- and protective factors and the effects of present interventions; and (3) models to predict disease occurrence at unmeasured locations using data on associated underlying risk and protective factors [70,71,73]. With GIS, such model analyses can be visualised through maps in order to derive insights about observed and predicted disease occurrences. In turn, this information can be used for health systems optimisation and resource allocation strategies [74].

Open-source population surveys that collect data on disease biomarkers and associated risk factors and that georeferenced the locations of data collection are very suitable for the analyses described above. The quantity and quality of such surveys increased rapidly over the last two decades. For HIV, Demographic and Health Surveys (DHSs) collected under the USAID Demographic and Health Survey Programme provide such data [75]. This programme conducts national, population-level surveys in low-income and middle-income countries (LMICs), with more than 400 completed surveys in over 90 different countries, among which 44 countries in sub-Saharan Africa. Per country and survey round, approximately 350 locations are randomly sampled throughout the country of interest, weighted based on the underlying population density per area. At each location, adult residents of about 25 households are sampled and interviewed about a wide range of behavioural, socioeconomic, and epidemiological parameters. In addition, they are tested for various diseases and health indicators, including voluntary HIV tests. GPS coordinates of sample locations are randomly displaced up to 2 km for urban and up to 5 km for rural sample locations, to ensure confidentiality of participants.

Next to that, technological advancements in collection and storage of satellite and remote-sensing data allow for accurate estimations of population density and data on environmental factors, such as temperature, vegetation, soil composition and water quality [76]. These data can be analysed together with population-based survey data to explore how such factors influence disease occurrence and transmission.

The availability of the DHSs and geospatial modelling techniques allow for fine-scale identification of high HIV prevalence areas among the general population. However, prevalence estimates do not reveal when persons have been infected, and thus high prevalence levels among adults do not necessarily reflect where transmission took place. However, areas with high rates of transmission could be approximated by looking at young adults. They are

most likely recently infected and, therefore, high prevalence areas among this subpopulation could signal ongoing transmission. This way, the available cross-sectional survey data, in combination with open-source environmental data, can be utilised to pinpoint areas with high levels of transmission and to explore to what extent sexual behavioural, socioeconomic and environmental factors explain the geospatial heterogeneity in prevalence and transmission.

Next to potential behavioural, socioeconomic, and environmental risk factors, variance in the uptake and effectiveness of interventions for HIV prevention and control could partly explain geospatial heterogeneity. For instance, information on HIV status and male circumcision status can be utilised to estimate the population-level impact of male circumcision, a procedure promoted among males in sub-Saharan Africa to curb HIV transmission. The effect of VMMC on individual-level HIV risk prevention in men is well-researched through conducted randomised-controlled trials [35–37], but the population-level impact of both traditional and medical circumcision practices on the HIV epidemic is still poorly known. However, male circumcision might be less effective outside of trials due differences in performance of the procedure (outside of trials, and for medical versus traditional circumcision) and variations in target populations and risk behaviours [77,78]. The cross-sectional nature of the DHSs makes it challenging to arrive at definite statements about the causal relationship between being circumcised and having HIV; after all, we do not know whether male circumcision preceded HIV acquisition in the sampled men. Quasi-experimental methods such as household fixed-effect model can be used to estimate the real-world impact of being circumcised on HIV status among men in sub-Saharan Africa countries and compare effect sizes for the different African regions.

Key populations

Worldwide, more than half of new HIV infections are among so-called key populations: subpopulations known to be at a higher risk of acquiring HIV – *i.e.* sex workers, men who have sex with men, transgender people, and injecting drug users [61,79]. Over 95% of new HIV infections in Eastern Europe and Central Asia, in the Middle East and North Africa, in Western and Central Europe and North America, and in Asia and the Pacific; and over 60% in Latin America and the Caribbean, and in West and Central Africa are estimated to occur among these populations [80]. Given that HIV occurrence in these countries accumulates among key populations, the epidemics are commonly classified as "concentrated". The only region in which key populations are estimated to hold a substantially lower relative share of total incidence is Eastern and Southern Africa. Here, only about 13% of new infections are estimated to occur among key populations, and 15% among their sexual partners [80]. The epidemics in these countries are often characterised as "generalised", as an estimated 72% of all infections occur among the so-called general population. However, prevalence levels

among key populations in these generalised epidemics are often still extremely high. For instance, HIV prevalence among adult female sex workers in Zimbabwe was estimated to be over 50% between 2018 and 2020 [81,82], while HIV prevalence among the Zimbabwean general population was about 15% at that time [75].

The association between geospatial heterogeneity in HIV prevalence among the general population and among key populations is, thus far, just partially known. Earlier it was found that 'upstream' transmission (*i.e.* transmission from key populations to the general population) in sex work remains important in African HIV epidemics, especially boosted by seasonal (migrant) labour in cities, mining areas and areas with growing economies, in turn associated with high demands for sex work [83,84]. However, the magnitude of importance of sex work in fuelling HIV epidemics in sub-Saharan Africa and the impact on geospatial heterogeneity of HIV prevalence are poorly understood. In order to effectively end the HIV pandemic, it is essential that we gain a better understanding of how important key populations are in driving the HIV epidemic. Geospatial mapping of hotspots for key populations and general population prevalence can provide more insight into whether there is a direct link between key populations and general population prevalence, or whether this relationship is more complex.

When aiming to end the HIV epidemic in both the concentrated and generalised epidemics of sub-Saharan Africa, interventions for key populations are an essential component. Such interventions may not only reduce the relatively high disease prevalence among key populations, but potentially also decrease transmission to the general population. However, many barriers remain in place to successfully scale up services for key populations in sub-Saharan Africa. Stigma and discrimination related to people's positive HIV status is still common, and discrimination is especially prominent towards the different key populations [85]. Key populations can also experience social exclusion, reinforced in many African countries by punitive laws and policies; for instance, those prohibiting same-sex relationships and sex work [86,87].

Due to discrimination and social and legal exclusion, key populations often stay under the radar, making it difficult to know how large existing key population groups and their HIV service needs are, and therefore nearly impossible to adequately scale-up treatment and prevention services [88,89]. For female sex workers, recent recognition of their importance has resulted in the scale-up of effective prevention and treatment interventions across sub-Saharan Africa, thereby curbing transmission substantially [90]. However, many other key populations, such as men who have sex with men, transgender people, and male and transgender sex workers remain largely underserved and hidden [91].

Developing effective targets, policies and interventions for these populations requires estimations of population sizes and HIV prevalence across countries and regions in sub-Saharan Africa. However, current estimates for men who have sex with men provided by the Joint United Nations Programme on HIV/AIDS (UNAIDS) largely rely on country-reported numbers from a single survey or expert opinion - and are potentially biased [92] - while estimates for transgender people, and male sex workers and transgender sex workers are by and large absent [91]. Summarising and extrapolating HIV prevalence estimates from recent existing scientific literature to estimate country-specific HIV prevalences for these key populations in sub-Saharan Africa could help improve our understanding of the current HIV prevalence among these populations.

1.3 OPTIMISING HIV SERVICE DELIVERY TOWARDS ENDING THE PANDEMIC

The goal of ending the HIV pandemic can likely only be achieved through the scale-up of effective, affordable, efficient, and sustainable HIV treatment and prevention services across the globe [93]. An unprecedented response to the pandemic by the global community over the past decades has led to an impressive increase in access to ART. In 2020, it was estimated that about 27 million people were accessing ART; covering 73% of all people living with HIV [80]. Nevertheless, questions remain on how to reach the 'last mile' of HIV control – *i.e.*, to ensure treatment access for all and reach zero new infections by 2030 – in the context of challenging financial and health systems constraints, and changing global health landscapes.

ART was first discovered in 1996, but the high costs and complexity of the treatment initially restricted access to wealthier counties and populations. However, by the early 2000s, the continuing spread of HIV and the ever-increasing mortality rates in LMICs, especially sub-Saharan Africa, prompted the international community to respond. The Global Fund to Fight AIDS, Tuberculosis and Malaria was a created in 2002 as a large multi-country financing initiative aimed at, among others, the scale-up of ART in resource limited settings [94,95]. In 2003, US president George W. Bush announced the creation of the United States President's Emergency Plan for AIDS Relief (PEPFAR), a billion-dollar plan to make ART accessible for countries with a high number of HIV infections, at that time predominantly the US and countries in Eastern and Southern Africa [96]. Following these developments, in 2003 the WHO announced the "3 by 5" initiative, a global goal to bring treatment to 3 million people in resource limited countries by 2005 [97].

To enable the rapid large-scale delivery of ART, stand-alone healthcare delivery systems for HIV were built throughout sub-Saharan Africa and other regions affected by the pandemic

to scale-up access to testing and treatment [98,99]. Efforts resulted in a rapid increase in the number of clinics offering ART in the 30 highest-burden countries; from about 300 clinics in 2004 to over 6400 clinics in 2009 [100,101]. By 2005, about 1 million people in LMICs were receiving ART in low resource settings. Although a great achievement, the ambitious "3 by 5" target was not reached and access to HIV treatment continues to fall short of the growing need [102]. Still, a substantial reduction in AIDS-related deaths was seen globally after the initial scale-up of ART, from about 1.900.000 in 2005 to about 1.000.000 in 2015 and 680.000 in 2020 (**Figure 5**) [103], and this number continues to decline [100,103,104].

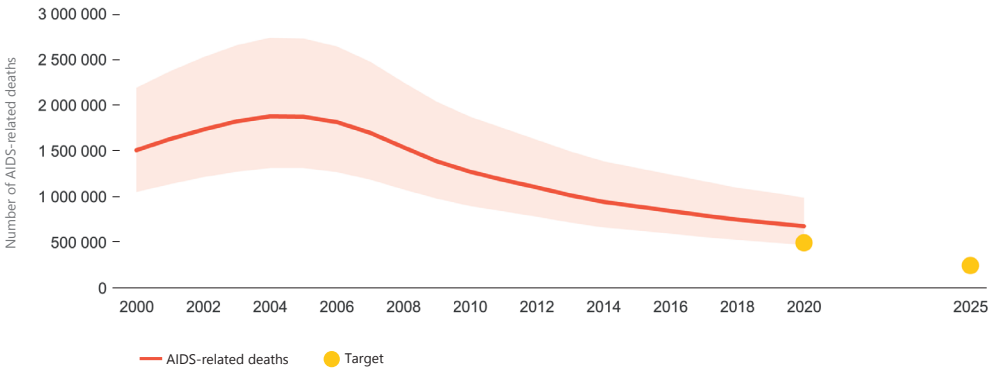

Figure 5. AIDS-related deaths, global, 1990–2020. Source: UNAIDS epidemiological estimates, 2021 (https://AIDSinfo.unAIDS.org/) [103].

Due to the high costs of treatment and limited availability in early years, ART could initially not be prescribed to all people living with HIV during the start of the scale-up. Instead, initiation after diagnosis was guided by the level of immunosuppression of the patient, indicated by CD4 counts in the blood. In the early 2000s, ART was initiated once an individual's CD4 count fell below 200 cells/μL (in contrast to around 1100 cells/μL in healthy individuals). However, as evidence on the benefits of earlier treatment initiation for both individual patients and overall epidemiological dynamics started emerging [21,105–107], the WHO began to gradually expand its treatment recommendations. Treatment initiation eligibility criteria were first expanded to people with CD4 cell counts below 350 cells/μL in the 2009 guidelines [108], and further to people with CD4 cell counts below 500 cells/μL in the 2013 guidelines [109]. Following the release of the Strategic Timing of Antiretroviral Therapy (START) trial findings in 2015 [110], which demonstrated that treatment initiation at CD4 cell counts above 500 cells/μL would provide benefits to individual patients [107], the WHO released its landmark 2016 guidelines, recommending immediate ART initiation after diagnosis regardless of the level of immunosuppression [111]. As evidence on the potential benefits of earlier treatment on the epidemic as a whole was mounting [21,105,106], these guidelines increasingly emphasised that earlier treatment initiation is not only beneficial for the individual patient, but also an important tool in reaching epidemic control.

Current global targets

Current global targets for control of the HIV pandemic within the wider context of international health are captured within two broad targets: reaching '95-95-95'; and 'getting to zero'. These are part of the so-called Fast-Track commitments, which were adopted by the UN member states during the 2016 Political Declaration of the United Nations General Assembly on HIV and AIDS [112,113]. The first target, 95-95-95, aims for near-universal and effective coverage with HIV testing and treatment for people living with HIV [114–116]. This target calls for 95% of people living with HIV to know their status, 95% of all people with diagnosed HIV to receive sustained ART, and 95% of all people receiving antiretroviral therapy to have viral suppression by 2030. This target follows the intermediate "90-90-90" targets for HIV treatment that was set for 2020 [114]. The second target, 'getting to zero', aims to achieve "less than 200,000 new HIV infections worldwide, zero AIDS-related deaths, and zero discrimination by the end of 2030, as well as access to combination prevention for at least 90% of all key populations in the HIV response [116,117].

The international commitment towards ending the HIV pandemic is further emphasised by its explicit incorporation into the Sustainable Development Goals (SDGs). The SDGs were launched in 2015, replacing the Millennium Development Goals (MDGs), and call for 17 ambitious goals to be achieved by 2030 for a prosperous future for people and the planet. SDG 3 calls to "ensure healthy lives and promote wellbeing for all at all ages" and SDG 3.3 specifically calls to "end AIDS as a public health threat by 2030". However, despite the progress in service delivery for HIV over the last decade, the HIV response in sub-Saharan Africa was not sufficient to bring testing, treatment and care to all people in need [89], and two key challenges need to be met so that these ambitious global targets are achieved: the persistent and increasing health systems and funding constraints; and a changing global health landscape towards universal, integrated care.

Health systems and funding constraints

Only 14 countries in the world met the interim 90-90-90 targets in 2020: Australia, Botswana, Cambodia, Eswatini, Ireland, Namibia, The Netherlands, Rwanda, Spain, Switzerland, Thailand, Uganda, Zambia and Zimbabwe [80,89,103,118–120]. Arguably, reaching the 90-90-90 target was easier for some countries than for others. In Australia, Ireland, The Netherlands, Spain, and Switzerland a relatively large share of (financial) resources were available for HIV/AIDS and prevalence levels have always been low. In Cambodia and Thailand overall prevalence were already low, but the majority of cases were among key populations who largely live under the radar in their countries. In Botswana, Eswatini, Namibia, Rwanda, Uganda, Zambia and Zimbabwe HIV prevalence levels were relatively high while domestic (financial) resources were low. Meanwhile, other countries were off-track, with often large gaps in HIV testing and treatment provision [89]. Globally, an estimated 81% of people living with HIV

knew their HIV status, 82% of the people who know their status were on ART, and 88% of people on ART were virally suppressed by the end of 2019 (**Figure 6**) [89,121,122]. Shortcomings in reaching the 90-90-90 have been attributed earlier to the rapid rise in people needing testing and treatment in combination with insufficient access to services due to insufficient utilisation of healthcare workers and inability to provide sufficient services for children and key populations [121].

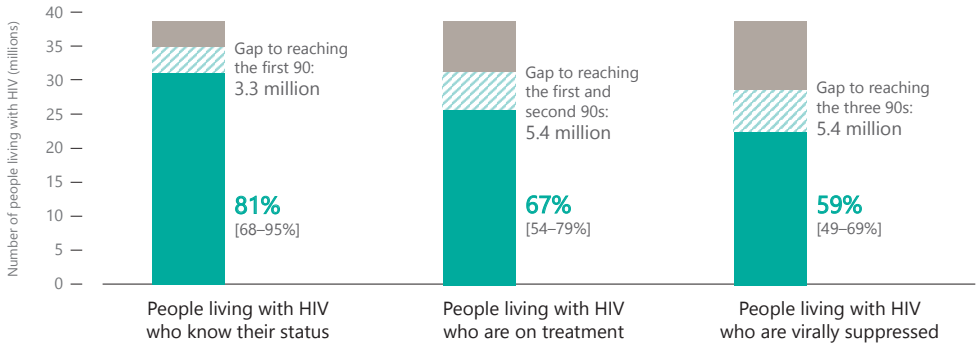

Figure 6. HIV 90-90-90 testing and treatment cascade targets and latest numbers (UNAIDS estimates, end 2019). Source: UNAIDS data, 2020 [89].

Up to around 2012, 95% of service delivery for HIV in sub-Saharan Africa was clinic-based [117,123]. However, the ever-growing need for scale-up of ART programmes has increased the pressure on current health systems and has therefore made purely clinic-based delivery increasingly unsustainable. Different service delivery strategies were introduced in later years to further scale-up testing and treatment on the subcontinent to respond to the high health service demands, changing needs and decreasing funding. For instance, self-testing and home-based testing via community-level outreaches were introduced to expand testing rates by taking service delivery out of clinical settings [124–126]. HIV services were also extended to other types of healthcare clinics—such as maternal and child healthcare clinics [127,128] and tuberculosis clinics [129,130]—by integrating the different services at these locations; aiming to improve care of HIV-patients and widen access to services [131,132]. Since 2015, the WHO endorses "differentiated service delivery" for HIV [133,134], a client-centred approach that simplifies and adapts HIV services across the cascade-of-care, such as allowing for less frequent ART pick-ups and offering support from community adherence peer-groups [135,136]. Alternative healthcare delivery strategies can thus release pressure from clinics and specialists as well as enable better healthcare reach for the people through task shifting and decentralisation.

On top of these service delivery challenges, the available funding for HIV programming has been declining. Annual international donor funding for HIV, comprising about 40% of

all funding for HIV for LMICs [137], has declined by about $100 million since the 2008-09 economic recession. Whereas funding steadily increased until the economic crisis, it has declined by about 30% between 2012 and 2015 and has flatlined in the years after (**Figure 7**) [95,138,139]. Next to the 2008-09 economic recession, further reasons for this decline are the loss of global momentum to fight HIV that was sparked by the initial MDGs [137] and reduced priority of donor countries to invest in Official Development Assistance (ODA) for foreign countries [140]. Although most LMICs are transitioning towards domestic public funding because of shrinking donor funding, with The Global Fund and PEPFAR as main contributors, ODA remains an essential component of HIV financing, especially in sub-Saharan Africa. Additional cuts to development assistance could hasten this decline, and risk slowing progress in the HIV response [140].

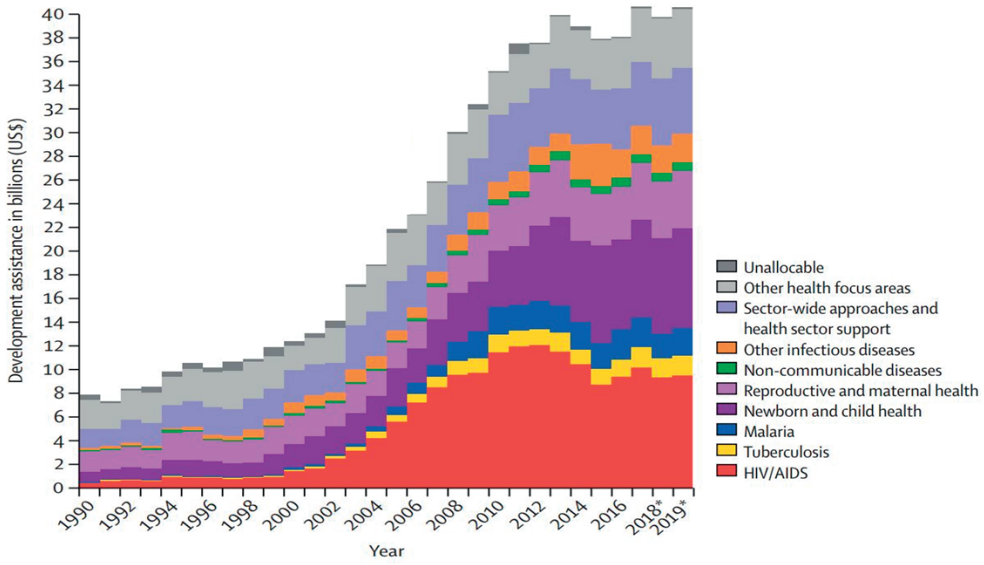

Figure 7. Development assistance for health between 1990 and 2019, red bars represent the development assistance for HIV/AIDS. Source: Global Burden of Disease Health Financing Collaborator Network, Lancet, 2020 [95].

The coronavirus disease 2019 (COVID-19) pandemic has put further financial strain on the HIV response [141]. Since the start of the COVID-19 pandemic, healthcare workers, financial resources and research and policy attention have been diverted from HIV efforts to fight the COVID-19 pandemic. Furthermore, strict lockdown measures have disrupted access to HIV prevention, treatment and care—possibly causing a resurge in HIV incidence and mortality and exacerbating social and economic inequalities in access to HIV services [142,143]. Potentially even more devasting are the effects on the financing of the HIV response. The COVID-19 pandemic produced an economic crisis characterised as the worst since the Great Depression in the 1930s [141]. Both domestic and donor funding are put under enormous

pressure, as economies have shrunk, and donor countries increasingly divert funding towards domestic goals.

These developments can have devastating effects on donor and domestic healthcare financing for the years to come, including for HIV. Hence, next to ensuring short-term HIV service continuation, we need to quantify how big the impact of the COVID-19 pandemic on HIV funding gaps will be and find suitable mitigation strategies to ensure continued service delivery in the future, especially in the countries with the largest ART programs. Mitigating these financial and health systems challenges in the HIV response and ensuring that we stay on track to reaching the ambitious targets of ending the epidemic by 2030 requires rapid innovations of service delivery strategies and financing schemes. Summarising and discussing the range of available service delivery strategies could help policymakers in deciding on which interventions to implement.

HIV control and universal health coverage through health service integration

Efforts towards ending the HIV pandemic by meeting international targets need to be embedded within the context of the SDGs and broader global health goals. Next to the ambitious HIV targets, the SDGs urge that people should have access to a wider range of affordable and high-quality health services by 2030 through 'universal health coverage' (UHC) [94,144]. For the HIV response, UHC represents a paradigm shift towards offering patient-centred high-quality health services beyond HIV testing and treatment and "promoting wellness rather than mere survival" [145]. Moving towards UHC for many countries requires restructuring and reshaping healthcare systems to improve availability, accessibility, and capacity of health services. A promising way to achieve this, is health service integration.

Health service integration is defined as the joining of two or more health services that were previously separated in some way (for instance, delivered by different health workers or at different locations) [146,147]. In sub-Saharan Africa, it often entails the merging of two or more previously vertical healthcare programmes (*e.g.*, for HIV and tuberculosis) [127,129,130] or adding additional services into vertical systems to broaden the scope of the offered services (*e.g.*, offering hypertension and diabetes screening at HIV clinics) [128,147]. Although integration of HIV services and other health services has been implemented and studied widely in Africa's health systems, the impacts on the HIV care cascade, health outcomes, and cost-effectiveness, and how potential benefits of integration depend on local contexts have never been systematically summarised and analysed.

Improving our knowledge on the effects of service integration on a range of service delivery and health outcomes for HIV and other diseases would provide valuable information to

inform policy and implementation strategies aimed at improving the reach, quality, impact and sustainability of the HIV response while moving towards the future ambition of UHC. Nevertheless, local policymakers will always be faced with the inherent context specific nature of the association between implementation and impact. Accelerating progress in the HIV response necessitates optimal application of available service delivery models, requiring knowledge on what determines suitability of certain integration models in different contexts, especially those with the highest service needs and lowest resources.

1.4 AIM AND RESEARCH QUESTIONS

The overarching aim of this thesis is to describe and improve our understanding of HIV epidemiology in sub-Saharan Africa, and to provide insight into which health systems innovations could mitigate global challenges in the HIV response. To achieve this aim, we have formulated the following four research questions:

1) Where is the HIV burden highest in sub-Saharan Africa, the epicentre of the pandemic, and what drives the geographical heterogeneity in HIV transmission and prevalence on the subcontinent?
2) What is the HIV burden among key populations and how does this contribute to the HIV epidemiology in sub-Saharan Africa?
3) Which service delivery and financing innovations could mitigate current global challenges in the HIV response?
4) How can HIV service integration contribute to optimising the HIV response and reaching universal health coverage?

1.5 OUTLINE OF THIS THESIS

This thesis focusses on mapping geographical heterogeneity in HIV epidemiology and researching the potential underlying dynamics as well as strategies for innovating healthcare delivery and financing for HIV control to face the new challenging and changing global and local needs are explored. This thesis covers the following chapters:

In **Chapter 2**, we identify and characterise areas of high HIV prevalence and transmission among the general population in 7 sub-Saharan African countries by geographic mapping using geolocated nationally representative cross-sectional DHS data. In **Chapter 3**, the real-world impact of male circumcision on HIV prevalence is assessed for different regions in sub-Saharan Africa, using a household fixed-effects analysis on nationally-representative survey data. Chapters 2 and 3 together address the first research question. In **Chapter 4**

we present the findings from a systematic review and meta-analysis to estimate HIV prevalence levels among different key populations—men who have sex with men, transgender people, and male and transgender sex workers—in sub-Saharan Africa; and compare the key population prevalence estimates to prevalence estimates from the general population in matched geographical areas. Using nationally representative cross-sectional survey data and data on sex work locations, we explore the potential link between sex workers and HIV risk in the general population nearby sex work locations in Zimbabwe in **Chapter 5**, to determine whether locations of sex work hotspots are directly affecting general population HIV prevalence. Chapters 4 and 5, together with insights from Chapter 2, address the second research question.

In **Chapter 6**, we set out and discuss which delivery model innovations could support sustainable HIV treatment and give an overview of implemented models in different African contexts. The potential impact of the COVID-19-related economic crisis on financing of the HIV response in the 10 countries with the largest treatment programmes is estimated using different forecasting scenarios in **Chapter 7**. Chapters 6 and 7 together provide insights to answer the third research question. The effects of integrating HIV services and other health services on uptake of healthcare, HIV and non-HIV health indicators and economic outcomes are systematically reviewed in **Chapter 8**. Finally, **Chapter 9** outlines which policy decisions could be taken when quantitative evidence on integration is absent or incomplete. Chapters 8 and 9 together address the fourth research question.

The answers to the research questions, a personal view about achieving the HIV targets, and overall conclusions and recommendations are provided in **Chapter 10**.

REFERENCES

1. Simon V, Ho DD, Karim QA. HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. Lancet. 2006;368: 489–504.
2. Engelman A, Cherepanov P. The structural biology of HIV-1: mechanistic and therapeutic insights. Nat Rev Microbiol. 2012;10: 279–290.
3. Miller WC, Rosenberg NE, Rutstein SE, Powers KA. The role of acute and early HIV infection in the sexual transmission of HIV. Curr Opin HIV AIDS. 2010;5: 277.
4. Lodi S, Phillips A, Touloumi G, Geskus R, Meyer L, Thiébaut R, *et al.* Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 cells/mm3: assessment of need following changes in treatment guidelines. Clin Infect Dis. 2011;53: 817–825.
5. Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 infection. N Engl J Med. 2011;364: 1943–1954.
6. Clerici M, Stocks NI, Zajac RA, Boswell RN, Bernstein DC, Mann DL, *et al.* Interleukin-2 production used to detect antigenic peptide recognition by T-helper lymphocytes from asymptomatic HIV-seropositive individuals. Nature. 1989;339: 383–385.
7. Colvin M, Karim SSA, Connolly C, Hoosen AA, Ntuli N. HIV infection and asymptomatic sexually transmitted infections in a rural South African community. Int J STD AIDS. 1998;9: 548–550.
8. Blattner W, Gallo RC, Temin HM, others. HIV causes AIDS. Science. 1988;241: 515–516.
9. Fauci AS. HIV and AIDS: 20 years of science. Nat Med. 2003;9: 839–843.
10. Weiss RA. How does HIV cause AIDS? Science. 1993;260: 1273–1279.
11. Fleming AF. Opportunistic infections in AIDS in developed and developing countries. Trans R Soc Trop Med Hyg. 1990;84: 1–6.
12. Gulick RM, Mellors JW, Havlir D, Eron JJ, Gonzalez C, McMahon D, *et al.* Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. N Engl J Med. 1997;337: 734–739.
13. Lawn SD, Myer L, Bekker L-G, Wood R. CD4 cell count recovery among HIV-infected patients with very advanced immunodeficiency commencing antiretroviral treatment in sub-Saharan Africa. BMC Infect Dis. 2006;6: 1–8.
14. Collaboration ATC, others. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet. 2008;372: 293–299.
15. Hontelez JAC, Vlas SJ de, Baltussen R, Newell M-L, Bakker R, Tanser F, *et al.* The impact of antiretroviral treatment on the age composition of the HIV epidemic in sub-Saharan Africa. AIDS. 2012;23: 1–7. doi:10.1038/jid.2014.371
16. Till Bärnighausen MD, MIA JN. HIV and aging - preparing for the challenges ahead. N Engl J Med. 2012;366: 1270.
17. Deeks SG, Lewin SR, Havlir D V. The end of AIDS: HIV infection as a chronic disease. Lancet. 2013;382: 1525–1533.
18. Kearney F, Moore AR, Donegan CF, Lambert J. The ageing of HIV: implications for geriatric medicine. Age Ageing. 2010;39: 536–541.
19. Coetzee L, Bogler L, De Neve J-W, Bärnighausen T, Geldsetzer P, Vollmer S. HIV, antiretroviral therapy and non-commu-

nicable diseases in sub-Saharan Africa: empirical evidence from 44 countries over the period 2000 to 2016. J Int AIDS Soc. 2019;22: e25364.

20. Cohen MS, Smith MK, Muessig KE, Hallett TB, Powers KA, Kashuba AD. Antiretroviral treatment of HIV-1 prevents transmission of HIV-1: where do we go from here? Lancet. 2013;382: 1515–1524.

21. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, others. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. N Engl J Med. N Engl J Med. 2011;365: 493–505. doi:10.1056/NEJMoa1105243

22. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'sullivan MJ, *et al.* Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med. 1994;331: 1173–1180.

23. Chigwedere P, Seage III GR, Lee T-H, Essex M. Efficacy of antiretroviral drugs in reducing mother-to-child transmission of HIV in Africa: a meta-analysis of published clinical trials. AIDS Res Hum Retroviruses. 2008;24: 827–837.

24. Donnell D, Baeten JM, Kiarie J, Thomas KK, Stevens W, Cohen CR, *et al.* Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. Lancet. 2010;375: 2092–2098.

25. Anglemyer A, Rutherford GW, Horvath T, Baggaley RC, Egger M, Siegfried N. Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples. Cochrane database Syst Rev. 2013.

26. Eaton JW, Johnson LF, Salomon JA, Bärnighausen T, Bendavid E, Bershteyn A, *et al.* HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. PLOS Med. 2012;9: e1001245.

27. Hontelez JAC, Chang AY, Ogbuoji O, De Vlas SJ, Bärnighausen T, Atun R. Changing HIV treatment eligibility under health system constraints in sub-Saharan Africa: Investment needs, population health gains, and cost-effectiveness. AIDS. 2016;30: 2341–2350. doi:10.1097/QAD.0000000000001190

28. Hontelez JAC, De Vlas SJ, Tanser F, Bakker R, Bärnighausen T, Newell M-L, *et al.* The impact of the new WHO antiretroviral treatment guidelines on HIV epidemic dynamics and cost in South Africa. PLOS ONE. 2011;6: e21919.

29. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009;373: 48–57.

30. Hontelez JAC, Lurie MN, Bärnighausen T, Bakker R, Baltussen R, Tanser F, *et al.* Elimination of HIV in South Africa through expanded access to antiretroviral therapy: a model comparison study. PLOS Med. 2013;10: e1001534.

31. Eisinger RW, Dieffenbach CW, Fauci AS. HIV viral load and transmissibility of HIV infection: undetectable equals untransmittable. Jama. 2019;321: 451–452.

32. Undetectable=Untransmissable. Prevention Access Campaign. 2016 [cited 11 Oct 2021]. Available: https://www.preventionaccess.org/undetectable

33. Pinkerton SD, Abramson PR. Effectiveness of condoms in preventing HIV transmission. Soc Sci Med. 1997;44: 1303–1312.

34. Weller SC, Davis-Beaty K. Condom effectiveness in reducing heterosexual HIV

transmission. Cochrane database Syst Rev. 2002.

35. Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, *et al.* Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet. 2007; 643–656.

36. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, *et al.* Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007;369: 657–666. doi:10.1016/S0140-6736(07)60313-4

37. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 trial. PLOS Med. 2005;2: 1112–1122. doi:10.1371/journal.pmed.0020298

38. Elliott T, Sanders EJ, Doherty M, Ndung'u T, Cohen M, Patel P, *et al.* Challenges of HIV diagnosis and management in the context of pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), test and start and acute HIV infection: a scoping review. J Int AIDS Soc. 2019;22: e25419.

39. Krakower DS, Jain S, Mayer KH. Antiretrovirals for primary HIV prevention: the current status of pre-and post-exposure prophylaxis. Curr HIV/AIDS Rep. 2015;12: 127–138. doi:10.1007/s11904-014-0253-5

40. Padian NS, Buvé A, Balkus J, Serwadda D, Cates Jr W. Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward. Lancet. 2008;372: 585–599.

41. Blankenship KM, Friedman SR, Dworkin S, Mantell JE. Structural interventions: concepts, challenges and opportunities for research. J Urban Heal. 2006;83: 59–72.

42. Mimiaga MJ. Structural interventions for HIV prevention. Lancet Infect Dis. 2019;19: 1180.

43. Korber B, Muldoon M, Theiler J, Gao F, Gupta R, Lapedes A, *et al.* Timing the ancestor of the HIV-1 pandemic strains. Science. 2000;288: 1789–1796.

44. Faria NR, Rambaut A, Suchard MA, Baele G, Bedford T, Ward MJ, *et al.* The early spread and epidemic ignition of HIV-1 in human populations. Science. 2014;346: 56–61.

45. Quammen D. The Chimp and the River: How AIDS Emerged from an African Forest. New York: Random House; 2015.

46. Barré-Sinoussi F, Chermann J-C, Rey F, Nugeyre MT, Chamaret S, Gruest J, *et al.* Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science. 1983;220: 868–871.

47. Centers for Disease Control (CDC). Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men-New York City and California. mmwr. 1981;30: 305–308.

48. Osmond DH, Page K, Wiley J, Garrett K, Sheppard HW, Moss AR, *et al.* HIV infection in homosexual and bisexual men 18 to 29 years of age: the San Francisco Young Men's Health Study. Am J Public Health. 1994;84: 1933–1937.

49. Shilts R. And the band played on: Politics, people, and the AIDS epidemic. Souvenir Press; 2011.

50. Moss AR, Bacchetti P. Natural history of HIV infection. AIDS. 1989;3: 55–62.

51. Catania JA, Osmond D, Stall RD, Pollack L, Paul JP, Blower S, *et al.* The continuing HIV epidemic among men who have sex with men. Am J Public Health. 2001;91: 907.

52. Valleroy LA, MacKellar DA, Karon JM, Rosen DH, McFarland W, Shehan DA, *et*

al. HIV prevalence and associated risks in young men who have sex with men. Jama. 2000;284: 198–204.

53. Mann JM. AIDS: A worldwide pandemic. Curr Top AIDS. 1989;2: 1–10.

54. UNAIDS, World Health Organization (WHO). 2008 report on the global AIDS epidemic. World Health Organization; 2008.

55. Veronika G. History of AIDS. New York: Lulu.com; 2013.

56. Wang H, Wolock TM, Carter A, Nguyen G, Kyu HH, Gakidou E, *et al.* Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980-2015: the Global Burden of Disease Study 2015. Lancet HIV. 2016;3: e361–e387.

57. Leach-Kemon K, Shepard D, O'Rourke K, VanderZanden A, others. HIV Worldwide 1990-2013. Jama. 2015;314: 1552.

58. Selik RM, Chu SY, Buehler JW. HIV infection as leading cause of death among young adults in US cities and states. Jama. 1993;269: 2991–2994.

59. Conti S, Farchi G, Prati S. AIDS as a leading cause of death among young adults in Italy. Eur J Epidemiol. 1994;10: 669–673.

60. UNAIDS. Global HIV statistics - Fact sheet 2021. End AIDS epidemic. 2021.

61. United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS data 2021. 2021. Available: https://www.unAIDS.org/sites/default/files/media_asset/JC3032_AIDS_Data_book_2021_En.pdf

62. Dwyer-Lindgren L, Cork MA, Sligar A, Steuben KM, Wilson KF, Provost NR, *et al.* Mapping HIV prevalence in sub-Saharan Africa between 2000 and 2017. Nature. 2019. doi:10.1038/s41586-019-1200-9

63. Mbogo CM, Mwangangi JM, Nzovu J, Gu W, Yan G, Gunter JT, *et al.* Spatial and temporal heterogeneity of Anopheles mosquitoes and Plasmodium falciparum transmission along the Kenyan coast. Am J Trop Med Hyg. 2003;68: 734–742.

64. Yared S, Deribe K, Gebreselassie A, Lemma W, Akililu E, Kirstein OD, *et al.* Risk factors of visceral leishmaniasis: a case control study in north-western Ethiopia. Parasites \& vectors. 2014;7: 1–11.

65. Lemke LD, Lamerato LE, Xu X, Booza JC, Reiners JJ, Raymond Iii DM, *et al.* Geospatial relationships of air pollution and acute asthma events across the Detroit--Windsor international border: Study design and preliminary results. J Expo Sci \& Environ Epidemiol. 2014;24: 346–357.

66. Woudenberg T, van Binnendijk RS, Sanders EAM, Wallinga J, de Melker HE, Ruijs WLM, *et al.* Large measles epidemic in the Netherlands, May 2013 to March 2014: changing epidemiology. Eurosurveillance. 2017;22: 30443.

67. Okoyo C, Campbell SJ, Williams K, Simiyu E, Owaga C, Mwandawiro C. Prevalence, intensity and associated risk factors of soil-transmitted helminth and schistosome infections in Kenya: impact assessment after five rounds of mass drug administration in Kenya. PLOS Negl Trop Dis. 2020;14: e0008604.

68. Palk L, Blower S. Geographic variation in sexual behaviour can explain geospatial heterogeneity in the severity of the HIV epidemic in Malawi. BMC Med. 2018;16: 22. doi:10.1186/s12916-018-1006-x

69. Cuadros DF, Li J, Branscum AJ, Akullian A, Jia P, Mziray EN, *et al.* Mapping the spatial variability of HIV infection in Sub-Saharan Africa: Effective information for localized HIV prevention and control. Nature. 2017;7: 1–11. doi:10.1038/s41598-017-09464-y

70. Diggle PJ, Tawn JA, Moyeed RA. Model-Based Geostatistics. J R Stat Soc. 1998;67: 617–666.

71. Tanser FC, Le Sueur D. The application of geographical information systems to important public health problems in Africa. Int J Health Geogr. 2002;1: 1–9.

72. Snow J. Mode of Communication of Cholera. London John Churchill, New Burlingt Street, Engl. 1855;44: 1794–1799.

73. Mclafferty S. Disease cluster detection methods: Recent developments and public health implications. Ann GIS. 2015;21: 127–133.

74. McLafferty SL. GIS and health care. Annu Rev Public Health. 2003;24: 25–42.

75. USAID. DHS Program - Demographic and Health Surveys. [cited 10 Nov 2021]. Available: https://dhsprogram.com/

76. Hay SI, George DB, Moyes CL, Brownstein JS. Big data opportunities for global infectious disease surveillance. PLOS Med. 2013;10: e1001413.

77. Weiss HA, Dickson KE, Agot K, Hankins CA. Male circumcision for HIV prevention: current research and programmatic issues. AIDS. 2010;24: S61.

78. Mehta SD, Moses S, Agot K, Odoyo-June E, Li H, Maclean I, *et al.* The long-term efficacy of medical male circumcision against HIV acquisition. AIDS. 2013;27: 2709–2899.

79. Macdonald V, Verster A, Baggaley R. A call for differentiated approaches to delivering HIV services to key populations. J Int AIDS Soc. 2017;20: 21658.

80. Joint United Nations Programme on HIV/AIDS (UNAIDS). Joint United Nations Programme on HIV/AIDS. UNAIDS data 2020. Geneva; 2020. Available: https://www.unAIDS.org/sites/default/files/media_asset/2020_AIDS-data-book_en.pdf

81. Fearon E, Chabata ST, Magutshwa S, Ndori-Mharadze T, Musemburi S, Chidawanyika H, *et al.* Estimating the Population Size of Female Sex Workers in Zimbabwe: Comparison of Estimates Obtained Using Different Methods in Twenty Sites and Development of a National-Level Estimate. J Acquir Immune Defic Syndr. 2020;85: 30–38. doi:10.1097/QAI.0000000000002393

82. Chabata ST, Hensen B, Chiyaka T, Mushati P, Mtetwa S, Hanisch D, *et al.* Changes Over Time in HIV Prevalence and Sexual Behaviour Among Young Female Sex - Workers in 14 Sites in Zimbabwe , 2013 – 2016. AIDS Behav. 2019;23: 1494–1507. doi:10.1007/s10461-019-02410-1

83. Steen R, Hontelez JAC, Mugurungi O, Mpofu A, Matthijsse SM, de Vlas SJ, *et al.* Economy, migrant labour and sex work: interplay of HIV epidemic drivers in Zimbabwe over three decades. AIDS. 2019;33: 123.

84. Steen R, Hontelez JAC, Veraart A, White RG, de Vlas SJ. Looking upstream to prevent HIV transmission: can interventions with sex workers alter the course of HIV epidemics in Africa as they did in Asia? AIDS. 2014;28: 891–899.

85. Friedland BA, Sprague L, Nyblade L, Baral SD, Pulerwitz J, Gottert A, *et al.* Measuring intersecting stigma among key populations living with HIV: implementing the people living with HIV Stigma Index 2.0. J Int AIDS Soc. 2018;21.

86. Chitando E, Mateveke P. Africanizing the discourse on homosexuality: challenges and prospects. Crit African Stud. 2017;9: 124–140.

87. Platt L, Grenfell P, Meiksin R, Elmes J, Sherman SG, Sanders T, *et al.* Associations between sex work laws and sex workers' health: A systematic review and meta-

analysis of quantitative and qualitative studies. PLOS Med. 2018;15: e1002680.

88. Barr D, Garnett GP, Mayer KH, Morrison M. Key populations are the future of the African HIV/AIDS pandemic. J Int AIDS Soc. 2021;24.

89. Joint United Nations Programme on HIV/AIDS (UNAIDS). Seizing the moment: Tackling entrenched inequalities to end epidemics - Global AIDS update 2020. Geneva; 2020. Available: https://www.unAIDS.org/sites/default/files/media_asset/2020_global-AIDS-report_en.pdf

90. Baral S, Beyrer C, Muessig K, Poteat T, Wirtz AL, Decker MR, *et al.* Burden of HIV among female sex workers in low-income and middle-income countries: A systematic review and meta-analysis. Lancet Infect Dis. 2012;12: 538–549. doi:10.1016/S1473-3099(12)70066-X

91. Sabin K, Zhao J, Garcia Calleja JM, Sheng Y, Arias Garcia S, Reinisch A, *et al.* Availability and quality of size estimations of female sex workers, men who have sex with men, people who inject drugs and transgender women in low-and middle-income countries. PLOS ONE. 2016;11: e0155150.

92. United Nations Programme on HIV/AIDS (UNAIDS), World Health Organization (WHO). Monitoring HIV Impact Using Population-Based Surveys. 2015. Available: https://www.unAIDS.org/sites/default/files/media_asset/JC2763_Population-BasedSurveys_en.pdf

93. Bekker LG, Alleyne G, Baral S, Cepeda J, Daskalakis D, Dowdy D, *et al.* Advancing global health and strengthening the HIV response in the era of the Sustainable Development Goals: the International AIDS Society—Lancet Commission. Lancet. 2018;392: 312–358. doi:10.1016/S0140-6736(18)31070-5

94. World Bank, JICA, The Global Fund, WHO. UHC in Africa: A Framework for Action Executive Summary. 2016;35: 155–160. Available: https://www.unAIDS.org/sites/default/files/media_asset/20181122_UNAIDS_PCB43_Way_fw_achieving_sustainable_AIDS_resp_results_EN.pdf

95. Micah AE, Su Y, Bachmeier SD, Chapin A, Cogswell IE, Crosby SW, *et al.* Health sector spending and spending on HIV/AIDS, tuberculosis, and malaria, and development assistance for health: progress towards Sustainable Development Goal 3. Lancet. 2020;6736: 1–32. doi:10.1016/S0140-6736(20)30608-5

96. Fauci AS, Eisinger RW. PEPFAR — 15 Years and Counting the Lives Saved. N Engl J Med. 2018;378: 314–316. doi:10.1056/nejmp1715127

97. Taylor K, DeYoung P. WHO's 3-by-5 target. Lancet. 2003;362: 918.

98. Rabkin M, Melaku Z, Bruce K, Reja A, Koler A, Tadesse Y, *et al.* Strengthening health systems for chronic care: leveraging HIV programs to support diabetes services in Ethiopia and Swaziland. J Trop Med. 2012;2012.

99. Atun R, Bataringaya J. Building a durable response to HIV/AIDS: Implications for health systems. J Acquir Immune Defic Syndr. 2011;57: 91–95. doi:10.1097/QAI.0b013e3182218441

100. El-Sadr WM, Holmes CB, Mugyenyi P, Thirumurthy H, Ellerbrock T, Ferris R, *et al.* Scale-up of HIV treatment through PEPFAR: a historic public health achievement. J Acquir Immune Defic Syndr. 2012;60: S96.

101. Joint United Nations Programme on HIV/AIDS (UNAIDS). Global Report: UNAIDS Report on the Global AIDS Epidemic 2010. Geneva, Switzerland; 2010.

102. World Health Organization (WHO). Progress on Global Access to HIV Antiretroviral Therapy An update on "3 by 5." Geneva, Switzerland; 2005. Available: https://www.who.int/3by5/fullreportJune2005.pdf?ua=1

103. UNAIDS. Confronting inequalities: Lessons for pandemic responses from 40 years of AIDS. Geneva; 2021. Available: https://www.unAIDS.org/sites/default/files/media_asset/2021-global-AIDS-update_en.pdf

104. Granich R, Gupta S, Hersh B, Williams B, Montaner J, Young B, *et al.* Trends in AIDS deaths, new infections and ART coverage in the top 30 countries with the highest AIDS mortality burden; 1990--2013. PLOS ONE. 2015;10: e0131353.

105. Tanser F, Vandormael A, Cuadros D, Phillips AN, De Oliveira T, Tomita A, *et al.* Effect of population viral load on prospective HIV incidence in a hyperendemic rural African community. Sci Transl Med. 2017;9: 1–11. doi:10.1126/scitranslmed.aam8012

106. Tanser F, Bärnighausen T, Graspa E, Zaidi J, Newell ML. High Coverage of ART Associated with Decline in Risk of HIV Acquisition in Rural KwaZulu-Natal, South Africa. Science. 2013;339: 966–972. doi:10.1177/1045389X05047210

107. Insight Start Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;373: 795–807.

108. World Health Organization (WHO). Rapid advice: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants, version 2. World Health Organization; 2009.

109. World Health Organization (WHO). Clinical Guidelines: Antiretroviral Therapy. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2013. p. 129. Available: http://www.who.int/hiv/pub/arv/chapter4.pdf?ua=1

110. Babiker AG, Emery S, Fätkenheuer G, Gordin FM, Grund B, Lundgren JD, *et al.* Considerations in the rationale, design and methods of the Strategic Timing of AntiRetroviral Treatment (START) study. Clin Trials. 2013;10: S5–S36.

111. World Health Organization (WHO). Progress report 2016: prevent HIV, test and treat all: WHO support for country impact. 2016.

112. United Nations. Political Declaration on HIV and AIDS: On the Fast-Track to Accelerate the Fight against HIV and to End the AIDS Epidemic by 2030. New York; 2016. doi:10.1093/oxfordhb/9780199560103.003.0005

113. World Health Organization (WHO). Global health sector strategy on HIV 2016-2021. Towards ending AIDS. Geneva, Switzerland; 2016. Available: https://apps.who.int/iris/bitstream/handle/10665/246178/WHO?sequence=1

114. Joint United Nations Programme on HIV/AIDS (UNAIDS). 90-90-90: An ambitious treatment target to help end the AIDS epidemic. Geneva; 2014. Available: https://www.unAIDS.org/sites/default/files/media_asset/90-90-90_en.pdf

115. Cuadros DF, Li J, Mukandavire Z, Musuka GN, Branscum AJ, Sartorius B, *et al.* Towards UNAIDS Fast-Track goals: targeting priority geographic areas for HIV prevention and care in Zimbabwe. AIDS. 2019;33: 305–314. doi:10.1097/QAD.0000000000002052

116. United Nations. Political Declaration on HIV and AIDS: Ending Inequalities and Getting on Track To End AIDS By 2030 United Nations General Assembly. Geneva, Switzerland; 2021. Available: https://www.unAIDS.org/sites/default/files/media_as-

set/2021_political-declaration-on-hiv-and-AIDS_en.pdf

117. Joint United Nations Programme on HIV/AIDS (UNAIDS). Fast-Track - Ending the AIDS epidemic by 2030. Geneva; 2014. Available: https://www.unAIDS.org/sites/default/files/media_asset/JC2686_WAD-2014report_en.pdf

118. Marukutira T, Stoovée M, Lockman S, Mills LA, Gaolathe T, Lebelonyane R, *et al.* A tale of two countries: Progress towards UNAIDS 90-90-90 targets in Botswana and Australia. J Int AIDS Soc. 2018;21: 1–6. doi:10.1002/jia2.25090

119. Maheu-Giroux M, Marsh K, Doyle CM, Godin A, Delaunay CL, Johnson LF, *et al.* National HIV testing and diagnosis coverage in sub-Saharan Africa: a new modeling tool for estimating the 'first 90' from program and survey data. AIDS. 2019;33: S255.

120. Floyd S, Shanaube K, Yang B, Schaap A, Griffith S, Phiri M, *et al.* HIV testing and treatment coverage achieved after 4 years across 14 urban and peri-urban communities in Zambia and South Africa: An analysis of findings from the HPTN 071 (PopART) trial. PLOS Med. 2020;17: e1003067.

121. Marsh K, Eaton JW, Mahy M, Sabin K, Autenrieth CS, Wanyeki I, *et al.* Global, regional and country-level 90--90--90 estimates for 2018: assessing progress towards the 2020 target. AIDS. 2019;33: S213.

122. Hardy WD. Fundamentals of HIV Medicine 2021: CME Edition. Oxford University Press; 2021.

123. WHO. Chapter 6: Service Delivery (Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection). World Health Organisation (WHO). 2015. pp. 238–294.

124. Sabapathy K, den Bergh R, Fidler S, Hayes R, Ford N. Uptake of home-based voluntary HIV testing in sub-Saharan Africa: a systematic review and meta-analysis. PLOS Med. 2012;9: e1001351.

125. Fylkesnes K, Sandøy IF, Jürgensen M, Chipimo PJ, Mwangala S, Michelo C. Strong effects of home-based voluntary HIV counselling and testing on acceptance and equity: a cluster randomised trial in Zambia. Soc Sci \& Med. 2013;86: 9–16.

126. Medley A, Ackers M, Amolloh M, Owuor P, Muttai H, Audi B, *et al.* Early uptake of HIV clinical care after testing HIV-positive during home-based testing and counseling in western Kenya. AIDS Behav. 2013;17: 224–234.

127. Suthar AB, Hoos D, Beqiri A, Lorenz-Dehne K, McClure C, Duncombe C. Integrating antiretroviral therapy into antenatal care and maternal and child health settings: a systematic review and meta-analysis. Bull World Health Organ. 2013;91: 46–56.

128. Lindegren M Lou, Kennedy CE, Bain-Brickley D, Azman H, Creanga AA, Butler LM, *et al.* Integration of HIV/AIDS services with maternal, neonatal and child health, nutrition, and family planning services. Cochrane Database Syst Rev. 2012.

129. Uyei J, Coetzee D, Macinko J, Guttmacher S. Integrated delivery of HIV and tuberculosis services in sub-Saharan Africa: A systematic review. Lancet Infect Dis. 2011;11: 855–867. doi:10.1016/s1473-3099(11)70145-1

130. Howard AA, El-Sadr WM. Integration of Tuberculosis and HIV Services in Sub-Saharan Africa: Lessons Learned. Clin Infect Dis. 2010;50: S238–S244. doi:10.1086/651497

131. Dudley L, Garner P. Strategies for integrating primary health services in low- and middle-income countries at the point of delivery. Cochrane Database Syst Rev.

2011;6: CD003318. doi:10.1002/14651858.CD003318.pub3

132. Fortenberry JD, Koenig LJ, Kapogiannis BG, Jeffries CL, Ellen JM, Wilson CM. Implementation of an integrated approach to the national HIV/AIDS strategy for improving human immunodeficiency virus care for youths. JAMA Pediatr. 2017;171: 687–693.

133. Duncombe C, Rosenblum S, Hellmann N, Holmes C, Wilkinson L, Biot M, *et al.* Reframing HIV care: putting people at the centre of antiretroviral delivery. Trop Med \& Int Heal. 2015;20: 430–447.

134. Phillips A, Shroufi A, Vojnov L, Cohn J, Roberts T, Ellman T, *et al.* Sustainable HIV treatment in Africa through viral load-informed differentiated care. Nature. 2015;528: S68.

135. Grimsrud A, Bygrave H, Doherty M, Ehrenkranz P, Ellman T, Ferris R, *et al.* Reimagining HIV service delivery: the role of differentiated care from prevention to suppression. J Int AIDS Soc. 2016;19: 21484.

136. Barker C, Dutta A, Klein K. Can differentiated care models solve the crisis in HIV treatment financing? Analysis of prospects for 38 countries in sub-Saharan Africa. J Int AIDS Soc. 2017;20: 21648. doi:10.7448/IAS.20.5.21648

137. United Nations Joint Programme on HIV/AIDS (UNAIDS). Update: HIV financing gap widening. Jul 2020. Available: https://www.unAIDS.org/en/resources/presscentre/featurestories/2020/november/20201116_hiv-financing-gap-widening

138. Atun R, Silva S, Knaul FM. Innovative financing instruments for global health 2002–15: a systematic analysis. Lancet Glob Heal. 2017;5: e720–e726. doi:10.1016/S2214-109X(17)30198-5

139. U.S. Department of State, Office of the U.S. Global AIDS Coordinator and Health Diplomacy. The United States President's Emergency Plan for AIDS Relief: 2019 Annual Report to Congress. Washington; 2019. Available: https://www.state.gov/wp-content/uploads/2019/09/PEPFAR-2019ARC.pdf

140. Dieleman JL, Haakenstad A, Micah A, Moses M, Abbafati C, Acharya P, *et al.* Spending on health and HIV/AIDS: domestic health spending and development assistance in 188 countries, 1995–2015. Lancet. 2018;391: 1799–1829. doi:10.1016/S0140-6736(18)30698-6

141. Glied S, Wagner RF, Service P, Levy H, Robert F. The Potential Effects of Coronavirus on National Health Expenditures. JAMA. 2020;10012: 19–20. doi:10.1001/jama.2020.6644

142. Lancet T. Maintaining the HIV response in a world shaped by COVID-19. Lancet (London, England). 2020;396: 1703.

143. Jewell BL, Mudimu E, Stover J, ten Brink D, Phillips AN, Smith JA, *et al.* Potential effects of disruption to HIV programmes in sub-Saharan Africa caused by COVID-19: results from multiple mathematical models. Lancet HIV. 2020;7: e629–e640. doi:10.1016/S2352-3018(20)30211-3

144. UHC2030 Initiative. UHC2030 launches "Key Asks from the UHC Movement" for the UN High-Level Meeting on Universal Health Coverage. 2019. Available: https://www.uhc2030.org/blog-news-events/uhc2030-news/uhc2030-launches-key-asks-from-the-uhc-movement-for-the-un-high-level-meeting-on-universal-health-coverage-544846/

145. Safreed-Harmon K, Anderson J, Azzopardi-Muscat N, Behrens GMN, Monforte A d'Arminio, Davidovich U, *et al.* Reorienting health systems to care for people with HIV beyond viral suppression. Lancet HIV. 2019;6: e869--e877.

146. World Health Organization (WHO). Integrated Health Services - What and Why? Making health systems work series. Geneva; 2008. Available: https://www.who.int/healthsystems/technical_brief_final.pdf

147. Atun R, De Jongh T, Secci F, Ohiri K, Adeyi O. Integration of targeted health interventions into health systems: A conceptual framework for analysis. Health Policy Plan. 2010;25: 104–111. doi:10.1093/heapol/czp055

Chapter 2

Mapping and characterising areas with high levels of HIV transmission in sub-Saharan Africa: A geospatial analysis of national survey data

Caroline A. Bulstra[‡], Jan A.C. Hontelez[‡], Federica Giardina, Richard Steen, Nico J.D. Nagelkerke, Till Bärnighausen, Sake J. de Vlas

[‡] *Shared first co-authorship*

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ABSTRACT

Background: In the generalised epidemics of sub-Saharan Africa, human immunodeficiency virus (HIV) prevalence shows patterns of clustered micro-epidemics. We mapped and characterised these high-prevalence areas for young adults (15–29 years of age), as a proxy for areas with high levels of transmission, for 7 countries in Eastern and Southern Africa: Kenya, Malawi, Mozambique, Tanzania, Uganda, Zambia, and Zimbabwe.

Methods and findings: We used geolocated survey data from the most recent United States Agency for International Development (USAID) Demographic and Health Surveys (DHSs) and AIDS indicator surveys (AISs) (collected between 2008–2009 and 2015–2016), which included about 113,000 adults—of which there were about 53,000 young adults (27,000 women, 28,000 men)—from over 3,500 sample locations. First, ordinary kriging was applied to predict HIV prevalence at unmeasured locations. Second, we explored to what extent behavioural, socioeconomic, and environmental factors explain HIV prevalence at the individual- and sample-location level, by developing a series of multilevel multivariable logistic regression models and geospatially visualising unexplained model heterogeneity. National-level HIV prevalence for young adults ranged from 2.2% in Tanzania to 7.7% in Mozambique. However, at the subnational level, we found areas with prevalence among young adults as high as 11% or 15% alternating with areas with prevalence between 0% and 2%, suggesting the existence of areas with high levels of transmission. Overall, 15.6% of heterogeneity could be explained by an interplay of known behavioural, socioeconomic, and environmental factors. Maps of the interpolated random effect estimates show that environmental variables, representing indicators of economic activity, were most powerful in explaining high-prevalence areas. Main study limitations were the inability to infer causality due to the cross-sectional nature of the surveys and the likely under-sampling of key populations in the surveys.

Conclusions: We found that, among young adults, micro-epidemics of relatively high HIV prevalence alternate with areas of very low prevalence, clearly illustrating the existence of areas with high levels of transmission. These areas are partially characterised by high economic activity, relatively high socioeconomic status, and risky sexual behaviour. Localised HIV prevention interventions specifically tailored to the populations at risk will be essential to curb transmission. More fine-scale geospatial mapping of key populations—such as sex workers and migrant populations—could help us further understand the drivers of these areas with high levels of transmission and help us determine how they fuel the generalised epidemics in sub-Saharan Africa.

AUTHOR SUMMARY

Why was this study done?

- Previous studies showed that heterogeneity in HIV prevalence exists among the general population in Eastern and Southern Africa; the geographic area most severely affected by the HIV pandemic.
- Whereas HIV prevalence among adults does not reveal when persons have been infected, young adults are most likely recently infected and, therefore, high prevalence areas among this subpopulation can proxy locations of ongoing transmission.
- The underlying determinants of these high HIV prevalence areas among young adults are poorly understood and can help to shape spatially targeted and risk-group tailored interventions to reduce transmission.

What did the researchers do and find?

- We found clear areas of high prevalence in young adults in between vast regions with relatively low prevalence for all seven countries in Eastern and Southern Africa.
- HIV prevalence in young adults was partly explained by an interplay of behavioural, socioeconomic and environmental (*i.e.*, economic activity) factors, and especially environmental factors were predictive of high transmission locations.

What do these finding mean?

- Our findings, together with the existing evidence, indicate that key population dynamics, especially related to seasonal and economic migration and associated sex work, might play a major role in fuelling HIV transmission.
- In further reducing HIV transmission in Eastern and Southern Africa, areas of high HIV prevalence in young adults should be priority areas for tailored HIV prevention interventions towards reaching the fast-track commitments to end the HIV epidemic by 2030.

INTRODUCTION

Sustainable Development Goal (SDG) 3 "to ensure healthy lives and promote well-being for all at all ages" [1], together with the Joint United Nations Programme on HIV/AIDS (UNAIDS) fast-track strategy, explicitly call to end the pandemic by 2030 [2]. In 2017, about 37 million people were living with human immunodeficiency virus (HIV) worldwide, of whom 70% residing in sub-Saharan Africa [3]. Especially the countries in Eastern and Southern Africa are severely affected by the pandemic, with general population prevalences ranging from 5% in Tanzania to 27% in Swaziland [3]. Mounting evidence suggests that these HIV epidemics are heterogeneous [4,5], and that the transmission of HIV is largely concentrated across clustered micro-epidemics of different scales [6,7]. As these high prevalence areas are likely important drivers of the epidemic [8,9], identifying their location and underlying determinants is essential to further optimise HIV prevention and treatment interventions.

Although mapping overall HIV prevalence in the adult population gives an adequate indication of treatment service needs [4,5], it is not straightforward to use such data to inform policy makers on areas with high levels of transmission, as many, especially older, adults were infected many years prior to any survey, and possibly at other locations. Mapping heterogeneity of HIV prevalence in young adults, who are most likely to have been recently infected, will more directly pinpoint areas of high HIV transmission [10]. Furthermore, identifying underlying determinants of heterogeneity in HIV prevalence among young adults in the high endemic countries can help shape spatially targeted and risk-group tailored interventions to reduce transmission.

We identified areas of high HIV prevalence in young adults (women 15-24 years and men 15-29 years) for seven countries in Eastern and Southern Africa (Kenya, Malawi, Mozambique, Tanzania, Uganda, Zambia, and Zimbabwe), using geolocated HIV prevalence data from Demographic and Health Surveys (DHSs) and AIDS Indicator Surveys (AISs). Next, we explored to what extent sexual behavioural, socioeconomic and environmental factors explain the geospatial heterogeneity in young adults, and what heterogeneity remains unexplained.

METHODS

Data

DHS is a programme of national, population-level surveys in which individuals are interviewed about- and tested for a wide range of behavioural, socioeconomic and epidemiological parameters. The AIS and many DHS surveys include voluntary HIV testing in adults. Approximately 350 sample locations (primary sampling units) are randomly sampled throughout the

country of interest, and at each location residents of about 25 households are sampled. All individuals that were at home during one of the visits and were between 15 and 49 (women) or 54 years of age (men) were eligible for the survey. GPS coordinates of sample locations are randomly displaced up to 2 km for urban and up to 5 km for rural sample locations, to ensure confidentiality of participants. Sample weights are incorporated in the DHS to translate unbalanced sampling into national representative data. In our study, we used these sample weights to estimate national HIV prevalence among adults and young adults for all seven countries. For the other analyses, we combined data of multiple countries and explored local level variances, and thus did not use the sampling weights. More details on survey protocols and questionnaires can be found on the DHS website (https://dhsprogram.com/).

We extracted data from countries in Eastern and Southern African that had a DHS or AIS conducted and for which behavioural data, geographical coordinates of the sample locations, and HIV biomarker surveys were available. In case of multiple eligible surveys for a country, we selected the most recent one. The countries and surveys chosen for this study were: Kenya (years 2008-2009), Malawi (2015-2016), Mozambique (2009), Tanzania (2011-2012), Uganda (2011), Zambia (2013-2014), and Zimbabwe (2015). The overall study area with DHS sample locations for each country included in the study are shown in **Supplementary Figure 1**. We selected all adults (women 15-49 years and men 15-54 years) and sub selected young adults (women 15-24 years and men 15-29 years). The discrepancy in age cut-off reflects the common age-difference in sexual debut and relationships between women and men [11].

A typical DHS survey dataset contains over 250 variables. For the purpose or our study, we only extracted individual-level candidate variables that were deemed of interest, based on findings from previous studies_[4,6,8,12–15]: age, sex, HIV status, educational level, wealth index, primary occupation, whether the person is a *de jure* household member (usual resident) or *de facto* household member (slept in the household last night) as proxy for mobility, number of lifetime sexual partners, number of sexual partners during the past 12 months, having had a sexually transmitted infection (STI) or signs of an STI during the past 12 months, condom use during last intercourse, male circumcision and paid sexual intercourse during the past 12 months (only men). HIV status is determined by testing a blood sample from a finger prick with an enzyme-linked immunosorbent assay (ELISA). The other variables were self-reported by participants via the survey questionnaires.

We used the following environmental variables at sample locations: urban versus rural classification, population density, proximity to highways, proximity to (major) cities with more than 250 000 inhabitants, proximity to border crossings and major ports, enhanced

vegetation index (EVI) and global human footprint (GHF). EVI reflects the vegetation in an area, where low values represent areas with no or little green vegetation (*e.g.* big cities) and high values represent areas where vegetation is more abundant (*e.g.* agricultural land, forests, grassland), and can be used as proxy for degree of urbanisation [4]. GHF represents the relative human influence and economic activity, incorporating nine layers covering infrastructure, land use, population density, and access (coastlines, roads, railroads, navigable rivers). Areas of large human influence and high levels of economic activity are characterised by high GHF values. Population density estimates were originally obtained from WorldPop (https://www.worldpop.org/), data from 2010, the most recent year, were utilised. EVI and GHF were available from National Aeronautics and Space Administration (NASA) Earth Observatory Group (http://sedac.ciesin.columbia.edu/). EVI data were available for 2010 and GHF for 2005. Because DHS sample locations are to some extent randomly displaced, the DHS programme has made population density, EVI, and GHF available at each un-displaced DHS sample location. Locations of major cities were extracted from the World Population Review website (www.worldpopulationreview.com/worldcities/), and highways were derived from GADM national infrastructure shape files (http://www.gadm.org/) based on Google Maps. Locations of border crossings and major ports were obtained through the Southern Africa Integrated Regional Transport Programme report (2010) [16]. The shortest Euclidean distances from each DHS sample location to the nearest highway, major city and border crossing or port were calculated. An overview and description of all included variables can be found in the supplementary information (**Supplementary Table 2**). Maps of the included environmental variables are provided in **Supplementary Figure 2A to 2G**.

Statistical analyses

Our study was explorative in nature, and we did not have a formal pre-specified analysis plan. First, we determined the spatial distribution in HIV prevalence among adults and young adults by interpolating logit-transformed DHS sample location-level HIV prevalence data using ordinary kriging [17]. Kriging is an interpolation method based on the spatial autocorrelation of variables [18]. Spatial autocorrelation was measured by means of Moran's *I*, using the inverse distance between sample locations as weights. Spatial autocorrelation structures were obtained through fitting semivariograms, where the average squared difference in HIV prevalence between each pair of data points (on the y-axis) is plotted against the corresponding distance between the point-pairs (on the x-axis). The overall relation between HIV prevalence and distance was estimated by fitting an exponential curve through these points. We used this model to create continuous surface maps of HIV prevalence, where the HIV prevalence at each five km^2 grid cell was estimated using the above method. The equations and model estimates are provided in the supplementary information (**Supplementary Equations 1**). To enhance the power of our study, we decided to not stratify the kriging by sex in the main analysis. However, we also present sex-specific

maps of kriged HIV prevalence (**Supplementary Figure 5**). We compared the sex-specific surfaces of HIV prevalence by means of mapping the square root of the squared difference in HIV prevalence, to illustrate the absolute differences in HIV prevalence (per 5 km2 grid cell) (**Supplementary Figure 6A**), and by plotting the predicted HIV prevalence (per 5 km grid cell) of women against the predicted HIV prevalence of men (**Supplementary Figure 6C**). Both comparisons show that there are only minor differences in terms of the locations of high HIV prevalence for both sexes.

Second, we developed a series of multiple multilevel logistic regression models to determine to what extent behavioural, socioeconomic and environmental determinants of HIV can explain individual and location-level HIV prevalence among young adults. Missing values (up to 2.6%) were checked to be missing at random and, if so, imputed using multiple imputation. First, bivariate associations were tested, and excluded all variables with a p-value of larger than 0.1. We then developed multiple models using a stepwise approach. In the first step, we fitted an 'empty' model, with HIV prevalence as the dependent variable and only age and sex fixed-effects, and location random effects as predictors. In the second step, we used stepwise forward selection to construct three separate multiple regression models for behavioural, socioeconomic and environmental factors respectively, out of the nested model. Likelihood tests were used to determine whether the addition of a variable improved the statistical fit of the regression models significantly ($p<0.05$). In the third step, we used the same stepwise forward selection to construct a full model containing both behavioural, socioeconomic and environmental factors. We did not adjust for country-level confounding in the main analysis, because we expect the associations between HIV and the predictor variables to be similar across countries. However, we did perform a sensitivity analysis in which we added country fixed-effects to the final model. We compared the marginal and conditional R^2 of the models at each step. The marginal R^2 indicates how much of the HIV heterogeneity is explained by the fixed factors in the model. The conditional R^2 represents the amount of heterogeneity explained by both fixed and random factors in the model. By comparing both R^2 values, we assessed how much of HIV heterogeneity is explained by the fixed factors in the models, and how much is additionally captured by the location-level random effect in each model [19]. We translated variance of random effects into Median Odds Ratios (MORs) as an indicator geographical heterogeneity. For each model, the MOR would be equal to 1.0 if there were no differences in probability to being HIV infected per sample location, and can be interpreted as the increase in (median) HIV risk that is associated with moving from a location with a low random effect to a location with a high random effect. See elsewhere for a more detailed explanation [20]. The MOR equation is provided in the supplementary information (**Supplementary Equations 1**). The final model is also fitted as modified Poisson (with robust variance) for easier interpretation of the estimates, here as relative risks (RRs) instead of odds ratios (ORs).

Third, we extracted and compared the location-specific random effect estimates from the empty model, the three separate models for behavioural, socioeconomic and environmental factors, and the 'full' regression model. We kriged random effect estimates from the five models to visualise to what extent the variables in the different models explain the geospatial HIV heterogeneity and areas with a high HIV prevalence.

Next to the main analyses, we performed an internal validation of our regression models and an external validation of our kriging results. The internal validation was done using non-random cross-validation [21,22] to check for each country individually how much heterogeneity (indicated by the conditional R^2) was explained by the final regression model. For the external validation, we searched peer-reviewed literature reporting on age-stratified HIV prevalence estimates in population-based cohorts, such as those part of the ALPHA network [23], situated in one of the countries of our study. We compared our predicted HIV prevalence among young adults, obtained through kriging, with the estimates from these cohorts.

All analyses were done using in ArcGIS Pro version 2.3 and R version 3.4.3. Reporting of study design and analysis followed STROBE RECORD guidelines [24].

RESULTS

Our study included 112,785 adults, of which 53,234 young adults (25,536 women, 27,698 men), from 3,665 different sample locations throughout the seven countries. The number of individuals included in the study and location-level HIV prevalence in the study population for adults and young adults are provided in **Figure 1**. Among adults, the mean country-level HIV prevalence ranges from 5.4% (Tanzania) to 14.4% (Zimbabwe). Among young adults, mean country-level HIV prevalences are generally lower, ranging from 2.2% (Tanzania) to 7.7% (Mozambique), while the median HIV prevalences are (close to) zero. This reflects the fact that most sample locations have very low HIV prevalence, and only a minority of sample locations has high prevalence. HIV prevalence among adults and young adults is strongly spatially clustered (p-value <0.001), the observed Moran's *I* index values were 0.13 and 0.05 respectively (on a scale going from -1, fully scattered, to 1, fully clustered). A detailed overview of the Moran's *I* and (logit-transformed) HIV prevalence density plots can be found in the supplementary information (**Supplementary Table 2 and Supplementary Figures 3 and 4**).

Figure 2 shows the geospatial distribution of HIV prevalence in adults (panel A) and young adults (panel B) in seven countries of Eastern and Southern Africa. All countries showed substantial levels of heterogeneity in HIV prevalence at the subnational level. Overall, HIV prevalence is higher among adults, with high prevalence areas being in the same locations,

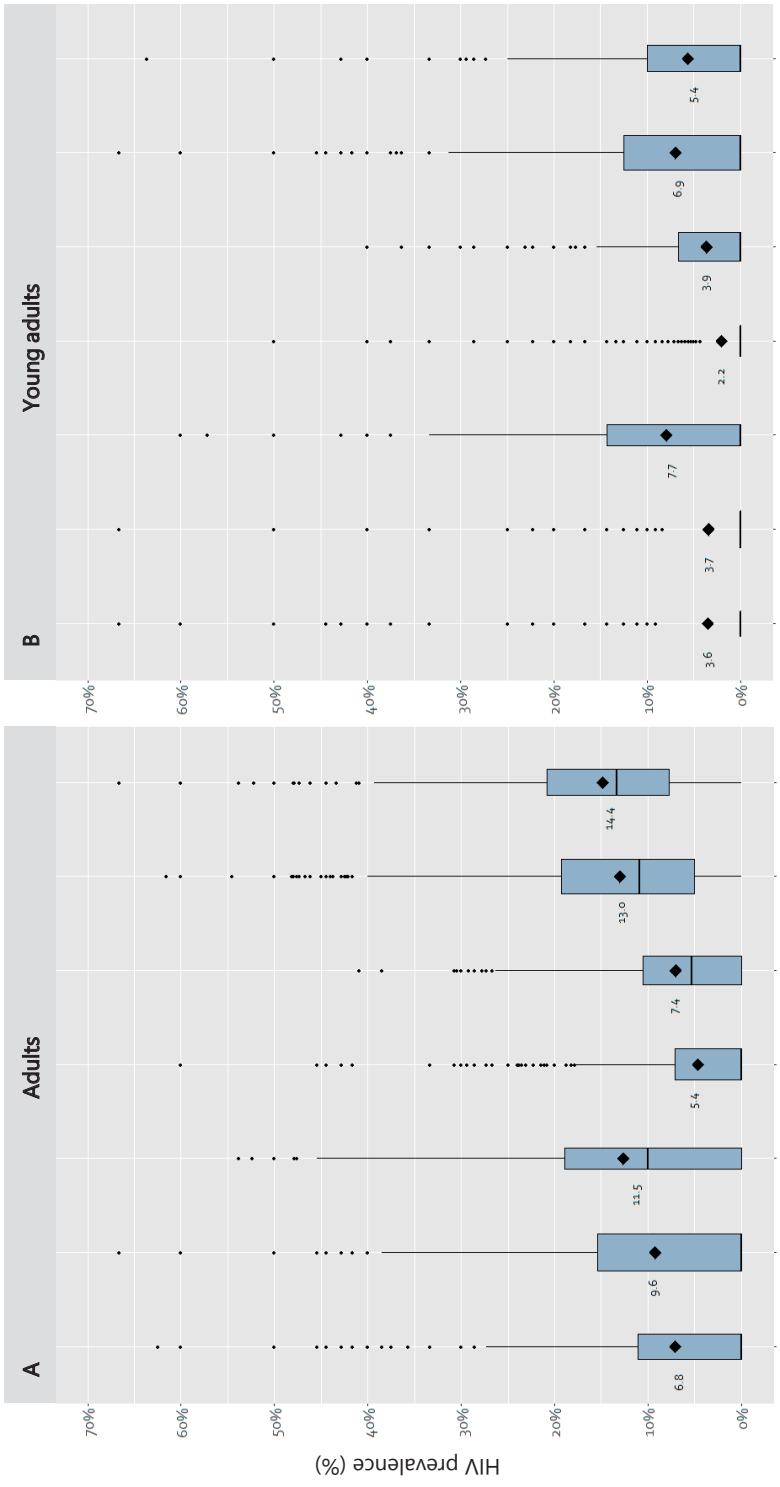

Figure 1. Median, mean and DHS sample location variance in national HIV prevalence estimates among adults (A) and young adults (B) for each country included in this study. The mean, presented in the labels left of the bars, represents the weighted HIV prevalence per country. Data obtained through https://dhsprogram.com/.

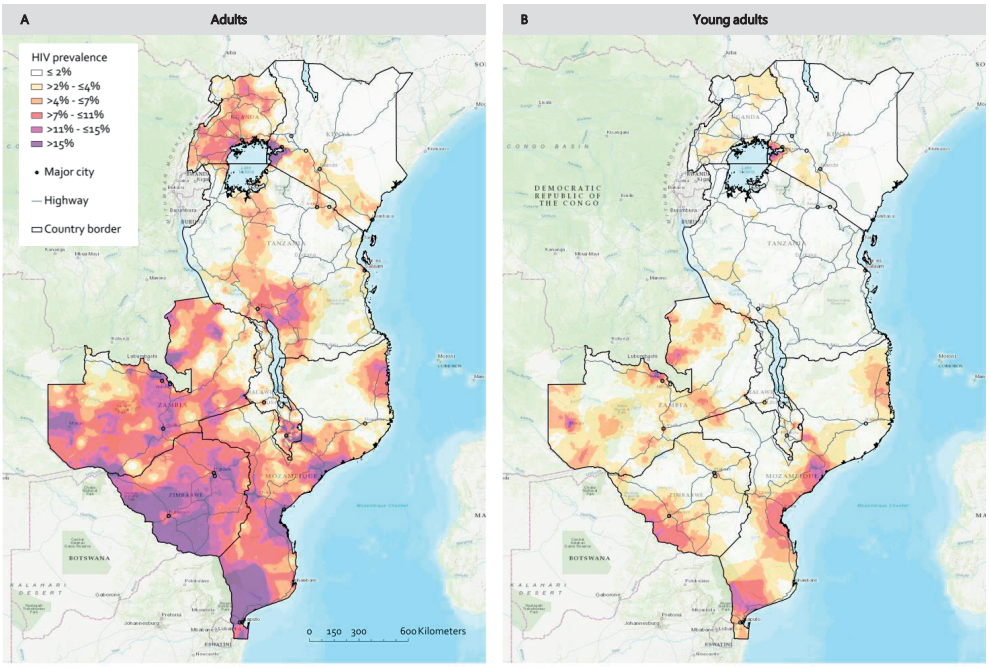

Figure 2. Continuous surface maps of HIV prevalence in adults (women 15-49 years and men 15-54 years) (A) and young adults (women 15-24 years and men 15-29 years) (B) for seven countries in Eastern and Southern Africa. Predicted geographical distribution of HIV prevalence resulted from interpolating data on HIV prevalence in geolocated sample locations derived from the most recent DHS or AIS in each country - using ordinary kriging. Major cities (more than 250 000 inhabitants) were indicated on the maps. To enhance comparison between both panels, we applied the same legend for HIV prevalence levels. The HIV prevalence maps for women and men separately are provided in the supplementary information (**Supplementary Figure 4**). Data obtained through https://dhsprogram.com/.

but larger and more spread out compared to young adults (illustrated by the large red and purple areas). Geospatial heterogeneity in HIV prevalence among young adults was more profound than among adults in most of the countries in our analysis, illustrated by clear concentrated micro-epidemics (red and purple areas) located in between areas of very low prevalence (white, yellow and orange areas). In both Zambia and Zimbabwe, high prevalence areas of over 15% HIV prevalence in young adults were found. The national HIV prevalence among young adults in Malawi is about 3.6%, yet our analysis identified several high prevalence areas where HIV prevalence reached levels of up to 11%, in particular around the highways and major cities in the South. Similarly, in Kenya HIV prevalence in young adults is about 3.9% nationally, yet prevalence around Lake Victoria reach levels of over 15%. Maps and scatterplots illustrating the more detailed differences in HIV prevalence (per 5 km^2 grid cell) between adults and young adults are provided in **Supplementary Figure 6**.

According to the resulting best fitting multiple multilevel logistic regression model on the association between HIV status and sexual behavioural variables in young adults, the

following variables were strongly associated with being infected with HIV: having 10 or more reported lifetime sex partners, having had an STI or STI symptoms over the past 12 months, condom use during last intercourse, and not being circumcised (men only). Educational level, wealth index and occupation were variables associated with HIV in the final socioeconomic model. The highest level of education was most protective (adjusted Odds Ratio {aOR} 0.52 [0.26; 0.78], p-value <0.001), while being from asset quintile 4, the second wealthiest quintile, was associated with the highest risk of HIV (aOR 1.46 [1.31; 1.62], p-value <0.001). Several variables were significantly associated with HIV in the environmental model. Young adults living in rural sample locations were less likely to be infected with HIV than those with urban residence: in cities the overall HIV prevalence among adults was over 7%, compared to below 4% in rural settings. Also, population density, proximity to nearest major city, EVI and GHF at location of a DHS cluster showed a significant association with HIV. HIV prevalence levels were highest (about 6%) in areas with the highest population density (more than 500 people per km2), but was also relatively high (about 5%) in areas with the lowest population density (less than 25 people per km2). HIV prevalence levels did not differ considerably between sample locations with different levels of greenness (indicated by the EVI). Living in an area with a relatively high GHF, as proxy for economic activity, was associated with a high HIV risk (aOR 1.68 [1.41; 1.94], p-value <0.001): HIV prevalence levels for the highest two levels of GHF were almost 7%, compared to around 4% at the lower levels. The best fitting combined 'full' model contains both behavioural, socioeconomic, and environmental variables: lifetime number of sex partners, STIs, male circumcision, education, type of residence, EVI, and GHF. A complete overview of the bivariate models, nested model (only adjusted for age and sex), best fitting models and final model can be found in the supplementary information (**Supplementary Tables 3 to 8** and **Supplementary Figure 7**). Finally, the combined 'full' model was also fitted as a modified Poisson regression model, resulting in adjusted relative risks (aRRs) that were comparable to the respective aORs from the logistic regression model (**Supplementary Table 9**).

The maps in **Figure 3** show the interpolated random effects estimates – *i.e.* the unexplained heterogeneity in HIV prevalence – for the five models. The white areas represent locations where relatively most heterogeneity is explained by the model. The red and purple areas represent locations where relatively the least heterogeneity is explained. As expected, random effect estimates in the nested model were highest in high prevalence areas (panel A), and decline as fixed-effects are added to the models (panels B to E). Interpolated random effects estimates from the combined model (panel B) are substantially reduced. However, the geospatial heterogeneity in many areas with a high prevalence remains unexplained, for example, around Lake Victoria (1), at the major ports of Mozambique (2-4), at Plumtree (5), around Mongu (6) and the Copperbelt (7) and Nchelenge (8) districts in Zambia. In most of

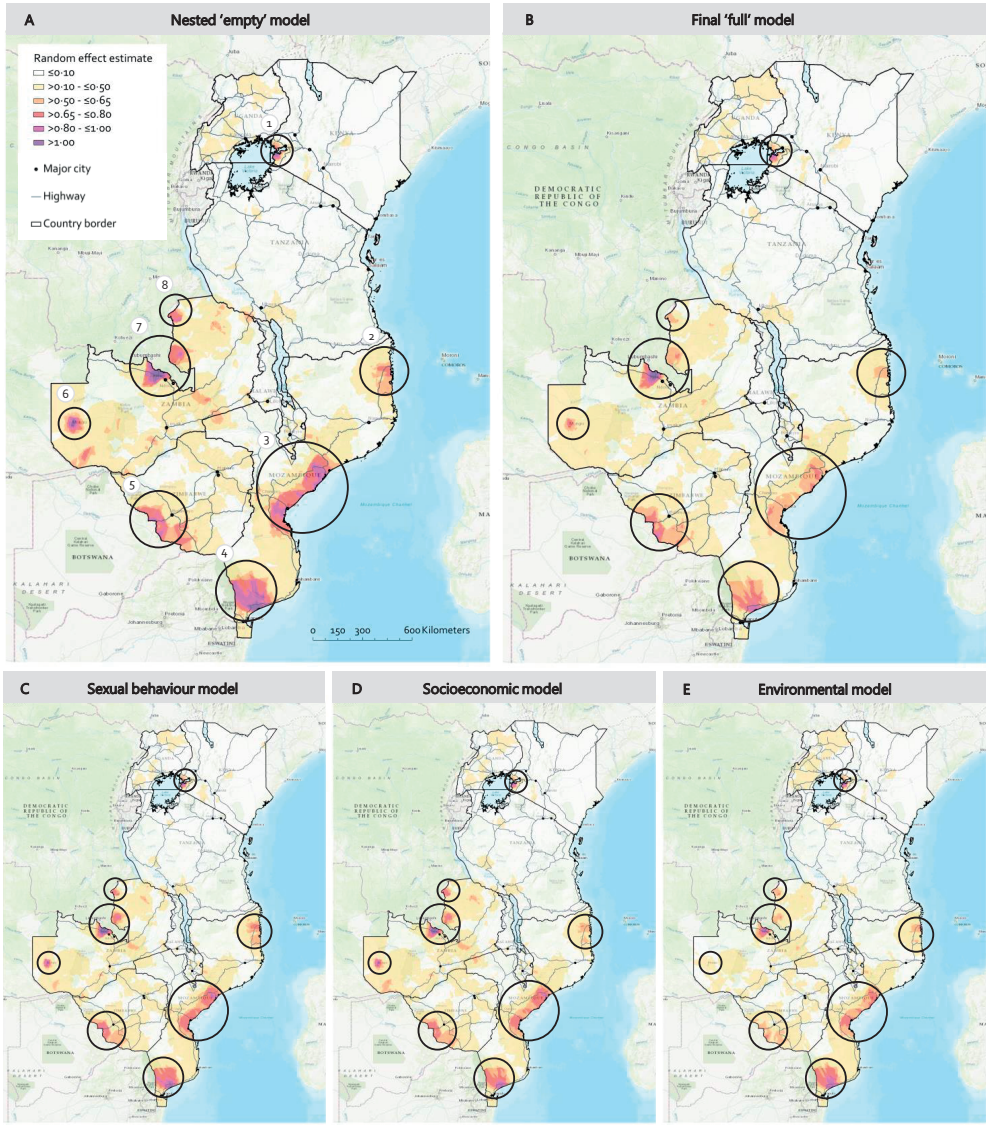

Figure 3. Maps present the interpolated random effect estimates of the nested 'empty' logistic regression model (A), best fitting logistic regression model (B), and the separate models including only sexual behavioural (C), socioeconomic (D) and environmental variables (E) among young adults (women 15-24 years and men 15-29 years) for seven countries in Eastern and Southern Africa. For the nested 'empty' model (A), random effect estimates reflect HIV prevalence levels among young adults (see **Figure 2B**). For the other models (B to E), random effect estimates are lower at (some of the) areas with high HIV prevalence levels, indicating that the additional variables in each model to some extent explain HIV heterogeneity at these locations. Circles point out high prevalence areas of HIV among young adults: around Lake Victoria (1); around Nacala (and Pemba) port (2); around Beira (and Quelimane) port (3); around Maputo city and port (4); around Plumtree border crossing (5); around Mongu city (6); in the Copperbelt mining area (7); and in Nchelenge district (8).

these locations, environmental variables were better at explaining heterogeneity (panel E) than sexual behavioural or socioeconomic variables (panels C and D respectively).

The results in **Table 1** show that, looking at the nested 'empty' model, 7.2% (marginal R^2) of the 26.3% (conditional R^2) of the HIV heterogeneity could be explained by age and sex alone. The remaining variance captured by the model (19.1%) is attributed to location-level random effects. Environmental fixed-effects explain most of the heterogeneity in HIV prevalence among young adults (marginal R^2 11.4%, conditional R^2 26.8%), higher than sexual behavioural (marginal R^2 10.2%, conditional R^2 27.8%) or socioeconomic (marginal R^2 8.6%, conditional R^2 25.8%) fixed-effects. According to the R^2 of the combined 'full' best fitting model, HIV heterogeneity could be best explained (marginal R^2 15.6%, conditional R^2 29.6%) by an interplay of sexual behavioural, socioeconomic and environmental variables. The MOR of the nested model is 2.41, whereas the MOR of the final model is 1.94. This illustrates that, although some of the location-level heterogeneity is captured by the model fixed-effect covariates, almost two-thirds of the heterogeneity in HIV prevalence at sample locations could still not be explained by the covariates in the model. Overall, environmental fixed-effects reduce the location-level heterogeneity more than sexual behavioural and socioeconomic fixed-effects (MORs of 1.95, 2.35, and 2.30 respectively). Adjusting for country improves the model fit, but does not change the importance of the different predictors and does not considerably increase the degree of explained heterogeneity (marginal R^2 17.9%, conditional R^2 29.3%), see **Supplementary Table 10**.

Table 1. Overview of the heterogeneity (R^2) explained by the best fitting multilevel multiple logistic regression models and random effects Median Odds Ratio (MOR).

	Conditional R^2 – total heterogeneity explained by model (%)	Marginal R^2 – heterogeneity explained by included fixed effects (%)	Random effect R^2 – location-level heterogeneity captured by model (%)	Median Odds Ratio (MOR)
Nested 'empty' model	26.3	7.2	19.1	2.41
Sexual behavioural model	27.8	10.2	17.6	2.35
Socioeconomic model	25.8	8.6	17.2	2.30
Environmental model	26.8	11.4	15.4	1.95
Combined 'full' model	29.6	15.6	14.0	1.94

DISCUSSION

Our findings showed that substantial levels of spatial heterogeneity in HIV prevalence exists among adults and young adults throughout all seven Eastern and Southern African countries analysed in this study. Especially in young adults, micro-epidemics of relatively high prevalence alternated with areas of very low prevalence, clearly illustrating the existence of areas

with high levels of transmission. HIV prevalence heterogeneity could for 15.6% (marginal R^2) be explained by an interplay of behavioural, socioeconomic and environmental factors, including number of sex partners, STIs, global human footprint, and urbanisation. Maps of interpolated random effect estimates at each sample location showed that environmental predictors were better at specifically predicting HIV prevalence at the high prevalence areas than sexual behavioural or socioeconomic variables, yet substantial heterogeneity at other high prevalence areas remains unexplained.

The geospatial patterns of HIV prevalence heterogeneity among adults shown in our study (**Figure 2A**) are very comparable to patterns shown in other recent studies in which other methods for spatial interpolation were used [4,5], confirming that our approach was suitable for creating reliable estimates. As an external validation for our geospatial patterns of HIV prevalence in young adults, we compared our estimates to the estimates from multiple small-scale surveillance sites from the ALPHA network [23]. We found that most estimates are comparable, but our estimates were lower for the Rakai (Uganda) and Manicaland (Zimbabwe) areas (**Supplementary Figure 8**). Both areas are characterised by well-known high levels of HIV transmission and relatively low numbers of sample locations in the utilised data with varying prevalence levels, possibly leading to underestimation of the HIV prevalence. This indicates that our approach of kriging, in which prevalence at a specific location is estimated by the prevalence in surrounding clusters as a function of the distance between the location and surrounding clusters, may have resulted in an underestimation (*i.e.*, smoothing) of HIV prevalence estimates, especially in high prevalence areas.

Our finding that environmental factors were the most important determinants of geospatial heterogeneity plausible, since all high HIV prevalence areas among young adults are in locations with known high levels of economic activity; characterised by high production and flow of goods and services [25,26]. This suggests that high-risk dynamics (involving seasonal work and commercial sex) in these areas might be important in generating this heterogeneity [27,28]. For instance, the fishing communities around Lake Victoria in Uganda (circle 1 in **Figure 3**) have frequently been reported as sites with high levels of transactional sex and HIV [29,30]. Furthermore, many high prevalence areas in our analyses cluster around border crossings, major highways or major ports (*e.g.*, circles 2 to 5 in **Figure 3**). Also long distance truck driving and associated commercial sex have been documented as important contributors to HIV transmission [27,29]. In addition, some of the high prevalence areas are in regions known to have high levels of migration, either work-related (seasonal) migration or other types of migration. For example, the Copperbelt mining area (circle 7 in **Figure 3**) or Nchelenge district in Zambia (circle 8 in **Figure 3**) in Zambia, which is known for its active fishing industry and a big refugee settlement. Mining and fishing areas have long been recognised as high risk settings for HIV transmission, as domestic or foreign male workers

often work long stints, separated from their families surrounded by an active sex industry [29–33].

Individual HIV prevalence in young adults was strongly associated with the reported number of lifetime sex partners and reported prevalence of STIs or STI symptoms, providing further evidence that geospatial clustering of HIV is linked to the clustering of risk behaviour, across all countries [12]. We found that individuals who reported having used a condom during the last sex act had an increased risk of being infected with HIV. This is a well-known counter-intuitive finding, and reflects the fact that condom use tends to be higher (yet sometimes insufficient) among people with riskier sexual behaviour, or reflects bias due to the fact that people who are aware of their positive HIV status are more likely to use a condom, to protect their partner [34]. This finding highlights the need to stimulate condom use, but more importantly, to increase access to effective HIV prevention interventions more broadly. Our finding that having education beyond the primary level seems to be strongly protective against HIV, is consistent with observations in the literature [13], and suggests that structural interventions to improve educational attainment [14] could help reduce HIV transmission in adolescent women.

Our results have important implications for the planning of prevention and treatment programs. High HIV prevalence areas in young adults are likely areas of high transmission [10], requiring prioritisation of tailored prevention interventions. Our key findings that (i) high HIV prevalence areas among young adults are located at economically active or developing areas and that (ii) HIV among young adults is driven by risky sexual behaviour; indicate that preventive interventions targeted at young adults at these specific locations could strongly impact HIV transmission. Prevention programmes aimed at improving exposure and uptake of effective prevention interventions for young adults [35,36] – such as pre-exposure prophylaxis (PrEP) [37], condoms [38], or voluntary male medical circumcision programmes [15,39] – should be prioritised in these areas. Also, intervention programmes for young adults should aim at early diagnosis and treatment initiation of those who get infected with HIV, by creating accessible, affordable and youth-friendly HIV testing and counselling services [35,40]. Furthermore, governments typically have prior knowledge about future economic developments. Improving the resilience of affected populations against the associated health risks could be considered as an integral part of such development. Moreover, as the population in these areas is likely to be highly mobile [41,42], effective prevention for young adults in high prevalence areas may not only affect the local HIV epidemics, but also the wider epidemic. Ultimately, our results demonstrate that the decade-old mantra of "know your epidemic, know your response" [43] is still highly relevant for sub-Saharan Africa. Our study found important common denominators that are associated with increased HIV risk in areas with high levels of transmission, but it will be essential for policy makers

to specifically evaluate the behavioural and socioeconomic context, and the interventions already in place at specific high-risk settings, to tailor interventions appropriately.

To our knowledge, we are the first to utilise geolocated HIV prevalence data from young adults specifically, to explore geospatial heterogeneity in the HIV epidemics of Eastern and Southern Africa and identify potential areas with high levels of transmission. Previously, Cuadros *et al.* proposed a co-kriging approach to estimate sub-national HIV prevalence estimates, incorporating HIV prevalence and environmental determinants [4], yet they did not stratify by age. In addition, Palk and Blower recently showed that places of high HIV prevalence in adults (aged 15-49 years) in Malawi are associated with reported higher rates of high-risk sex, defined as the number of lifetime partners [12]. Our results show that heterogeneity in HIV is associated with a range of sexual behavioural, socioeconomic and environmental variables, and that these are highly affected by age. Therefore, a standardised approach to map heterogeneity of an HIV epidemic should take age stratifications into account, and future studies on geospatial heterogeneity and its drivers should include behavioural, socioeconomic and environmental determinants.

Our results have limitations. First, DHSs are cross-sectional data designed to give an impression of HIV prevalence and behaviour among the general population; and thus, high-risk subpopulations such as female sex workers, men who have sex with men, and mobile populations such as truck drivers and seasonal workers, are thought to be underrepresented in these surveys. Therefore, we cannot make definitive conclusions on economic activity and key populations driving HIV transmission in at these locations. Nevertheless, our analyses showed that high HIV prevalence areas in DHS data, especially among young adults, were almost invariably located near economically active areas suggesting that these key population dynamics are still visible through general population-based surveys. Extending DHS surveys with other data sources that allow for mapping of key populations or performing incidence essays on HIV samples will allow for more accurate identification of HIV transmission areas and can further enhance our understanding of the epidemic. Second, DHS sampling locations are randomly selected, based on the underlying population density within a country. Consequently, very few locations were sampled from areas with large nature and wildlife conservation reserves, such as in Northern Kenya, Central Tanzania, and Northern and Southwestern Mozambique, and our interpolated prevalence estimates for such areas should be interpreted with caution. Designing alternative sampling techniques that over-sample areas with low densities could increase reliability of interpolated survey results. Third, we used survey data from a relatively wide range of years; 2008-2009 to 2015-2016. This time period in the study coincides with major initiatives to curb the pandemic, in particular the scale-up of antiretroviral treatment, as well as voluntary male circumcision campaigns and other HIV prevention interventions. Although these initiatives were potentially disproportionally tar-

geted at high transmission areas, we expect that the disproportionate impact would not be so extreme that it completely alters the locations of high transmission areas. Furthermore, although the scale-up of these interventions may have reduced HIV incidence, the associations between HIV and the hypothesised main drivers of HIV transmission – the (sexual) behavioural, socioeconomic and environmental factors explored in this study – likely did not change substantially by these interventions. Fourth, explorative statistical analyses always run the risk of identifying patterns of random noise [44]. However, we believe this risk to be extremely low in our study, due to the very large sample size (n = 53,234), the rigid pre-selection of variables based on substantive knowledge, and the directions and magnitudes of association between the included covariates and HIV found in our study are in line with of findings from previous studies [2–5]. In addition, we performed non-random cross-validation by testing the final fitted model for each country separately. Reassuringly we found that, despite the differences in underlying epidemic and scale-up of interventions across countries, the conditional R^2 of the model was strikingly similar for six out of the eight countries in our analysis, ranging between 23.5% and 36.0% (compared to 29.6% in the main analysis). Only the conditional R^2 for Kenya (45.0%) and Zimbabwe (17.6%) deviated a little bit more from the combined model, yet not to an alarming extend (**Supplementary Table 11**).

In conclusion, our findings show that consistent clustering of HIV prevalence exists among young adults in seven high burden countries in Eastern and Southern Africa, with clearly identifiable high prevalence areas. This heterogeneity is driven by an interplay of behavioural, socioeconomic and environmental factors, and the locations of high prevalence areas suggest that key population dynamics, especially related to seasonal and economic migration and associated sex work, play a major role. In further reducing HIV transmission in Eastern and Southern Africa, areas of high HIV prevalence in young adults could be priority areas for tailored HIV prevention interventions in line with SDG3 and UNAIDS targets to end the HIV pandemic by 2030.

Ethical approval

All the utilised DHS and AIS datasets are publicly available, and the DHS programme de-identifies all data before making them available to the public. The geospatial data (WorldPop, NASA) do not contain variables at the level of human subjects. Therefore, this work did not require ethical approval.

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Author contributions

CAB, JACH and NJDN conceptualised and designed the study. CAB and JACH performed the analyses, and wrote the first draft of the manuscript. SJdeV supervised the project, assisted in interpreting the findings, and contributed to writing the final manuscript. FG, RS and TB contributed to interpreting the findings and writing the final manuscript.

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Declaration of interests

The authors declare that they have no competing interests.

REFERENCES

1. United Nations. Transforming our World: The 2030 Agenda for Sustainable Development. [Internet]. United Nations Division for Social Policy and Development, Indigenous Peoples; 2017. Available: https://sustainabledevelopment.un.org/post2015/
2. UNAIDS. Fast-track: ending the AIDS epidemic by 2030. 2014.
3. UNAIDS. UNAIDS report 2017, Joint United Nations Programme on HIV/AIDS (UNAIDS). 2017.
4. Cuadros DF, Li J, Branscum AJ, Akullian A, Jia P, Mziray EN, *et al.* Mapping the spatial variability of HIV infection in Sub-Saharan Africa: Effective information for localized HIV prevention and control. Nature. 2017;7: 1–11. doi:10.1038/s41598-017-09464-y
5. Dwyer-Lindgren L, Cork MA, Sligar A, Steuben KM, Wilson KF, Provost NR, *et al.* Mapping HIV prevalence in sub-Saharan Africa between 2000 and 2017. Nature. 2019; doi:10.1038/s41586-019-1200-9
6. Tanser F, LeSueur D, Solarsh G, Wilkinson D. HIV heterogeneity and proximity of homestead to roads in rural South Africa: An exploration using a geographical information system. Trop Med Int Heal. 2000;5: 40–46. doi:10.1046/j.1365-3156.2000.00513.x
7. Zulu LC, Kalipeni E, Johannes E. Analyzing spatial clustering and the spatiotemporal nature and trends of HIV/AIDS prevalence using GIS: The case of Malawi, 1994-2010. BMC Infect Dis. 2014;14: 1–21. doi:10.1186/1471-2334-14-285
8. Barankanira E, Molinari N, Niyongabo T, Laurent C. Spatial analysis of HIV infection and associated individual characteristics in Burundi: Indications for effective prevention. BMC Public Health. 2016;16: 1–11. doi:10.1186/s12889-016-2760-3
9. Anderson SJ, Cherutich P, Kilonzo N, Cremin I, Fecht D, Kimanga D, *et al.* Maximising the effect of combination HIV prevention through prioritisation of the people and places in greatest need: A modelling study. Lancet. 2014;384: 249–256. doi:10.1016/S0140-6736(14)61053-9
10. Mahy M, Garcia-Calleja JM, Marsh KA. Trends in HIV prevalence among young people in generalised epidemics: implications for monitoring the HIV epidemic. Sex Transm Infect. 2012;88: i65–i75. doi:10.1136/sextrans-2012-050789
11. Luke N, Kurz K. Cross-generational and transactional sexual relations in sub-Saharan Africa. Washington, DC Int Cent Res Women. 2002;
12. Palk L, Blower S. Geographic variation in sexual behaviour can explain geospatial heterogeneity in the severity of the HIV epidemic in Malawi. BMC Med. 2018;16: 22. doi:10.1186/s12916-018-1006-x
13. Neve J De, Fink G, Subramanian S V, Moyo S, Bor J. Length of secondary schooling and risk of HIV infection in Botswana: evidence from a natural experiment. Lancet. 2015;3: 470–477. doi:10.1016/S2214-109X(15)00087-X
14. Baird SJ, Garfein RS, McIntosh CT, Özler B. Effect of a cash transfer programme for schooling on prevalence of HIV and herpes simplex type 2 in Malawi: A cluster randomised trial. Lancet. 2012;379: 1320–1329. doi:10.1016/S0140-6736(11)61709-1
15. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 trial. PLOS Med. 2005;2: 1112–1122. doi:10.1371/journal.pmed.0020298

16. JICA. Preparatory Survey for Southern Africa Integrated Regional Transport Program [Internet]. 2010. Available: http://open_jicareport.jica.go.jp/pdf/11991007_01.pdf

17. Diggle PJ, Tawn JA, Moyeed RA. Model-Based Geostatistics. J R Stat Soc. 1998;67: 617–666.

18. Miller HJ. Tobler's First Law and Spatial Analysis. Ann Assoc Am Geogr. 2004;94: 284–289. doi:10.1111/j.1467-8306.2004.09402005.x

19. Nakagawa S, Schielzeth H. A general and simple method for obtaining R^2 from generalized linear mixed-effects models. Methods Ecol Evol. 2013;4: 133–142. doi:10.1111/j.2041-210x.2012.00261.x

20. Merlo J, Chaix B, Ohlsson H, Beckman A, Johnell K, Hjerpe P, *et al.* A brief conceptual tutorial of multilevel analysis in social epidemiology: Using measures of clustering in multilevel logistic regression to investigate contextual phenomena. J Epidemiol Community Health. 2006;60: 290–297. doi:10.1136/jech.2004.029454

21. Steyerberg EW, Harrell FE. Prediction models need appropriate internal, internal--external, and external validation. J Clin Epidemiol. 2016;69: 245–247.

22. Steyerberg EW. Validation in prediction research: the waste by data splitting. J Clin Epidemiol. 2018;103: 131–133.

23. Reniers G, Wamukoya M, Urassa M, Nyaguara A, Nakiyingi-Miiro J, Lutalo T, *et al.* Data resource profile: network for analysing longitudinal population-based HIV/AIDS data on Africa (ALPHA Network). Int J Epidemiol. 2016;45: 83–93.

24. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014;12: 1495–1499.

25. Parkhurst JO. Structural approaches for prevention of sexually transmitted HIV in general populations: definitions and an operational approach. J Int AIDS Soc. 2014;17: 19052.

26. University of Toronto. The Nature of Economic Activity [Internet]. [cited 25 Nov 2019] p. 1. Available: https://www.economics.utoronto.ca/jfloyd/modules/neastkf.html

27. Cassels S, Camlin CS. Geographical mobility and heterogeneity of the HIV epidemic. Lancet HIV. 2016;3: e339–e341. doi:10.1016/S2352-3018(16)30048-0

28. Steen R, Hontelez JAC, Mugurungi O, Mpofu A, Matthijsse SM, de Vlas SJ, *et al.* Economy, migrant labour and sex work: interplay of HIV epidemic drivers in Zimbabwe over three decades. AIDS. 2019;33: 123–131. doi:10.1097/QAD.0000000000002066

29. Chang LW, Health R, Program S, Program BI, Hopkins J, Grabowski MK, *et al.* Heterogeneity of the HIV epidemic: an observational epidemiologic study of agrarian, trading, and fishing communities in Rakai, Uganda. Lancet HIV. 2016;3: 1–20. doi:10.1016/S2352-3018(16)30034-0. Heterogeneity

30. Tumwesigye NM, Atuyambe L, Wanyenze RK, Kibira SP, Li Q, Wabwire-Mangen F, *et al.* Alcohol consumption and risky sexual behaviour in the fishing communities: Evidence from two fish landing sites on Lake Victoria in Uganda. BMC Public Health. 2012;12: 1–11. doi:10.1186/1471-2458-12-1069

31. Faria NR, Rambaut A, Suchard MA, Baele G, Bedford T, Ward MJ, *et al.* The early spread and epidemic ignition of HIV-1 in human populations. Science. 2014;346: 56–61.

32. Corno L, Walque D De. Mines , Migration and HIV / AIDS in Southern Africa. J Afr Econ. 2012;21: 465–498. doi:10.1093/jae/ejs005

33. Clift S, Anemona A, Watson-Jones D, Kanga Z, Ndeki L, Changalucha J, *et al.* Variations of HIV and STI prevalences within communities neighbouring new goldmines in Tanzania: importance for intervention design. Sex Transm Infect. 2003;79: 307 LP – 312.

34. Bachanas P, Medley A, Pals S, Antelman G, Benech I, Deluca N, *et al.* Disclosure, Knowledge of Partner Status, and Condom Use Among HIV-Positive Patients Attending Clinical Care in Tanzania, Kenya, and Namibia. AIDS Patient Care STDS. 2013;27: 425–435. doi:10.1089/apc.2012.0388

35. Mavedzenge SMN, Doyle AM, Ross DA. HIV prevention in young people in sub-Saharan Africa: a systematic review. J Adolesc Heal. 2011;49: 568–586.

36. Pettifor A, Bekker L-G, Hosek S, DiClemente R, Rosenberg M, Bull S, *et al.* Preventing HIV among young people: research priorities for the future. J Acquir Immune Defic Syndr. 2013;63: S155.

37. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, *et al.* Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. N Engl J Med. 2012;367: 399–410. doi:10.1056/NEJMoa1108524

38. Creese A, Floyd K, Alban A, Guinness L. Cost-effectiveness of HIV / AIDS interventions in Africa : a systematic review of the evidence. Lancet. 2002;359: 1635–1642.

39. Samuelson J, Dickson K. Progress in scale-up of male circumcision for HIV prevention in Eastern and Southern Africa: Focus on service delivery. World Health Organization and UNAIDS. 2011.

40. Wong VJ, Murray KR, Phelps BR, Vermund SH, McCarraher DR. Adolescents, young people, and the 90-90-90 goals: a call to improve HIV testing and linkage to treatment. AIDS. 2017;31: S191.

41. Deane KD, Samwell Ngalya P, Boniface L, Bulugu G, Urassa M. Exploring the relationship between population mobility and HIV risk: Evidence from Tanzania. Glob Public Health. 2016; 1–16. doi:10.1080/17441692.2016.1178318

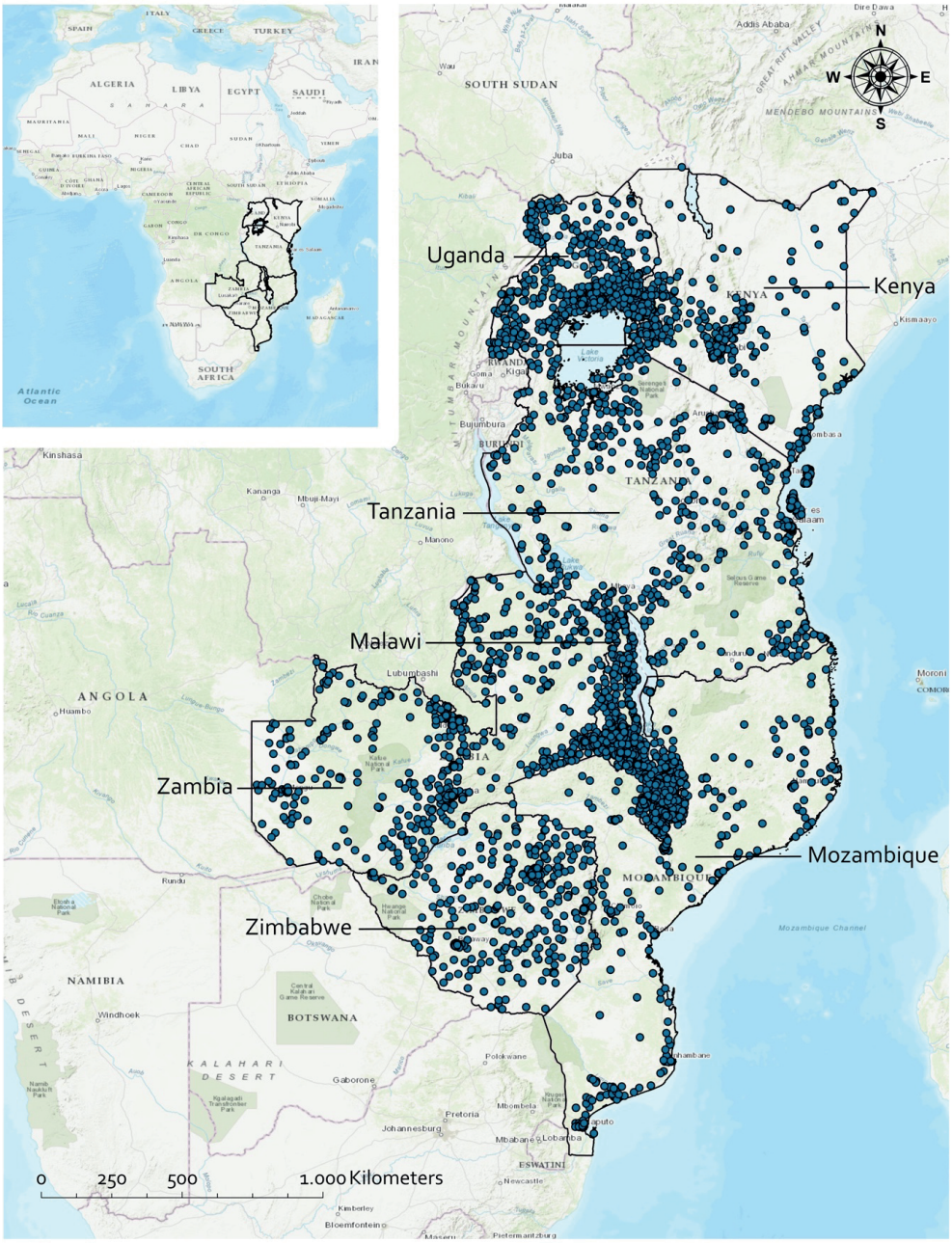
42. McGrath N, Hosegood V, Newell ML, Eaton JW. Migration, sexual behaviour, and HIV risk: A general population cohort in rural South Africa. Lancet HIV. 2015;2: e252–e259. doi:10.1016/S2352-3018(15)00045-4

43. Wilson D, Halperin DT. "Know your epidemic, know your response": a useful approach, if we get it right. Lancet. 2008;372: 423–426. doi:https://doi.org/10.1016/S0140-6736(08)60883-1

44. Gasser T, Sroka L, Jennen-Steinmetz C. Residual variance and residual pattern in nonlinear regression. Biometrika. 1986;73: 625–633.

SUPPORTING INFORMATION TO CHAPTER 2

Supplementary Figure 1. Overview of the study area in sub-Saharan Africa (top right panel) and the Demographic and Health and AIDS Indicator Survey sample locations (blue dots) for the seven countries included in this study: Kenya (*n* = 394), Malawi (*n* = 847)[1], Mozambique (*n* = 270), Tanzania (*n* = 570)[1], Uganda (*n* = 470)[1], Zambia (*n* = 719), and Zimbabwe (*n* = 400). [1]AIDS Indicator Survey (AIS).



Supplementary Table 1. Overview of all variables included in the study.

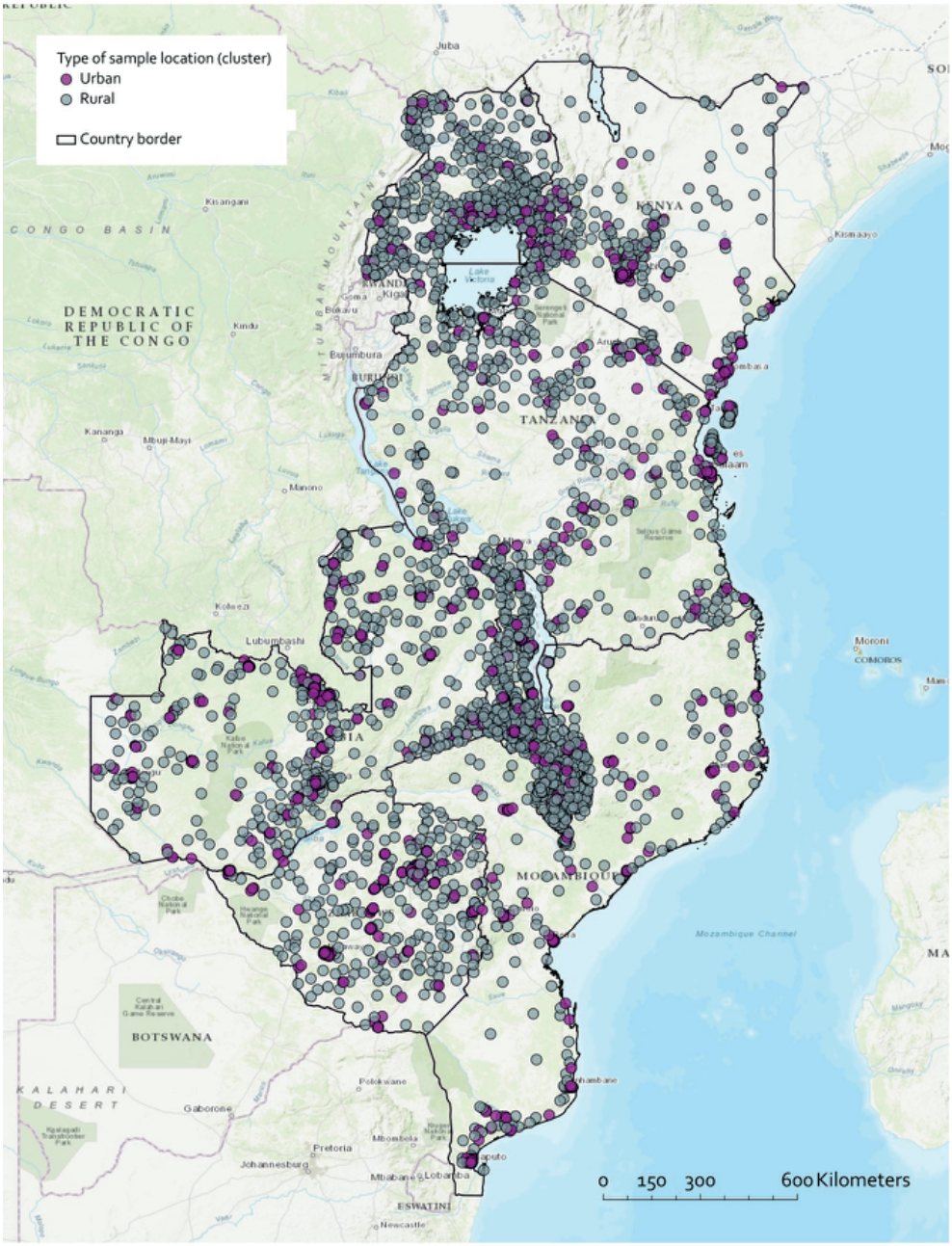
Variable name	Original value type	Scale or levels	Type of transformation for regression analysis	How were they measured?	Data source	Website
HIV status	Dichotomous	0, 1	N/A	HIV testing	DHSs, AISs	https://dhsprogram.com/
Sex	Dichotomous	1, 2	N/A	Self-reported	DHSs, AISs	https://dhsprogram.com/
Age	Continuous	15 - 54	Categorised; 5-year age groups	Self-reported	DHSs, AISs	https://dhsprogram.com/
Lifetime number of sex partners	Continuous	0 - 95	Categorised; 4 levels	Self-reported	DHSs, AISs	https://dhsprogram.com/
Number of sex partners past 12 months	Continuous	0 - 95	Categorised; 4 levels	Self-reported	DHSs, AISs	https://dhsprogram.com/
STI or signs of STI past 12 months	Dichotomous	0, 1	N/A	Self-reported	DHSs, AISs	https://dhsprogram.com/
Condom used last sexual intercourse	Dichotomous	0, 1	N/A	Self-reported	DHSs, AISs	https://dhsprogram.com/
Circumcised (only men)	Dichotomous	0, 1	N/A	Self-reported	DHSs, AISs	https://dhsprogram.com/
Paid for sexual intercourse 12 months (only men)	Dichotomous	0, 1	N/A	Self-reported	DHSs, AISs	https://dhsprogram.com/
Education	Categories	4 levels; 0, 1, 2, 3	N/A	Self-reported	DHSs, AISs	https://dhsprogram.com/
Wealth index	Categories	5 levels; 1, 2, 3, 4, 5	N/A	Weighted index	DHSs, AISs	https://dhsprogram.com/
Occupation	Categories	11 levels; 1 – 10, 98	N/A	Self-reported	DHSs, AISs	https://dhsprogram.com/
Type of resident	Dichotomous	1, 2	N/A	Self-reported	DHSs, AISs	https://dhsprogram.com/
Type of place of residence	Dichotomous	1, 2	N/A	Estimated by USAID	DHSs, AISs	https://dhsprogram.com/
Population density (per km^2)	Continuous	0 – 40,000	Categorised; 6 levels	Estimated based on national census data	WorldPop (incorporated in DHSs)	https://www.worldpop.org/

Supplementary Table 1. Overview of all variables included in the study. (*continued*)

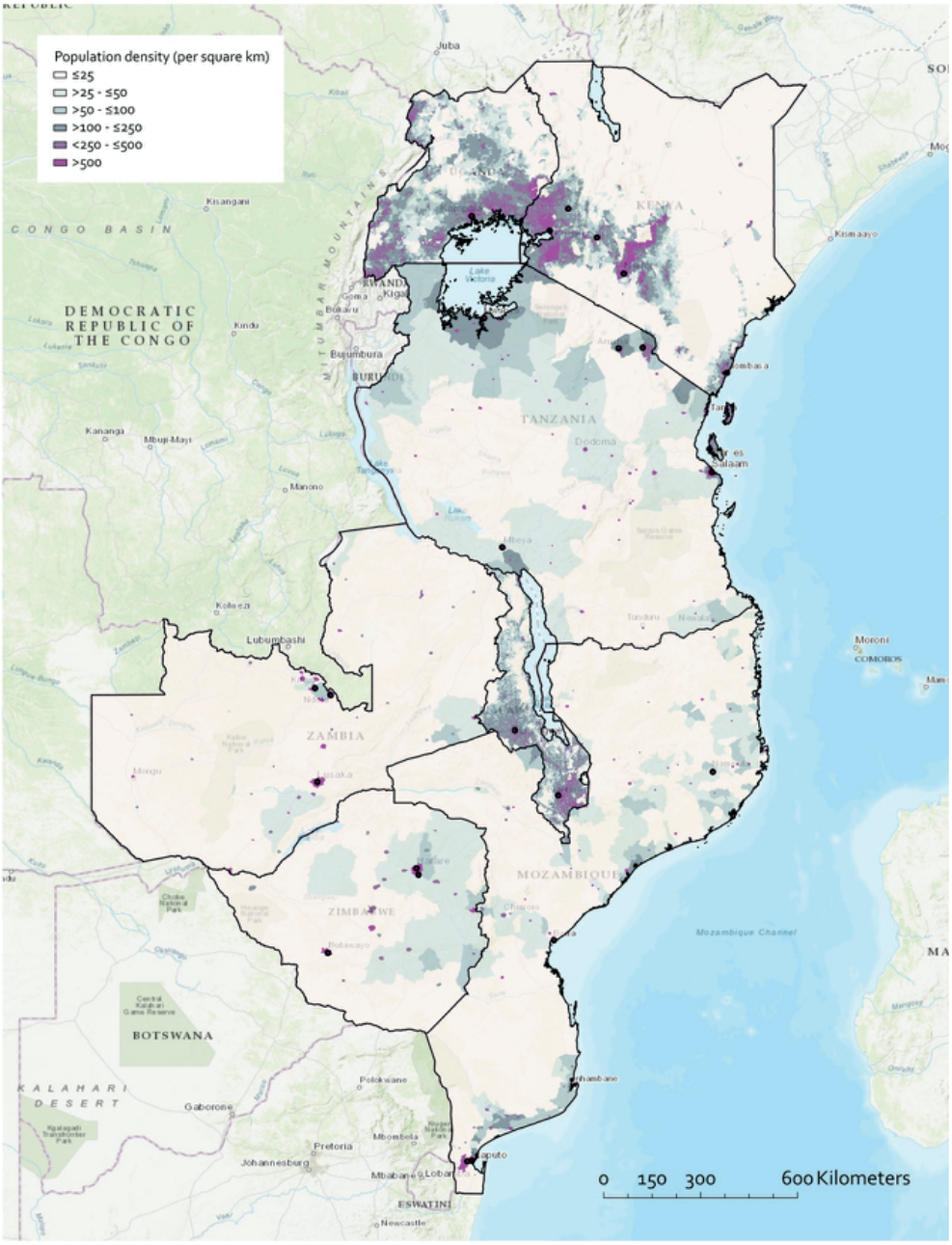
Variable name	Original value type	Scale or levels	Type of transformation for regression analysis	How were they measured?	Data source	Website
Proximity to nearest highway (km)	Continuous	0 - 431	Categorised; 4 levels	Calculated (using ArcGIS Pro)	GDAM	https://www.gadm.org/
Proximity to nearest major city (km)	Continuous	0 - 1531	Categorised; 5 levels	Calculated (using ArcGIS Pro)	World Population Review	www.worldpopulationreview.com/worldcities/
Proximity to nearest border crossing or port (km)	Continuous	0 - 523	Categorised; 5 levels	Calculated (using ArcGIS Pro)	Southern Africa Integrated Regional Transport Programme report (2010)	N/A
Enhanced vegetation index (EVI)	Continuous	0 - 234	Categorised; 6 levels	Satellite imaging	NASA, (incorporated in DHSs)	http://sedac.ciesin.columbia.edu/
Global human footprint (GHF) (%)	Continuous	5 - 100	Categorised; 5 levels	Estimated by NASA, using several data sources	NASA, (incorporated in DHSs)	http://sedac.ciesin.columbia.edu/

AISs = AIDS Indicator Surveys, DHSs = Demographic and Health Surveys, NASA = National Aeronautics and Space Administration, USAID = *United States Agency for International Development*

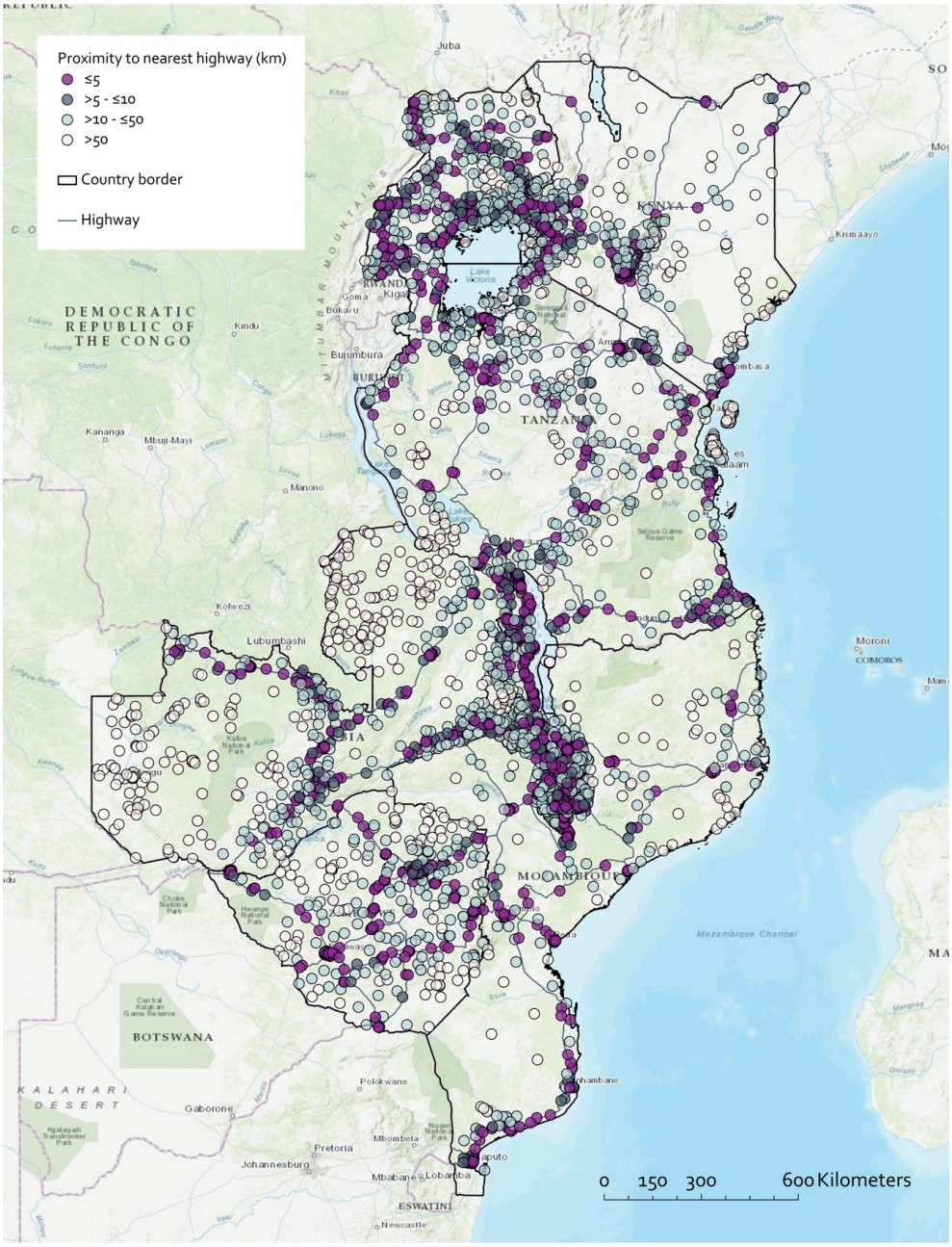
Supplementary Figure 2A. Map presents whether the sample location is classified as urban or rural.



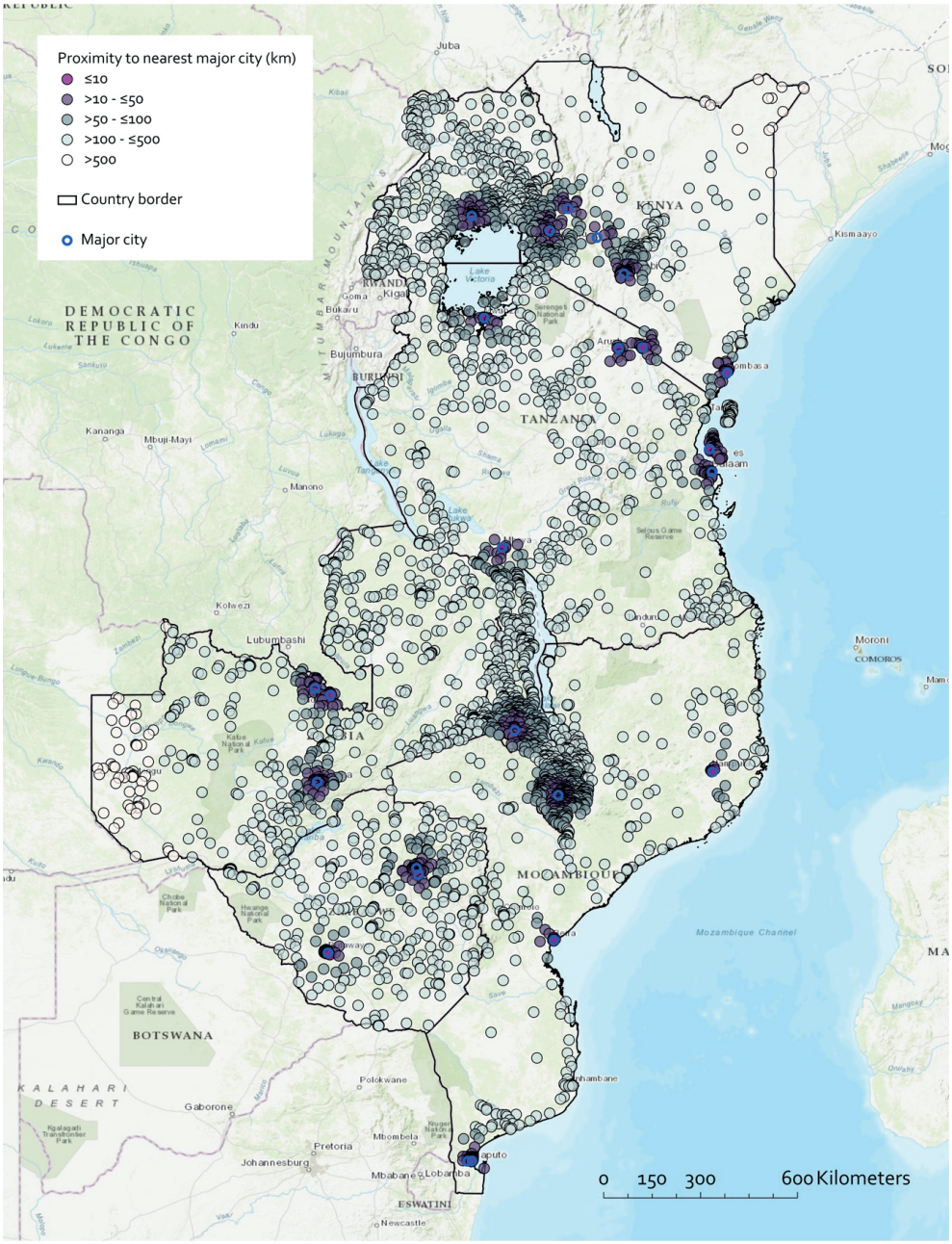
Supplementary Figure 2B. Map presents the population density for the study area.



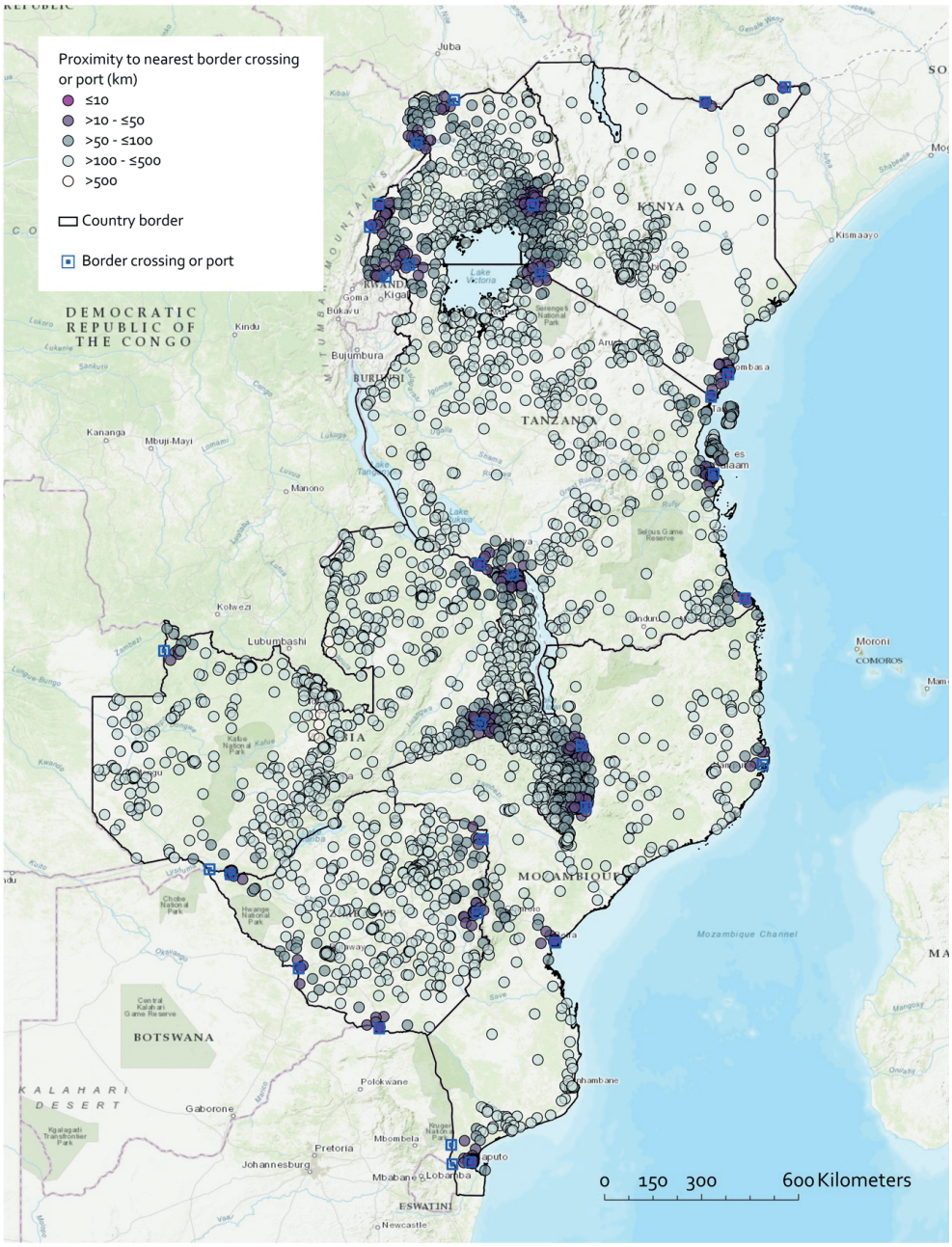
Supplementary Figure 2C. Map presents the proximity from each sample location to the nearest highway.



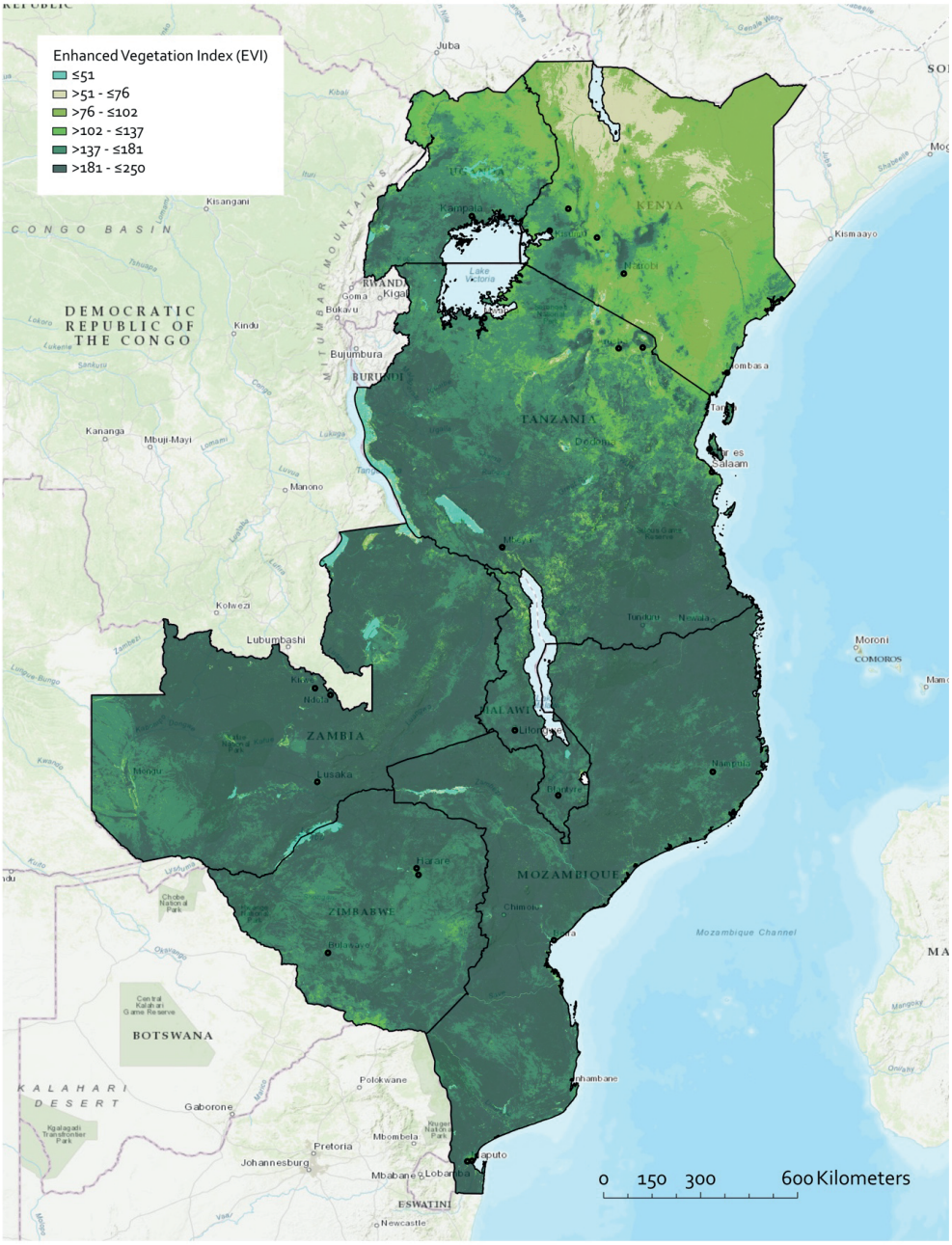
Supplementary Figure 2D. Map presents the proximity from each sample location to the nearest major city (more than 250 000 inhabitants).



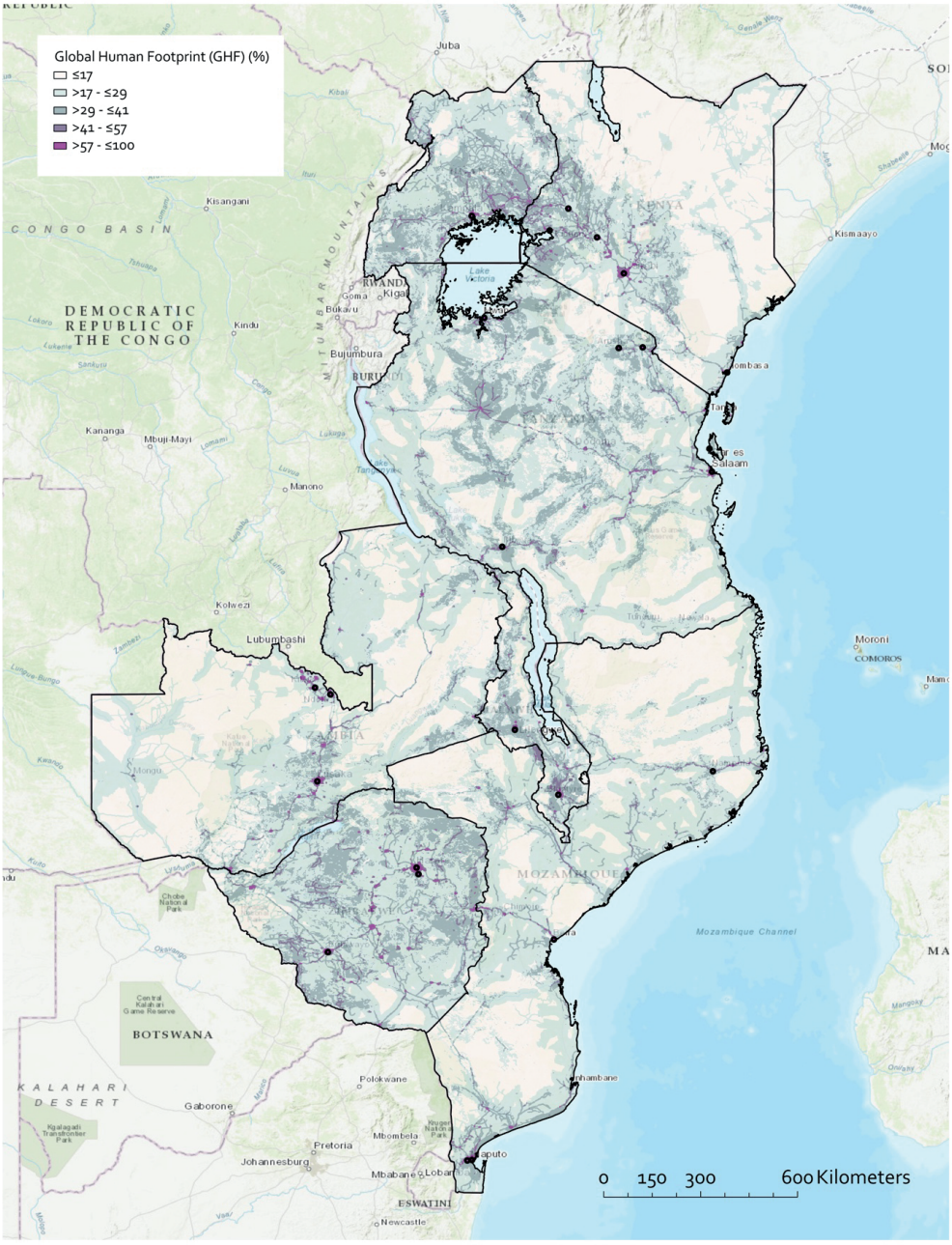
Supplementary Figure 2E. Map presents the proximity from each sample location to the nearest border crossing or major port.



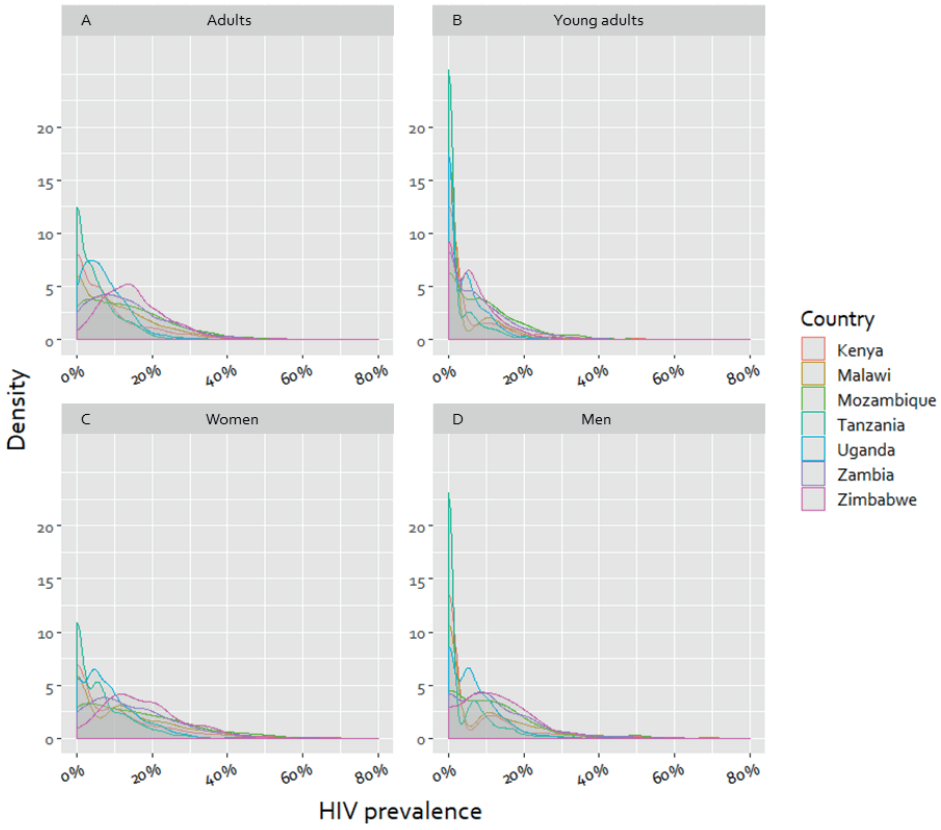
Supplementary Figure 2F. Map presents the enhanced vegetation index (EVI) for the study area.



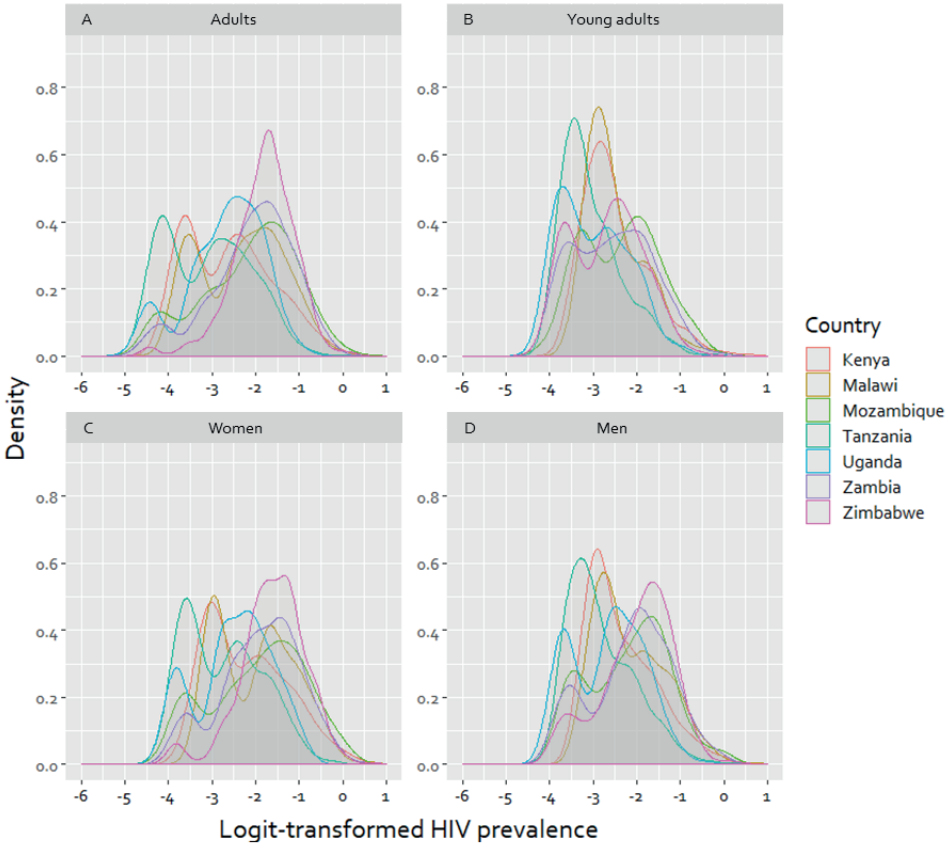
Supplementary Figure 2G. Map presents the global human footprint (GHF) for the study area.



Supplementary Figure 3. Density plots illustrating the overall sample location-level distributions of HIV prevalence among adults (A), young adults (B), women (C), and men (D) for each country included in this study.



Supplementary Figure 4. Density plots illustrating the overall logit-transformed sample location-level distributions of HIV prevalence among adults (A), young adults (B), women (C), and men (D) for each country included in this study, as used for fitting semivariograms and ordinary kriging. The logit-transformed HIV prevalence of -6 (on the x-axis) represents a prevalence of 0%, -5 of 1%, -4 of 2%, -3 of 5%, -2 of 12%, -1 of 27%, 0 of 50%, and 1 of 73%.

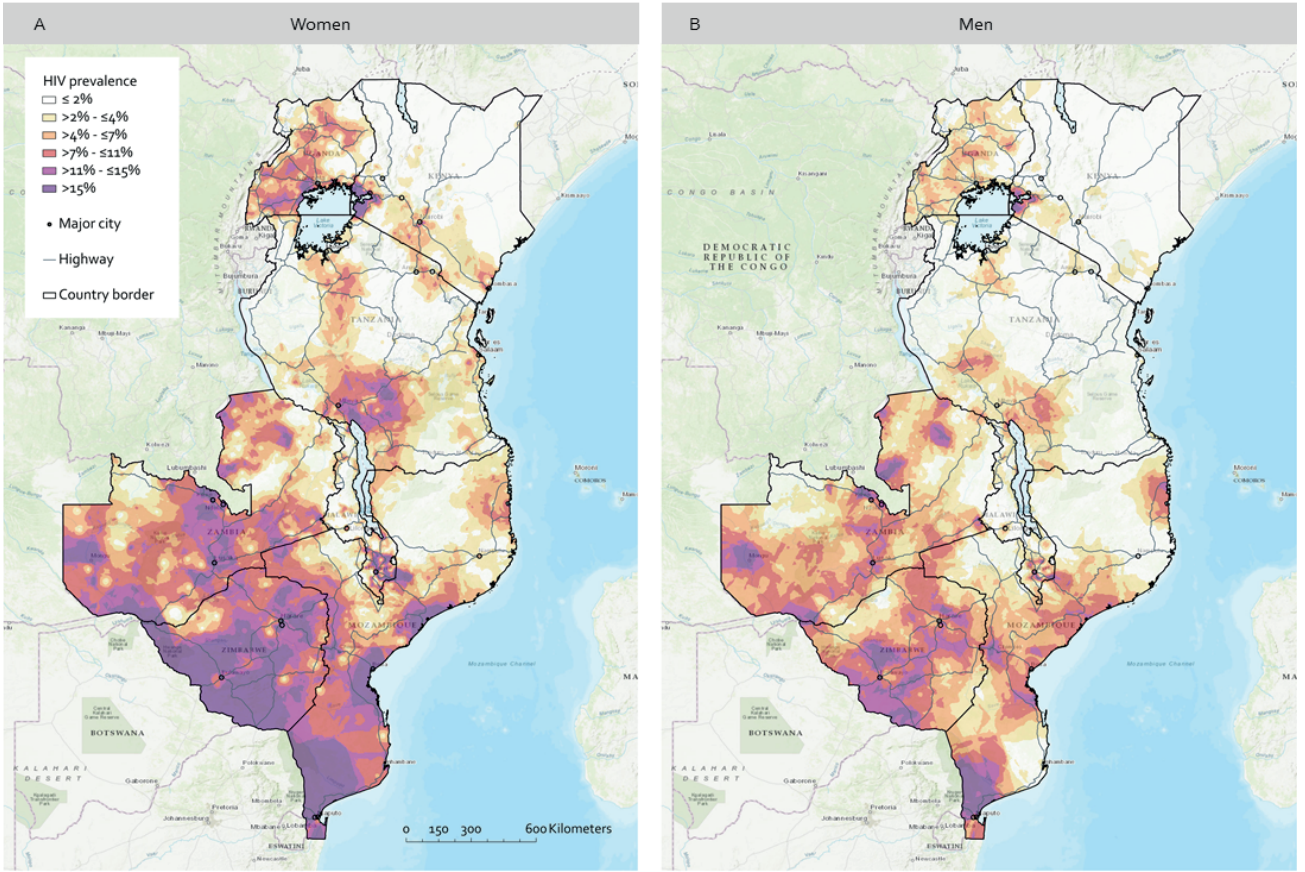


Supplementary Table 2. Spatial autocorrelation of HIV prevalence at the sample location-level, estimated by Moran's I index.

	Observed value	Standard deviation	p-value	
Adults				
Countries overall	***0.13***	***0.002***	***<0.001***	*****
Kenya	0.11	0.009	<0.001	***
Malawi	0.10	0.005	<0.001	***
Mozambique	0.24	0.016	<0.001	***
Tanzania	0.12	0.007	<0.001	***
Uganda	0.06	0.007	<0.001	***
Zambia	0.12	0.008	<0.001	***
Zimbabwe	0.02	0.012	0.024	*
Young adults				
Countries overall	***0.05***	***0.002***	***<0.001***	*****
Kenya	0.05	0.009	<0.001	***
Malawi	0.02	0.005	<0.001	***
Mozambique	0.05	0.016	<0.001	***
Tanzania	0.03	0.007	<0.001	***
Uganda	0.01	0.007	<0.001	***
Zambia	0.05	0.008	<0.001	***
Zimbabwe	0.02	0.012	0.067	.
Women				
Countries overall	***0.11***	***0.002***	***<0.001***	*****
Kenya	0.09	0.009	<0.001	***
Malawi	0.09	0.005	<0.001	***
Mozambique	0.22	0.016	<0.001	***
Tanzania	0.11	0.007	<0.001	***
Uganda	0.08	0.007	<0.001	***
Zambia	0.12	0.008	<0.001	***
Zimbabwe	0.03	0.012	0.002	**
Men				
Countries overall	***0.08***	***0.002***	***<0.001***	*****
Kenya	0.06	0.009	<0.001	***
Malawi	0.05	0.005	<0.001	***
Mozambique	0.12	0.016	<0.001	***
Tanzania	0.06	0.007	<0.001	***
Uganda	0.01	0.007	0.140	
Zambia	0.06	0.008	<0.001	***
Zimbabwe	0.02	0.012	0.077	.

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Supplementary Figure 5. Maps present the predicted HIV prevalence in women (15-49 years) (A) and men (15-54 years) (B) for seven countries in Eastern and Southern Africa. The maps of HIV prevalence among adults and young adults are shown in Figure 2. Continuous surface maps were created by kriging HIV prevalence data obtained from (https://dhsprogram.com/).



Supplementary Table 3. Bivariate logistic regression models of HIV status and behavioural, socioeconomic and environmental variables in young adults (women 15-24 years and men 15-29 years of age) in seven countries of Eastern and Southern Africa, adjusted for age and sex. Data obtained through (https://dhsprogram.com/).

Covariate	Young adults			
	N	HIV prevalence (%)	aOR [95% CI]	p-value
Lifetime number of sex partners				
None	16,532	2.4	1	
1-3	27,739	5.6	1.60 [1.48; 1.73]	<0.001 ***
4-9	7,002	7.3	2.53 [2.37; 2.69]	<0.001 ***
10+	1,961	8.5	3.18 [2.96; 3.39]	<0.001 ***
Sex				
Male	27,698	4.0	1	
Female	25,536	6.0	2.33 [2.23; 2.44]	<0.001 ***
Age (per 5-year age group)				
15-19	25,586	3.0	1	
20-24	20,548	6.7	1.82 [1.71; 1.92]	<0.001 ***
25-29	7,100	7.0	2.71 [2.55; 2.86]	<0.001 ***
Number of sex partners past 12 months				
None	21,802	3.2	1	
1	27,206	6.1	1.35 [1.24; 1.45]	<0.001 ***
2-3	3,902	6.5	1.67 [1.50; 1.84]	<0.001 ***
4+	324	6.5	1.77 [1.29; 2.25]	0.019 *
Sex				
Male	27,698	4.0	1	
Female	25,536	6.0	2.09 [1.99; 2.19]	<0.001 ***
Age (per 5-year age group)				
15-19	25,586	3.0	1	
20-24	20,548	6.7	2.05 [1.94; 2.15]	<0.001 ***
25-29	7,100	7.0	3.30 [3.15; 3.45]	<0.001 ***
STI or signs of STI past 12 months				
No	49,351	4.6	1	
Yes	3,883	9.1	1.82 [1.69; 1.95]	<0.001 ***
Sex				
Male	27,698	4.0	1	
Female	25,536	6.0	2.13 [2.03; 3.92]	<0.001 ***
Age (per 5-year age group)				
15-19	25,586	3.0	1	
20-24	20,548	6.7	2.22 [2.12; 2.31]	<0.001 ***
25-29	7,100	7.0	3.78 [3646; 3.92]	<0.001 ***

Supplementary Table 3. Bivariate logistic regression models of HIV status and behavioural, socioeconomic and environmental variables in young adults (women 15-24 years and men 15-29 years of age) in seven countries of Eastern and Southern Africa, adjusted for age and sex. Data obtained through (https://dhsprogram.com/). (*continued*)

Covariate	Young adults			
	N	**HIV prevalence (%)**	**aOR [95% CI]**	**p-value**
Condom used last sexual intercourse				
No	44,167	4.7	1	
Yes	9,067	6.2	1.35 [1.24; 1.45]	<0.001 ***
Sex				
Male	27,698	4.0	1	
Female	25,536	6.0	2.17 [2.07; 2.27]	<0.001 ***
Age (per 5-year age group)				
15-19	25,586	3.0	1	
20-24	20,548	6.7	2.27 [2.17; 2.36]	<0.001 ***
25-29	7,100	7.0	3.96 [3.82; 4.10]	<0.001 ***
Circumcised (only men)				
No	17,250	4.6	1	
Yes	10,448	2.9	0.65 [0.51; 0.79]	<0.001 ***
Sex				
Male	27,698	4.0	1	
Female	25,536	6.0	2.19 [2.08; 2.29]	<0.001 ***
Age (per 5-year age group)				
15-19	25,586	3.0	1	
20-24	20,548	6.7	2.32 [2.23; 2.41]	<0.001 ***
25-29	7,100	7.0	3.95 [3.81; 4.09]	<0.001 ***

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

N = Number of observations, aOR = adjusted Odds Ratio, CI = Confidence Interval, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, logLik = log likelihood, DF = Degrees of Freedom, SD = Standard Deviation, N/A = Not Applicable, '-' = Covariate not present in regression model

Supplementary Table 4. Multiple multilevel nested 'empty' logistic regression model of HIV status in young adults (women 15-24 years and men 15-29 years of age) for seven countries of Eastern and Southern Africa, adjusted for age and sex. Data obtained through (https://dhsprogram.com/).

Covariate	Young adults			
	N	**HIV prevalence (%)**	**aOR [95% CI]**	**p-value**
Sex				
Male	27,698	4.0	1	
Female	25,536	6.0	2.08 [1.98; 2.18]	<0.001 ***
Age (per 5-year age group)				
15-19	25,586	3.0	1	
20-24	20,548	6.7	2.31 [2.22; 2.41]	<0.001 ***
25-29	7,100	7.0	3.97 [3.83; 4.10]	<0.001 ***
Model summary: AIC = 19,822.9; BIC = 19,867.3; logLik = -9,906.4; DF = 53,229; Deviance = 19,812.9				
Random effect (CLUST.ID): Variance = 0.852; SD = 0.923				

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

N = Number of observations, aOR = adjusted Odds Ratio, CI = Confidence Interval, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, logLik = log likelihood, DF = Degrees of Freedom, SD = Standard Deviation, N/A = Not Applicable, '-' = Covariate not present in regression model

Supplementary Table 5. Multiple multilevel logistic regression model of HIV status and behavioural variables in young adults (women 15-24 years and men 15-29 years of age) for seven countries of Eastern and Southern Africa, adjusted for age and sex. Data obtained through (https://dhsprogram.com/).

Covariate	Young adults			
	N	HIV prevalence (%)	aOR [95% CI]	p-value
Lifetime number of sex partners				
None	16,532	2.4	1	
1-3	27,739	5.6	1.45 [1.32; 1.58]	<0.001 ***
4-9	7,002	7.3	2.20 [2.03; 2.37]	<0.001 ***
10+	1,961	8.5	2.74 [2.51; 2.96]	<0.001 ***
STI or signs of STI past 12 months				
No	49,351	4.6	1	
Yes	3,883	9.1	1.57 [1.44; 1.70]	<0.001 ***
Condom used last sexual intercourse				
No	44,167	4.7	1	
Yes	9,067	6.2	1.17 [1.07; 1.28]	0.004 **
Circumcised (only men)				
No	17,250	4.6	1	
Yes	10,448	2.9	0.62 [0.47; 0.76]	<0.001 ***
Sex				
Male	27,698	4.0	1	
Female	25,536	6.0	2.03 [1.91; 2.12]	<0.001 ***
Age (per 5-year age group)				
15-19	25,586	3.0	1	
20-24	20,548	6.7	1.81 [1.70; 1.91]	<0.001 ***
25-29	7,100	7.0	2.72 [2.57; 2.88]	<0.001 ***
Model summary: AIC = 19,579.0; BIC = 19,676.4; logLik = -9,778.5; DF = 53,223; Deviance = 19,557.0				
Random effect (CLUST.ID): Variance = 0.801; SD = 0.895				

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

N = Number of observations, aOR = adjusted Odds Ratio, CI = Confidence Interval, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, logLik = log likelihood, DF = Degrees of Freedom, SD = Standard Deviation, N/A = Not Applicable, '-' = Covariate not present in regression model

Supplementary Table 6. Multiple multilevel logistic regression model of HIV status and socioeconomic variables in young adults (women 15-24 years and men 15-29 years of age) for seven countries of Eastern and Southern Africa, adjusted for age and sex. Data obtained through (https://dhsprogram.com/).

Covariate	Young adults			
	N	HIV prevalence (%)	aOR [95% CI]	p-value
Education				
No education	2,410	5.2	1.00 [0.80; 1.20]	0.997
Primary	25,013	4.8	1	
Secondary	23,956	5.1	0.83 [0.73; 0.93]	<0.001 ***
Higher	1,855	4.5	0.52 [0.26; 0.78]	<0.001 ***
Wealth index				
1 'poorest'	8,102	3.8	1	
2	9,307	3.8	1.00 [0.84; 1.17]	0.973
3	10,027	4.8	1.26 [1.10; 1.42]	0.004 **
4	11,691	5.9	1.46 [1.31; 1.62]	<0.001 ***
5 'wealthiest'	14,107	5.6	1.42 [1.25; 1.59]	<0.001 ***
Occupation				
Not working	21,467	4.5	1	
Professional/technical/managerial	1,857	5.8	1.04 [0.81; 1.27]	0.733
Clerical	310	6.8	1.10 [0.62; 1.57]	0.706
Sales	3,619	9.0	1.38 [1.23; 1.52]	<0.001 ***
Agricultural – self employed	7,975	4.4	0.90 [0.75; 1.05]	0.174
Agricultural – employee	7,055	3.2	0.72 [0.55; 0.89]	<0.001 ***
Household/domestic	1,053	6.3	1.19 [0.91; 1.46]	0.225
Services	2,154	7.5	1.38 [1.31; 1.57]	<0.001 ***
Skilled manual	3,474	6.1	1.15 [0.98; 1.33]	0.114
Unskilled manual	4,008	4.6	0.91 [0.72; 1.09]	0.280
Don't know	262	3.1	1.07 [0.04; 1.44]	0.348
Sex				
Male	27,698	4.0	1	
Female	25,536	6.0	2.02 [1.92; 2.12]	<0.001 ***
Age (per 5-year age group)				
15-19	25,586	3.0	1	
20-24	20,548	6.7	2.32 [2.22; 2.42]	<0.001 ***
25-29	7,100	7.0	2.98 [2.83; 4.13]	<0.001 ***
Model summary: AIC = 19,723.6; BIC = 19,991.0; logLik = -9,839.8; DF = 53,212; Deviance = 19,679.6				
Random effect (CLUST.ID): Variance = 0.763; SD = 0.874				

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

N = Number of observations, aOR = adjusted Odds Ratio, CI = Confidence Interval, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, logLik = log likelihood, DF = Degrees of Freedom, SD = Standard Deviation, N/A = Not Applicable, '-' = Covariate not present in regression model

Supplementary Table 7. Multiple multilevel logistic regression model of HIV status and environmental variables in young adults (women 15-24 years and men 15-29 years of age) for seven countries of Eastern and Southern Africa, adjusted for age and sex. Data obtained through (https://dhsprogram.com/).

Covariate	Young adults				
	N	HIV prevalence (%)	aOR [95% CI]	p-value	
Type of place of residence					
Urban	18,519	7.2	1		
Rural	34,715	3.7	0.53 [0.36; 0.69]	<0.001	***
Population density (km^2)					
≤25	12,673	5.3	1.45 [1.26; 1.64]	<0.001	***
>25 - ≤50	6,996	4.2	1.20 [0.98; 1.41]	0.099	.
>50 - ≤100	4,650	3.2	0.90 [0.66; 1.15]	0.414	
>100 - ≤250	8,182	4.0	1		
>250 - ≤500	6,602	4.4	0.91 [0.69; 1.12]	0.376	
>500	14,131	6.4	1.08 [0.87; 1.30]	0.461	
Proximity nearest major city (km)					
≤10	6,114	5.9	0.77 [0.55; 1.00]	0.026	*
>10 - ≤50	6,221	4.5	0.91 [0.73; 1.09]	0.313	
>50 - ≤100	7,986	5.1	1.16 [1.01; 1.32]	0.052	.
>100 - ≤500	31,879	4.7	1		
>500	1,034	9.4	1.98 [1.65; 2.30]	<0.001	***
Enhanced vegetation index (EVI)					
≤51 (water bodies, no DHS clusters here)	N/A	N/A	N/A	N/A	
>51 - ≤76	495	4.1	0.52 [-0.10; 1.13]	0.035	*
>76 - ≤102	1,724	4.1	0.63 [0.31; 0.96]	0.006	**
>102 - ≤137	9,405	5.1	0.88 [0.72; 1.04]	0.106	
>137 - ≤181	22,949	5.0	1		
>181 - ≤250	18,661	4.9	1.16 [1.03; 1.29]	0.024	*
Global human footprint (GHF) (%)					
≤17	2,028	4.3	0.96 [0.67; 1.25]	0.800	
>17 - ≤29	15,924	3.8	1		
>29 - ≤41	18,675	4.3	1.28 [1.14; 1.43]	<0.001	***
>41 - ≤57	6,359	6.7	1.43 [1.20; 1.66]	0.003	**
>57 - ≤100	10,248	6.9	1.68 [1.41; 1.94]	<0.001	***
Sex					
Male	27,698	4.0	1		
Female	25,536	6.0	2.08 [1.98; 2.18]	<0.001	***
Age (per 5-year age group)					
15-19	25,586	3.0	1		
20-24	20,548	6.7	2.30 [2.20; 2.39]	<0.001	***
25-29	7,100	7.0	3.92 [3.78; 4.06]	<0.001	***
Model summary: AIC = 19,138.0; BIC = 19,351.2; logLik = -9,545.0; DF = 53,210; Deviance = 19,090.0					
Random effect (CLUST.ID): Variance = 0.528; SD = 0.727					

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

N = Number of observations, aOR = adjusted Odds Ratio, CI = Confidence Interval, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, logLik = log likelihood, DF = Degrees of Freedom, SD = Standard Deviation, N/A = Not Applicable, '-' = Covariate not present in regression model

Supplementary Table 8. Combined 'full' multiple multilevel logistic regression model of HIV status and behavioural, socioeconomic and environmental variables in young adults (women 15-24 years and men 15-29 years of age) for seven countries of Eastern and Southern Africa, adjusted for age and sex. Data obtained through (https://dhsprogram.com/).

Covariate	Young adults				
	N	HIV prevalence (%)	aOR [95% CI]	p-value	
Lifetime number of sex partners					
None	16,532	2.4	1		
1-3	27,739	5.6	1.53 [1.40; 1.66]	<0.001	***
4-9	7,002	7.3	2.30 [2.14; 2.46]	<0.001	***
10+	1,961	8.5	2.87 [2.65; 3.09]	<0.001	***
STI or signs of STI past 12 months					
No	49,351	4.6	1		
Yes	3,883	9.1	1.57 [1.44; 1.70]	<0.001	***
Circumcised (only men)					
No	17,250	4.6	1		
Yes	10,448	2.9	0.61 [0.47; 0.76]	<0.001	***
Education					
No education	2,410	5.2	0.99 [0.79; 1.20]	0.947	
Primary	25,013	4.8	1		
Secondary	23,956	5.1	0.84 [0.74; 0.93]	<0.001	***
Higher	1,855	4.5	0.52 [0.27; 0.77]	<0.001	***
Type of place of residence					
Urban	18,519	7.2	1		
Rural	34,715	3.7	0.46 [0.29; 0.62]	<0.001	***
Enhanced vegetation index (EVI)					
≤51 (water bodies, no DHS clusters here)	N/A	N/A	N/A	N/A	
>51 - ≤76	495	4.1	0.52 [-0.12; 1.15]	0.041	*
>76 - ≤102	1,724	4.1	0.65 [0.32; 0.97]	0.009	**
>102 - ≤137	9,405	5.1	0.85 [0.70; 1.01]	0.042	*
>137 - ≤181	22,949	5.0	1		
>181 - ≤250	18,661	4.9	1.17 [1.04; 1.29]	0.015	*
Global human footprint (GHF) (%)					
≤17	2,028	4.3	1.13 [0.84; 1.41]	0.418	
>17 - ≤29	15,924	3.8	1		
>29 - ≤41	18,675	4.3	1.15 [1.01; 1.29]	0.055	.
>41 - ≤57	6,359	6.7	1.23 [1.02; 1.44]	0.051	.
>57 - ≤100	10,248	6.9	1.28 [1.06; 1.50]	0.024	*
Sex					
Male	27,698	4.0	1		
Female	25,536	6.0	2.04 [1.91; 2.15]	<0.001	***

Supplementary Table 8. Combined 'full' multiple multilevel logistic regression model of HIV status and behavioural, socioeconomic and environmental variables in young adults (women 15-24 years and men 15-29 years of age) for seven countries of Eastern and Southern Africa, adjusted for age and sex. Data obtained through (https://dhsprogram.com/). (*continued*)

Covariate	Young adults			
	N	**HIV prevalence (%)**	**aOR [95% CI]**	**p-value**
Age (per 5-year age group)				
15-19	25,586	3.0	1	
20-24	20,548	6.7	1.82 [1.72; 1.93]	<0.001 ***
25-29	7,100	7.0	2.75 [2.60; 2.90]	<0.001 ***
Model summary: AIC = 19,369.8; BIC = 19,565.2; logLik = -9,662.9; DF = 53,212; Deviance = 19,325.8				
Random effect (CLUST.ID): Variance = 0.688; SD = 0.830				

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

N = Number of observations, aOR = adjusted Odds Ratio, CI = Confidence Interval, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, logLik = log likelihood, DF = Degrees of Freedom, SD = Standard Deviation, N/A = Not Applicable, '-' = Covariate not present in regression mode

Supplementary Table 9. Combined 'full' multiple multilevel model as modified Poisson regression (with robust variance) of HIV status and behavioural, socioeconomic and environmental variables in young adults (women 15-24 years and men 15-29 years of age) for seven countries of Eastern and Southern Africa, adjusted for age and sex. Data obtained through (https://dhsprogram.com/).

Covariate	Young adults				
	N	HIV prevalence (%)	aRR [95% CI]	p-value	
Lifetime number of sex partners					
None	16,532	2.4	1		
1-3	27,739	5.6	1.52 [1.39; 1.64]	<0.001	***
4-9	7,002	7.3	2.18 [2.03; 2.34]	<0.001	***
10+	1,961	8.5	2.63 [2.42; 2.84]	<0.001	***
STI or signs of STI past 12 months					
No	49,351	4.6	1		
Yes	3,883	9.1	1.46 [1.34; 1.58]	<0.001	***
Circumcised (only men)					
No	17,250	4.6	1		
Yes	10,448	2.9	0.64 [0.50; 0.77]	<0.001	***
Education					
No education	2,410	5.2	0.98 [0.79; 1.17]	0.812	
Primary	25,013	4.8	1		
Secondary	23,956	5.1	0.85 [0.77; 0.94]	<0.001	***
Higher	1,855	4.5	0.54 [0.30; 0.78]	<0.001	***
Type of place of residence					
Urban	18,519	7.2	1		
Rural	34,715	3.7	0.50 [0.35; 0.65]	<0.001	***
Enhanced vegetation index (EVI)					
≤51 (water bodies, no DHS clusters here)	N/A	N/A	N/A	N/A	
>51 - ≤76	495	4.1	0.61 [0.05; 1.17]	0.087	.
>76 - ≤102	1,724	4.1	0.70 [0.41; 1.00]	0.019	*
>102 - ≤137	9,405	5.1	0.87 [0.73; 1.01]	0.055	.
>137 - ≤181	22,949	5.0	1		
>181 - ≤250	18,661	4.9	1.17 [1.05; 1.22]	0.007	**
Global human footprint (GHF) (%)					
≤17	2,028	4.3	1.09 [0.82; 1.35]	0.537	
>17 - ≤29	15,924	3.8	1		
>29 - ≤41	18,675	4.3	1.13 [1.00; 1.26]	0.062	.
>41 - ≤57	6,359	6.7	1.21 [1.02; 1.39]	0.053	.
>57 - ≤100	10,248	6.9	1.25 [1.05; 1.44]	0.023	*
Sex					
Male	27,698	4.0	1		
Female	25,536	6.0	2.03 [1.94; 2.12]	<0.001	***

Supplementary Table 9. Combined 'full' multiple multilevel model as modified Poisson regression (with robust variance) of HIV status and behavioural, socioeconomic and environmental variables in young adults (women 15-24 years and men 15-29 years of age) for seven countries of Eastern and Southern Africa, adjusted for age and sex. Data obtained through (https://dhsprogram.com/). (*continued*)

Covariate	Young adults			
	N	**HIV prevalence (%)**	**aRR [95% CI]**	**p-value**
Age (per 5-year age group)				
15-19	25,586	3.0	1	
20-24	20,548	6.7	1.72 [1.62; 1.82]	<0.001 ***
25-29	7,100	7.0	2.51 [2.36; 2.65]	<0.001 ***
Model summary: AIC = 19,685.2; BIC = 19,880.7; logLik = -9,820.6; DF = 53,212; Deviance = 19,641.2				
Random effect (CLUST.ID): Variance = 0.473; SD = 0.688				

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

N = Number of observations, aRR = adjusted Relative Risk, CI = Confidence Interval, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, logLik = log likelihood, DF = Degrees of Freedom, SD = Standard Deviation, N/A = Not Applicable, '-' = Covariate not present in regression model

Supplementary Table 10. Combined 'full' multiple multilevel logistic regression model of HIV status and behavioural, socioeconomic and environmental variables in young adults (women 15-24 years and men 15-29 years of age) for seven countries of Eastern and Southern Africa, adjusted for age, sex, and country. Data obtained through (https://dhsprogram.com/).

Covariate	Young adults			
	N	HIV prevalence (%)	aOR [95% CI]	p-value
Lifetime number of sex partners				
None	16,532	2.4	1	
1-3	27,739	5.6	1.47 [1.35; 1.60]	<0.001 ***
4-9	7,002	7.3	2.18 [2.02; 2.35]	<0.001 ***
10+	1,961	8.5	2.66 [2.44; 2.88]	<0.001 ***
STI or signs of STI past 12 months				
No	49,351	4.6	1	
Yes	3,883	9.1	1.69 [1.56; 1.86]	<0.001 ***
Circumcised (only men)				
No	17,250	4.6	1	
Yes	10,448	2.9	0.68 [0.53; 0.83]	<0.001 ***
Education				
No education	2,410	5.2	1.01 [0.81; 1.21]	0.923
Primary	25,013	4.8	1	
Secondary	23,956	5.1	0.77 [0.67; 0.86]	<0.001 ***
Higher	1,855	4.5	0.49 [0.24; 0.74]	<0.001 ***
Type of place of residence				
Urban	18,519	7.2	1	
Rural	34,715	3.7	0.57 [0.40; 0.73]	<0.001 ***
Global human footprint (GHF) (%)				
≤17	2,028	4.3	0.95 [0.67; 1.23]	0.743
>17 - ≤29	15,924	3.8	1	
>29 - ≤41	18,675	4.3	1.25 [1.11; 1.39]	0.001 **
>41 - ≤57	6,359	6.7	1.25 [1.05; 1.45]	0.029 *
>57 - ≤100	10,248	6.9	1.16 [0.95; 1.36]	0.162
Sex				
Male	27,698	4.0	1	
Female	25,536	6.0	2.05 [1.92; 2.15]	<0.001 ***
Age (per 5-year age group)				
15-19	25,586	3.0	1	
20-24	20,548	6.7	1.85 [1.74; 1.95]	<0.001 ***
25-29	7,100	7.0	2.81 [2.66; 2.96]	<0.001 ***
Country				
Kenya	3,286	3.8	1	

Supplementary Table 10. Combined 'full' multiple multilevel logistic regression model of HIV status and behavioural, socioeconomic and environmental variables in young adults (women 15-24 years and men 15-29 years of age) for seven countries of Eastern and Southern Africa, adjusted for age, sex, and country. Data obtained through (https://dhsprogram.com/). (*continued*)

Covariate	Young adults			
	N	**HIV prevalence (%)**	**aOR [95% CI]**	**p-value**
Malawi	7,097	3.6	0.88 [0.63; 1.13]	0.304
Mozambique	4,129	8.6	1.84 [1.58; 2.09]	<0.001 ***
Tanzania	8,262	1.8	0.49 [0.22; 0.76]	<0.001 ***
Uganda	9,297	3.6	0.82 [0.57; 1.07]	0.115
Zambia	13,416	7.3	1.87 [1.64; 2.10]	<0.001 ***
Zimbabwe	7,747	5.6	1.55 [1.31; 1.80]	<0.001 ***

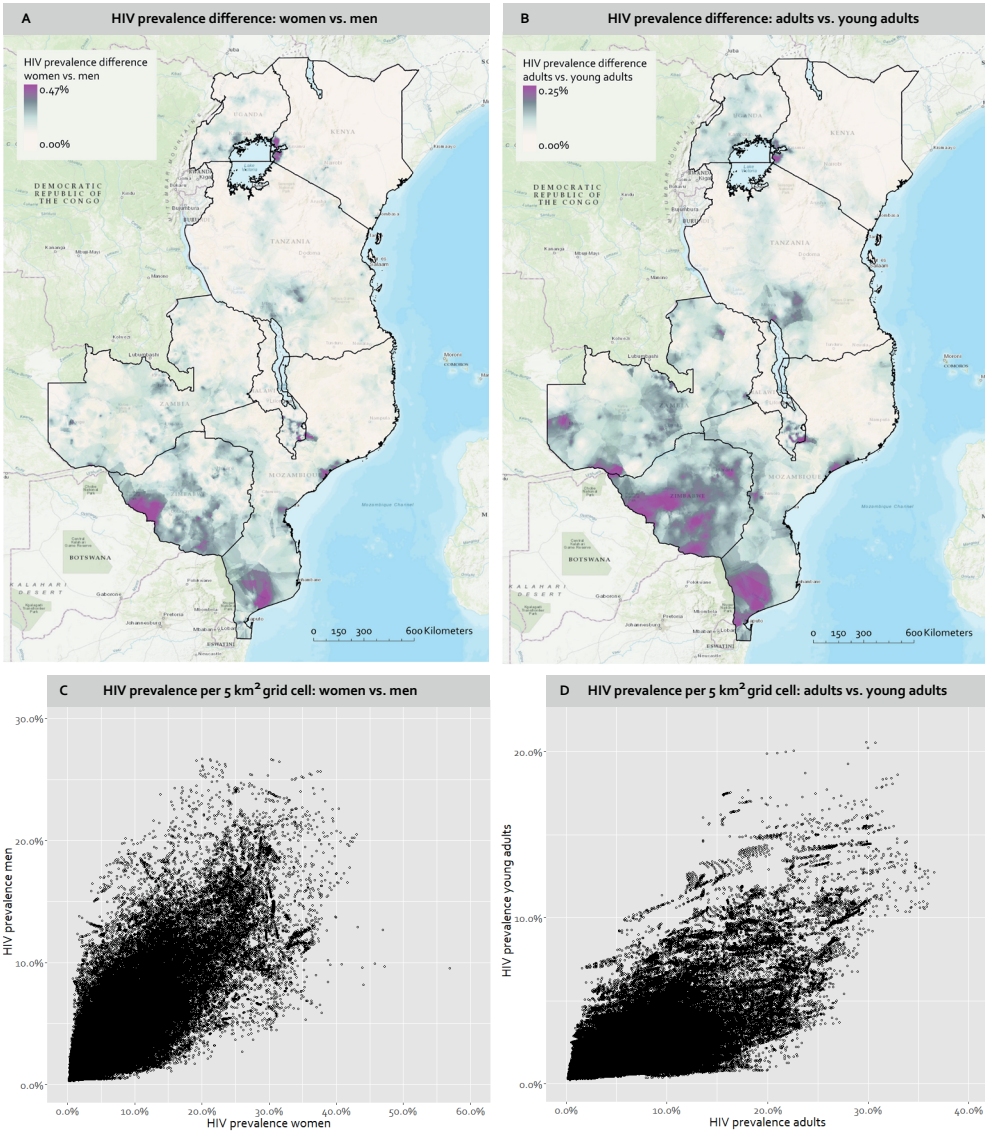
Model summary: AIC = 19,138.0; BIC = 19,351.2; logLik = -9,545.0; DF = 53,210; Deviance = 19,090.0
Random effect (CLUST.ID): Variance = 0.5277; SD = 0.7265
Marginal R^2 = 17.9, conditional R^2 = 29.3

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

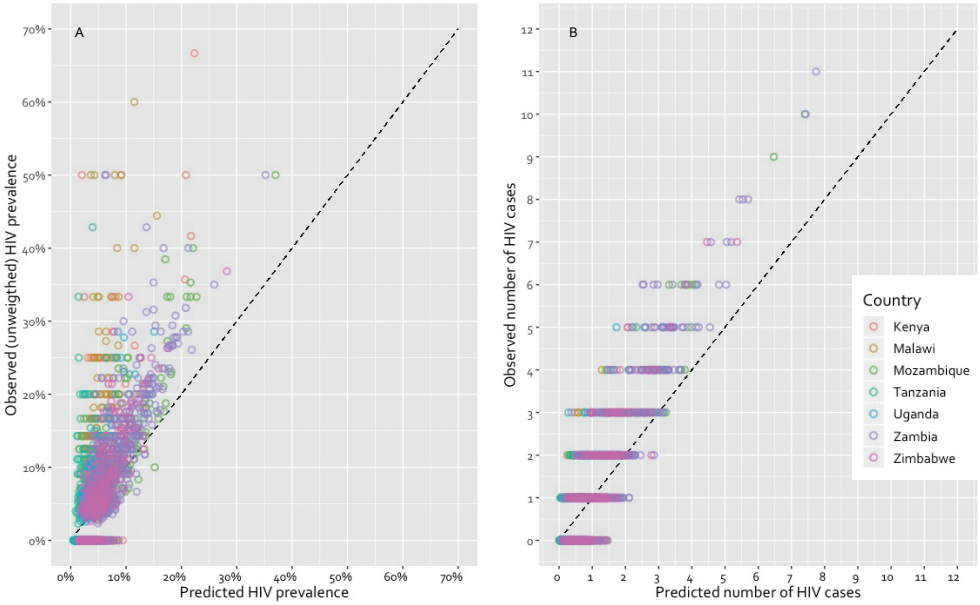
Supplementary Table 11. Overview of the heterogeneity (R^2) explained by the full final logistic regression model (see S8 Table), for each country separately.

Country	Conditional R^2 – total heterogeneity explained by model (%)	Marginal R^2 – heterogeneity explained by included fixed-effects (%)
Kenya	45.0	35.1
Malawi	31.3	16.2
Mozambique	27.3	17.8
Tanzania	36.0	20.8
Uganda	23.5	15.7
Zambia	31.6	21.5
Zimbabwe	17.6	13.0

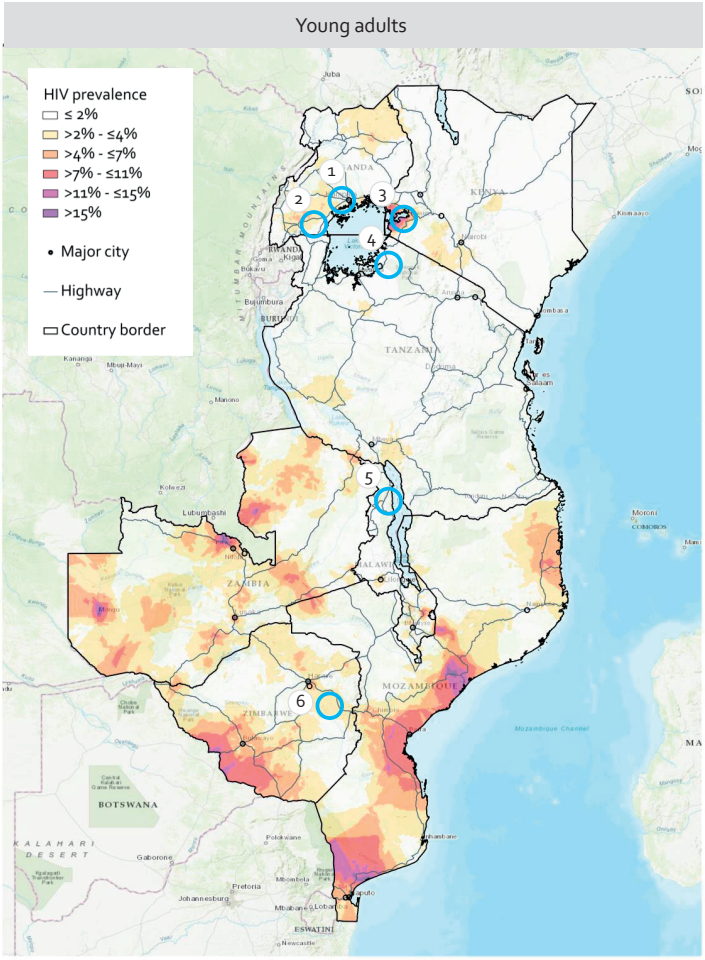
Supplementary Figure 6. Maps and scatterplots illustrating the difference in HIV prevalence (per 5 km² grid cell) between women and men (A and C respectively) and between adults and young adults (B and D respectively), for seven countries of Eastern and Southern Africa.



Supplementary Figure 7. Plots illustrating the observed versus the predicted sample location-level HIV prevalence (A) and the observed versus the predicted number of HIV cases (B) among young adults (women 15-24 years and men 15-29 years) for the combined 'full' best fitting multiple multilevel regression model per DHS sample location for seven countries of Eastern and Southern Africa (also see S8 Table).



Supplementary Figure 8. Map of HIV prevalence estimates for young adults, as interpolated in this study, and HIV prevalence estimates for young adults as reported from seven population-based cohorts at small-scale geographical sites (ALPHA network) within the area covered by this study.



1 Masaka, Uganda
Prevalence young adults
ALPHA = ~2%
Our study = ≤2% to >2% - ≤ 4%

2 Rakai, Uganda
Prevalence young adults
ALPHA = ~10%
Our study = ≤2% to >4% - ≤ 7%

3 Kisumu, Kenya
Prevalence young adults
ALPHA = ~11%
Our study = >4%- ≤ 7% to >15%

4 Kisesa, Tanzania
Prevalence young adults
ALPHA = ~2%
Our study = ≤2%

5 Karonga, Malawi
Prevalence young adults
ALPHA = ~3%
Our study = ≤2%

6 Manicaland, Zimbabwe
Prevalence young adults
ALPHA = ~8%
Our study = >2% - ≤4%

Chapter 3

The real-world effect of male circumcision on the risk of HIV infection in sub-Saharan Africa: a household fixed-effects analysis of 279,351 men from 29 countries

Caroline A. Bulstra, Xiaochen Dai, Molly S. Rosenberg, Beatrice M. Wamuti, Kenneth Ngure, Jan A.C. Hontelez, Joshua A. Salomon, Katrina F. Ortblad, Till Bärnighausen

Under review

ABSTRACT

Background: Male medical circumcision reduces the individual-level risk of HIV acquisition by approximately 60% in randomised-controlled trials. However, little is known about the 'real-world' long-term effect of male circumcision, including voluntary medical male circumcision (VMMC), on the cumulative risk of HIV infection. We estimate these effects for the first time using a quasi-experimental study design, household fixed-effects analysis, for sub-Saharan Africa, the world region with the largest burden of HIV.

Methods: We pooled individual-level data from the nationally-representative Demographic and Health Surveys (DHS) and AIDS Indicator Surveys (AIS) across all sub-Saharan African countries in which the surveys included data on both male circumcision and HIV status. We estimated the effect of men's circumcision status on HIV status using modified Poisson regression models with household fixed-effects, which control for unobserved and observed confounding shared by men living in the same household, and additional individual-level controls for demographic characteristics, socioeconomic factors, and sexual behaviour.

Results: We included individual data from 279,351 male participants in 48 nationally-representative surveys conducted in 29 countries between 2003 and 2018. Mean survey-level male circumcision prevalence was 65.9% (median 84.5%, interquartile range (IQR) 28.8%–68.1%) and mean survey-level HIV prevalence was 5.6% (median 2.5%, IQR 1.2%–10.2%). Circumcised men had 0.81 times (95% CI 0.73–0.89) the risk of living with HIV compared to uncircumcised men, implying a 19% (11%–27%) real-world reduction in HIV risk at the population level.

Conclusions: The 'real-world', long-term effect of male circumcision on the risk of HIV infection has been significant during the recent era of HIV antiretroviral treatment (ART) scale-up to very high coverage levels in sub-Saharan Africa. Increased political and financial commitment to VMMC would likely lead to further substantial reductions in HIV prevalence in the long term, in particular in the majority of countries in sub-Saharan Africa where circumcision coverage remains far below universal levels.

Key words: Male circumcision, voluntary medical male circumcision (VMMC), HIV prevention, survey data, quasi-experimental, sub-Saharan Africa

KEY MESSAGES

- Medical male circumcision has been highly efficacious in reducing HIV acquisition in clinical trials, but the evidence on 'real-world' long-term effects of male circumcision on the risk of HIV infection remains sparse, and traditional circumcision also confers protective effects on HIV acquisition.

- In our study of 279,351 men observed in 48 nationally-representative surveys in 29 countries we employ a robust quasi-experimental design, household fixed-effects analysis, to establish the effect of both medical and traditional circumcision on cumulative risk of HIV infection, over the period 2003-2018.

- Male circumcision reduced the risk of HIV infection by approximately one-fifth among men in sub-Saharan Africa during the period of antiretroviral treatment (ART) scale-up and treatment-as-prevention.

- Increased investments in male circumcision campaigns would likely substantially reduce HIV prevalence in sub-Saharan African countries where circumcision coverage remains low.

INTRODUCTION

Randomised-controlled trials in Uganda, Kenya, and South Africa have established the efficacy of medical male circumcision [1,2] in reducing HIV incidence [3–6], and it is likely that men who have been circumcised as part of traditional cultural practices also benefit from protective effects against HIV [7–9]. The World Health Organisation (WHO) and The Joint United Nations Programme on HIV/AIDS (UNAIDS) thus recommend voluntary medical male circumcision (VMMC) in uncircumcised men living in countries suffering from high burdens of HIV [2,10].

While the causal efficacy of male circumcision in randomised-controlled trials has to be established in terms of incident HIV infection, the ultimate aim of male circumcision campaigns is to reduce the burden of HIV in a population, *i.e.*, HIV prevalence. Strong protective effects of circumcision on HIV acquisition are not meaningful if they ultimately do not lead to substantial long-term reductions in HIV prevalence and thus the burden of HIV and HIV treatment needs in a population [10,11]. Randomised-controlled trials cannot be used to measure the long-term real-life effects of male circumcision on HIV prevalence in entire countries. The strongest approaches to causal inference available are thus quasi-experimental methods [12–14]. While mathematical models can try predict the effects of male circumcision on HIV prevalence, these predictions may not materialise in real-world implementation of circumcision, because these models are necessarily reductionist in their representation of reality and because empirical data on phenomena they do capture are not available or inaccurate [15].

We aim to advance the extant literature on the real-life effectiveness of male circumcision for HIV prevention in two important ways. First, we determine the effects of male circumcision on the cumulative risk of HIV infection, which is the individual-level correlate to population-level measure of HIV prevalence. For the effect estimation we use a strong method of causal inference, household fixed-effects analysis [12,13,16,17]. By including a fixed-effect for each household in our analysis, we control for all unobserved and observed confounding at the level of the household – including household culture, household social position, the distance of a person's residence to other men who are circumcised, the distance of a person's residence to traditional healers and circumcision infrastructures, household income and expenditures. This type of analysis controlling for all unobserved confounding at the household level comes at the price of large reductions in statistical efficiency and we thus require large sample sizes for effect estimation. We achieve such sample sizes by pooling 48 national surveys from 29 countries. Second, we quantify the real-life long-term effects of male circumcision on the cumulative risk of HIV infection in the world region that is most heavily affected by HIV during the era of antiretroviral treatment (ART) scale-up and treatment-as-prevention. The surveys we used cover the period 2003 to 2018.We estimate

the effect of all circumcision types, both medical and traditional, on the cumulative risk of HIV infection.

Our results will thus provide important insight to policy makers on the real-life effect of male circumcision on HIV burdens and treatment needs in the era of HIV treatment-as-prevention. Such results, if effects are large, can boost political and financial commitment to an efficacious prevention intervention that to this date has not been as vigorously supported as might have been expected based on the successful efficacy randomised-controlled trials, leading to male circumcision coverage being below major global policy goals [2,18–20].

METHODS

Setting

Our analyses focused on countries across sub-Saharan Africa. HIV prevalence among people ages 15-49 years is 6.7% in Eastern and Southern Africa and 1.4% in Western and Central Africa [21]. Male circumcision prevalence is over 95% in settings where traditional circumcision is common practice – *e.g.*, Western and Central Africa, but generally less than 40% in settings where it is not common practice – *e.g.*, most of Eastern and Southern Africa [22]. From 2008-2012, national VMMC campaigns were initiated and scaled-up in 14 countries including: Kenya, Malawi, South Africa, Swaziland and Zambia starting in 2008; Ethiopia, Mozambique, Namibia, Rwanda, Tanzania and Zimbabwe starting in 2009; Uganda and Rwanda starting in 2010; and Lesotho starting in 2012 [23].

Survey data

We used individual-level, cross-sectional Demographic and Health Survey (DHS) and AIDS Indicator Survey (AIS) data for our analyses. The DHSs are nationally-representative household surveys that include a wide range of socioeconomic, (sexual) behavioural, and epidemiological variables. The AISs are nationally-representative household surveys that were developed in addition to the DHS to measure additional indicators for effective monitoring of national HIV programmes. In both DHS and AIS, around 350 sample locations or 'clusters' are randomly sampled throughout the country. Within each cluster, around 25 households are sampled and all willing residents in the household are independently interviewed. Self-reported male circumcision is included in most men's questionnaires in both DHS and AIS surveys. Most DHS and AIS in sub-Saharan Africa also include HIV status data. HIV status is determined via voluntary, blood-based HIV testing that uses an enzyme-linked immunosorbent assay (ELISA). More details on survey protocols and questionnaires can be found on the DHS website (https://dhsprogram.com/). The DHS and AIS have been completed in 44 sub-Saharan African countries.

We included all DHSs and AISs that (i) were conducted between 2000 and 2020 in sub-Saharan African countries and (ii) contained both male circumcision and HIV status data in the same survey in our analysis. This resulted in a dataset that comprised 48 surveys from 29 countries. An overview of the available surveys by country, year, and survey type are provided in **Table 1** and **Supplementary Figure 1**. A flow chart of the data selection is provided in **Supplementary Figure 2**.

Variables

Our main variables of interest are male circumcision (self-reported as circumcised or not circumcised, not restricted by type of circumcision) and HIV status (based on ELISA blood test results; HIV-positive or HIV-negative). The effect size we are estimating by relating these variables to each other in regressions is the effect of male circumcision on the cumulative risk of HIV infection up to the average age at which men participated in the surveys in this study. We extracted the following additional variables from the DHS and AIS data: sociodemographic variables (age, educational attainment, marital status, and household wealth); sexual behaviour – (number of lifetime sex partners, number of sex partners in the past 12 months, and diagnosed sexual transmitted infection (STI) or signs of a STI (genital sore/ulcer or genital discharge) in the past 12 months); and variables on circumcision status and type of circumcision (medical or traditional)).

Statistical analyses

We used household fixed-effects analysis [12,13,24,25] to estimate the effect of male circumcision on the cumulative risk of HIV infection among men 15 years or older. Household fixed-effects control for all unobserved and observed confounding at the level of the household, *i.e.*, all factors that are shared by men belonging to the same household, including household culture, household social position, the distance of a person's residence to other men who are circumcised, the distance of a person's residence to traditional healers and circumcision infrastructures, household income and expenditures. Since household fixed-effects control for unobserved confounding, just like randomised-controlled trials, they are often classified as quasi-experiments [13]. While household fixed-effects control for all confounding at the household level, including unobserved confounding, they do not control for confounding at the individual level. We have thus included the following potential individual-level variables in our analysis: socioeconomic variables (age, highest completed education, marital status) and sexual behaviour (number of lifetime sex partners and having had an STI or symptoms of an STI in the past 12 months). We regress the outcome, HIV status, on the explanatory variables using modified Poisson models, because the risk ratios that Poisson models generate are easier to understand and interpret than the odds ratios that other binary models generate [26].

The household fixed-effects regression has the form:

$$\ln(Y_{ih}) = \alpha + \beta MC_{ih} + \gamma X_{ih} + \mu_h + \varepsilon_{ih}$$

where Y_{ih} is the HIV status of man *i* from household *h*. MC_{ih} is the man *i*'s self-reported circumcision. β is the main parameter of interest in this study: the conditional association between male circumcision and HIV status. X_{ih} is a vector of man *i*'s characteristics. μ_h is the household fixed-effect and ε_{ih} is the error term.

Sensitivity analyses

We ran different sensitivity analyses to verify robustness of our estimates: (1) an unadjusted model, (2) a model that only adjusted for age, and (3) a model that adjusted for age and educational attainment, and (4) a model adjusted for age, educational level and marital status. We also compared our findings from the main model to the outcomes from applying the model on only the sub-sample of men who live in the same household but differ in male circumcision status (discordant men).

Sub-group analyses

We performed various sub-group analyses to test the robustness of our outcomes and estimate potential heterogeneity in effect sizes across different sub-groups of interest. First, we conducted separate analyses for men from Central, Eastern, Southern, and Western Africa (regions according to the African Union [27]) to understand how effects vary in relation to the geographical location of the participants in our study (*i.e.*, Western and Central Africa with higher proportions of traditional circumcision versus Eastern and Southern Africa with higher proportions of VMMC). Second, we conducted separate analyses for younger (aged 15-34 years) and older (aged 35-54 years) men to explore possible effect modification by age. Third, we performed separate analyses for surveys conducted at times when VMMC campaigns were in place (*i.e.*, launched at least one year before collection of the survey data) versus when no VMMC campaigns were in place to understand the effect of circumcision during times of VMMC access. We obtained data on the start dates of VMMC campaigns from the latest available WHO and UNAIDS VMMC progress report [28], an overview is provided in **Supplementary Table 1**. The priority region for VMMC is shown in **Supplementary Figure 3**. We conducted separate analyses by family relatedness, *i.e.*, for brothers living in the same household, to explore possible biological heterogeneities in the effect of male circumcision on HIV status. Finally, we stratified by national-level HIV prevalence and national-level antiretroviral treatment coverage in the opposite sex (*i.e.*, women) to assess possible biases from antiretroviral treatment (ART).

Table 1. Survey characteristics by African region. Unweighted HIV and circumcision prevalence estimates.

African region, country	Survey year(s)	Sample size (N)	Survey type	HIV-positive men (HIV prevalence)	Circumcised men (circumcision prevalence)
Central Africa					
Burundi	2010	4,078	DHS	56 (1.4%)	1,450 (35.6%)
	2016-17	7,377	DHS	53 (0.7%)	3,191 (43.3%)
Chad	2014-15	4,925	DHS	61 (1.2%)	4,748 (96.8%)
Congo DR	2007	4,305	DHS	43 (1.0%)	4,167 (97.1%)
Gabon	2012	5,502	DHS	168 (3.1%)	5,460 (99.3%)
Eastern Africa					
Ethiopia	2011*	13,015	DHS	182 (1.4%)	11,987 (92.3%)
	2016*	11,327	DHS	115 (1.0%)	10,443 (92.5%)
Kenya	2008-09*	3,095	DHS	154 (5.0%)	2,597 (83.9%)
Rwanda	2005	4,728	DHS	115 (2.4%)	929 (19.7%)
	2010*	6,296	DHS	154 (2.4%)	853 (13.6%)
	2014-15*	6,191	DHS	161 (2.6%)	1,803 (29.1%)
Tanzania	2007-08	6,333	AIS	199 (3.1%)	4,822 (76.4%)
Uganda	2011*	9,920	AIS	595 (6.0%)	2,753 (27.8%)
Southern Africa					
Angola	2015-16	5,150	DHS	70 (1.4%)	4,953 (96.6%)
Eswatini	2006-07	3,602	DHS	704 (19.5%)	298 (8.3%)
Lesotho	2004	2,797	DHS	415 (18.6%)	1,433 (51.4%)
	2009	3,075	DHS	543 (17.7%)	1,724 (56.1%)
	2014*	2,775	DHS	527 (19.0%)	2,066 (74.5%)
Malawi	2010*	6,512	DHS	530 (8.1%)	1,203 (18.5%)
	2015-16*	6,855	DHS	477 (7.2%)	1,738 (25.4%)
Mozambique	2009*	4,404	AIS	442 (10.0%)	2,259 (51.4%)
	2015*	4,436	AIS	480 (10.9%)	2,667 (60.2%)
Namibia	2013*	3,874	DHS	419 (10.8%)	995 (25.8%)
South Africa	2016*	2,136	DHS	310 (14.5%)	1,170 (54.9%)
Zambia	2007	5,161	DHS	649 (12.6%)	805 (15.6%)
	2013-14*	13,574	DHS	1,573 (11.6%)	3,316 (24.5%)
	2018*	11,547	DHS	925 (8.0%)	3,642 (31.6%)
Zimbabwe	2005	5,566	DHS	782 (14.1%)	593 (10.7%)
	2010-11*	7,480	DHS	811 (13.4%)	696 (9.4%)
	2015*	7,420	DHS	889 (12.0%)	1,205 (16.3%)
Western Africa					
Burkina Faso	2003	3,605	DHS	46 (1.4%)	3,069 (85.1%)
	2010	7,039	DHS	60 (0.9%)	6,119 (87.0%)
Cameroon	2004	5,044	DHS	215 (3.1%)	4,782 (94.9%)

Table 1. Survey characteristics by African region. Unweighted HIV and circumcision prevalence estimates. (*continued*)

African region, country	Survey year(s)	Sample size (N)	Survey type	HIV-positive men (HIV prevalence)	Circumcised men (circumcision prevalence)
	2011	6,948	DHS	759 (3.9%)	6,629 (95.5%)
Cote d'Ivoire	2005	19,650	AIS	127 (2.9%)	18,798 (96.2%)
	2011-12	4,352	DHS	43 (1.3%)	4,197 (96.5%)
Ghana	2003	5,015	DHS	45 (1.1%)	4,648 (92.7%)
	2014	4,161	DHS	35 (1.2%)	3,860 (92.8%)
Guinea	2005	2,930	DHS	56 (1.5%)	2,896 (98.9%)
Liberia	2007	5,207	DHS	58 (1.1%)	5,093 (98.7%)
	2013	3,805	DHS	45 (1.2%)	3,767 (99.2%)
Mali	2006	3,886	DHS	32 (1.0%)	3,789 (97.6%)
	2012-13	3,751	DHS	31 (0.8%)	3,680 (98.3%)
Niger	2006	3,232	DHS	32 (1.0%)	3,215 (99.5%)
Senegal	2005	3,251	DHS	13 (0.4%)	3,185 (98.1%)
Sierra Leone	2008	3,009	DHS	32 (1.1%)	2,900 (97.9%)
	2013	6,735	DHS	81 (1.2%)	6,694 (99.6%)
Togo	2013-14	4,365	DHS	72 (1.6%)	4,240 (97.1%)
Sub-Saharan Africa (all data)					
Survey-level mean, median (IQR)	N/A	344,832	N/A	15,652 (4.7%)	181,696 (64.7%)

* Data collected in country and year when voluntary medical male circumcision (VMMC) campaigns in place.

Data management and analyses were done using R version 3.6.2 and Stata version 15.0, maps were created using ArcGIS version 2.3.0.

RESULTS

We obtained individual-level data from 29 countries and 48 surveys between 2003 and 2018 (**Table 1**). In the sample of complete-case analysis, 344,832 men from 241,447 different households were included. The number of men per survey ranged from 2,136 men (South Africa, 2016) to 19,650 men (Cote d'Ivoire, 2015-16). For 279,351 men, both circumcision and HIV status were available. These men resided in 195,803 different households; 94,609 men (33.9%) came from households where two or more men were included in the data subset. The mean age of men in the sample was 30.4 years (standard deviation 11.6 years). Survey-level mean (unweighted) HIV prevalence levels varied by African region, ranging from 0.5% to 3.1% in Central Africa, 0.5% to 3.9% in Western Africa, 1.0% to 6.0% in Eastern

Table 2. Characteristics of our data sample.

	All included men N (% of total)	Number of men living with HIV (HIV prevalence, %)	Number of circumcised men (circumcision prevalence, %)
Sample size	344,832	15,952 (4.7)	183,460 (64.7)
HIV status			
Positive	15,952 (4.7)	N/A	6,257 (42.6)
Negative	322,794 (95.3)	N/A	175,004 (66.1)
Male circumcision status			
Circumcised	183,460 (64.7)	6,257 (3.4)	N/A
Not circumcised	100,088 (35.3)	8,440 (8.4)	N/A
Sociodemographic characteristics			
Age (per 10-year age group)			
15-24	132,724 (38.5)	2,045 (1.6)	67,435 (61.9)
25-34	91,326 (26.5)	4,963 (5.5)	49,928 (66.4)
35-44	67,968 (19.7)	5,468 (8.2)	37,309 (67.1)
45-54	42,206 (12.2)	2,976 (7.2)	23,105 (66.0)
55+	10,608 (3.1)	500 (4.7)	5,683 (65.0)
Highest education			
No education	75,403 (21.9)	1,859 (2.5)	48,779 (82.0)
Primary	129,201 (37.5)	6,648 (5.2)	59,434 (55.2)
Secondary	120,958 (35.1)	6,398 (5.4)	63,559 (63.7)
Post-secondary	19,245 (5.6)	1,046 (5.6)	11,680 (71.0)
Socioeconomic status			
1 'Poorest'	66,980 (19.4)	2,422 (3.7)	35,093 (64.9)
2	66,485 (19.3)	2,698 (4.1)	34,643 (63.9)
3	65,708 (19.1)	2,970 (4.6)	33,607 (62.2)
4	67,275 (19.5)	3,707 (5.6)	34,781 (62.7)
5 'Wealthiest'	78,381 (22.7)	4,155 (5.5)	45,335 (69.0)
Marital status			
Never married	141,046 (41.6)	2,917 (2.1)	73,539 (62.8)
Currently married	184,183 (54.3)	10,880 (6.0)	101,967 (66.0)
Previously married	13,941 (4.1)	1,885 (13.8)	7,953 (66.2)
Family relatedness			
Brothers (living in the same household)	73,010 (22.5)	1,865 (2.6)	35,633 (48.8)
Other	250,959 (77.5)	13,262 (5.3)	127,231 (50.7)
(Sexual) behavioural characteristics			
Lifetime sex partners			
None	97,150 (29.2)	1,973 (2.1)	50,756 (65.6)
1-2	89,459 (26.9)	2,375 (2.7)	44,379 (59.8)
3-6	88,331 (26.5)	5,809 (6.6)	45,619 (61.5)
7+	58,127 (17.5)	4,910 (8.5)	34,485 (72.5)
Had STI during past 12 months			
Yes	18,541 (5.4)	1,819 (9.9)	10,010 (63.8)
No	325,962 (94.6)	14,122 (4.4)	173,321 (64.8)
Ever engaged in transactional sex			
Yes	19,794 (11.1)	1,844 (9.5)	9,392 (58.8)
No	159,146 (88.9)	7,213 (4.6)	84,905 (64.3)

Table 2. Characteristics of our data sample. (*continued*)

	All included men N (% of total)	Number of men living with HIV (HIV prevalence, %)	Number of circumcised men (circumcision prevalence, %)
Survey characteristics			
Region			
Central Africa	41,388 (12.0)	599 (1.5)	20,125 (73.8)
Eastern Africa	83,661 (24.3)	2,401 (3.0)	39,247 (61.0)
Southern Africa	98,768 (28.6)	10,789 (11.2)	32,527 (33.8)
Western Africa	121,015 (35.1)	2,163 (1.8)	91,561 (95.7)
Time of survey			
Between 2000-2004	40,308 (11.7)	1,451 (3.9)	28,853 (88.1)
Between 2005-2009	106,046 (30.8)	4,965 (4.7)	71,250 (76.3)
Between 2010-2014	136,072 (39.5)	6,111 (4.5)	60,358 (57.3)
Between 2015-2019	62,406 (18.1)	3,425 (5.5)	22,999 (44.1)
National VMMC campaigns in place			
Yes	127,751 (39.4)	8,963 (7.0)	51,240 (40.1)
No	196,218 (60.6)	6,164 (3.1)	111,624 (56.9)

Africa, and 1.4% to 19.5% in Southern Africa. Unweighted self-reported mean male circumcision prevalence ranged from 8.9% to 96.6% in Southern Africa, 13.6% to 92.5% in Eastern Africa, 35.6% to 99.3% in Central Africa, and 85.1% to 99.6% in Western Africa.

The sociodemographic characteristics for the men included in the sample – broken down by HIV-positive men (4.7%, n=15,952) and circumcised men (64.7%, n=183,460) – are presented in **Table 2**. HIV prevalence was lower in circumcised (3.5%, n=6,257) versus uncircumcised (8.6%, n=8,440) men. In the sample, 38.5% (n=132,724) of men were between 15-24 years of age and HIV prevalence was lowest among this age group (1.6%) and highest among men 35-44 years of age (8.2%), followed by men 45-54 years (7.2%). There was little variation in circumcision prevalence by age group.

The African regions and included countries are shown in **Supplementary Figure 3**. The prevalence of circumcision among men in sub-Saharan Africa is shown in **Figure 1: panels A, B and C**. Male circumcision varied widely across countries and across the African regions. In Western and Central Africa, circumcision prevalence was consistently high: over 85% of men, or in some countries over 98% of men, were circumcised. In Eastern and Southern Africa, larger variability in circumcision prevalence was observed: with prevalence levels of below 30% or 60% in the majority of the Southern African countries (*e.g.,* in Malawi, Zambia, Zimbabwe, Namibia, South Africa, and Lesotho), but circumcision prevalence levels of above 60% in Ethiopia and Kenya. The prevalence of HIV among men in sub-Saharan Africa is shown in **Figure 1: panels D, E and F**. HIV prevalence was highest (above 15%) in

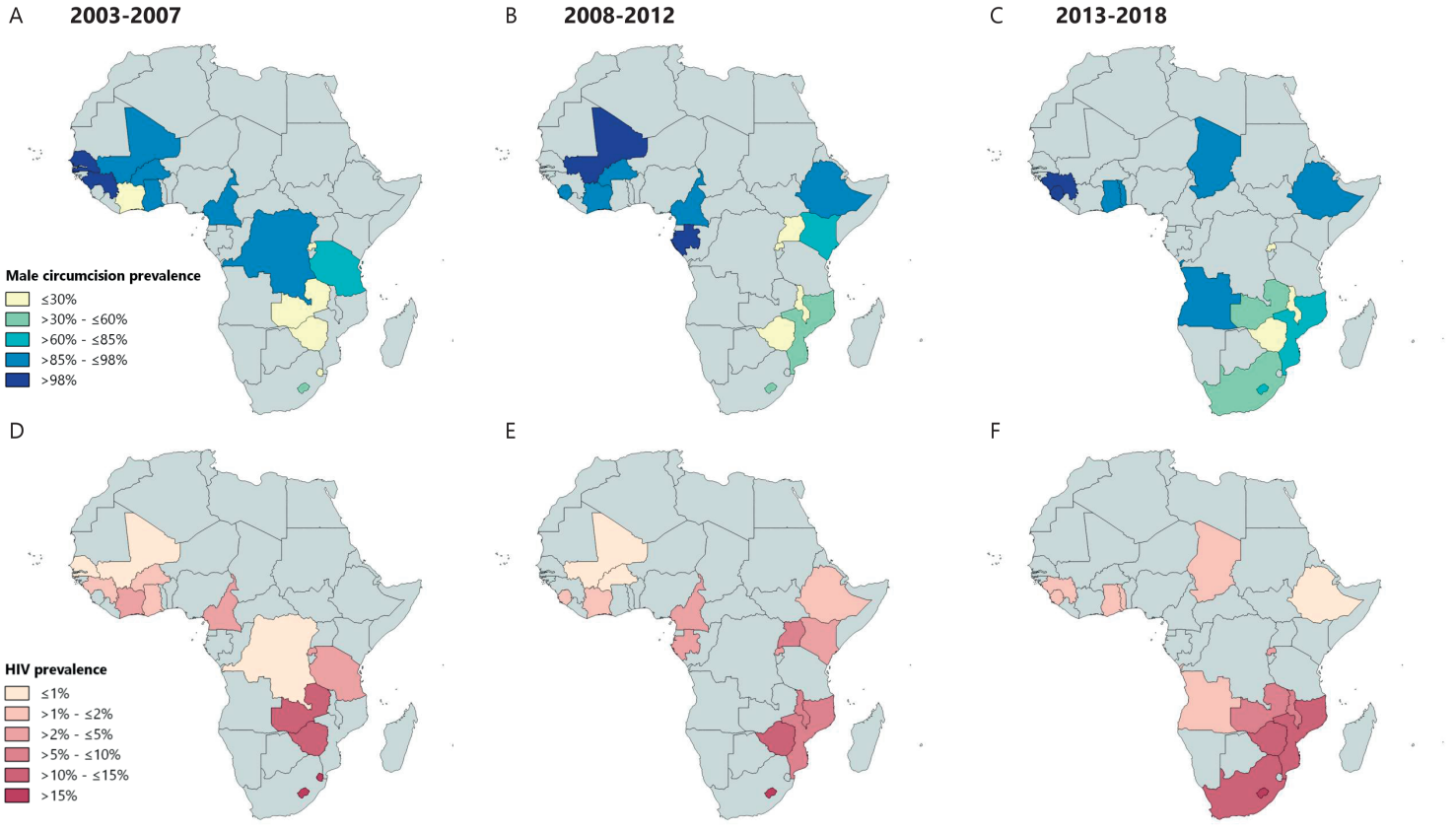


Figure 1. Maps show the national-level male circumcision prevalence from the surveys conducted between 2003-2007 (panel A), 2008-2012 (panel B), and 2013-2018 (panel C) and national-level HIV prevalence levels in men from the surveys conducted between 2003-2007 (panel D), 2008-2012 (panel E), and 2013-2018 (panel F). Countries without surveys for the representative time period are coloured grey. Data available via https://www.dhsprogram.com/

Eswatini and Lesotho. Namibia, South Africa, Zimbabwe, Malawi, and Mozambique had an HIV prevalence of between 10% and 15%. HIV prevalence was generally low below 1% or below 2%, in countries throughout Western and Central Africa.

Table 2. The estimated effect of male circumcision on living with HIV among men (15 years and older) in sub-Saharan Africa.

	Main model – adjusted for age, educational level, marital status and sexual behaviour	
Variable	**aRR [95% CI]**	**p-value**
Male circumcision status		
Circumcised	0.81 [0.73–0.89]	<0.001
Not circumcised	1 (ref)	-
Age		
15-24	1 (ref)	-
25-34	2.30 [2.06–2.57]	<0.001
35-44	2.92 [2.57–3.32]	<0.001
45-54	3.10 [2.70–3.57]	<0.001
55+	2.15 [1.71–2.71]	<0.001
Highest education		
No education	1.06 [0.94–1.21]	0.309
Primary	1 (ref)	-
Secondary	1.00 [0.92–1.09]	0.941
Post-secondary	1.00 [0.85–1.17]	0.961
Marital status		
Never married	1 (ref)	-
Currently married	1.51 [1.36–1.68]	<0.001
Previously married	2.01 [1.77–2.28]	<0.001
Lifetime sex partners		
None	0.99 [0.86–1.14]	0.902
1-2	1 (ref)	-
3-6	1.20 [1.08–1.32]	<0.001
7+	1.30 [1.16–1.45]	<0.001
Had STI during past 12 months		
Yes	1 (ref)	-
No	1.45 [1.30–1.61]	<0.001
Model summary		
N (observations)	18,836	
Pseudo R^2	0.239	

Adjusted risk ratios (aRR) are shown with 95% confidence intervals (CIs). The analysis includes household-level fixed-effects. Schooling levels are defined as the highest level of education attained. Previously married includes being divorced, separated, or widowed. The number of observations (N) includes men from all households where at least two circumcision discordant men (*i.e.,* at least one man circumcised and one uncircumcised).

Figure 1 shows geographical maps visualising national-level male circumcision prevalence and HIV prevalence from the DHSs and AISs in our sample. If multiple surveys were available for a country, the mean weighted prevalence levels were displayed. In our main analysis, the adjusted risk ratio (aRR) for living with HIV was 0.81 (95% confidence interval (CI) 0.73–0.89) among circumcised men compared to for uncircumcised men in sub-Saharan Africa, which

corresponds to a 19% (95% CI 11%–27%) real-world reduction in HIV risk at the population level (**Table 2**). These findings were confirmed in the other four sensitivity analyses, which resulted in similar outcomes (**Supplementary Table 2**) as well as in the main model based on the sub-sample of men living in the same household but with discordant circumcision status (**Supplementary Table 3**).

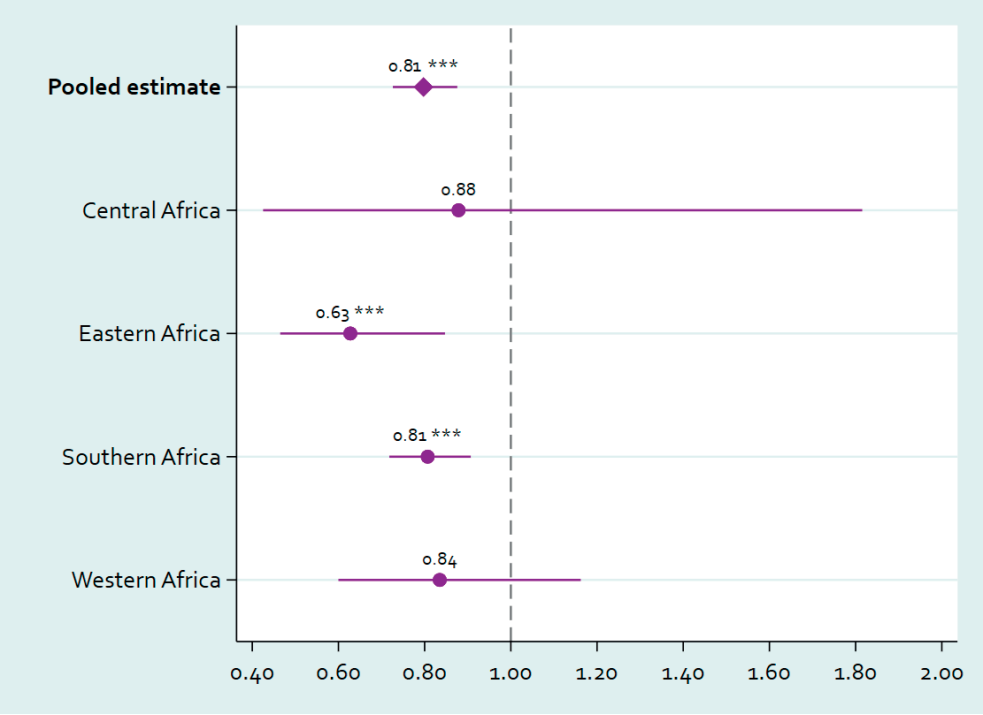


Figure 2. Population-wide effect of male circumcision on living with HIV for men (15 years or older) in the pooled sub-Saharan Africa sample and by African region. The figure shows the adjusted risk ratios (aRRs) and 95% confidence intervals (CIs) from modified Poisson regression models with household fixed-effects. All models were adjusted for age (by 10-year age group), educational level, and marital status. The RRs represent the effects of male circumcision on the cumulative risk of HIV infection. The full regression output and sub-group analyses are presented in **Table 2** and **Supplementary Table 4** respectively. Data available via https://dhsprogram.com/.

The estimated HIV risk reduction for circumcised men varied somewhat across regions, although smaller stratified samples prohibit precise comparison: Eastern Africa (aRR 0.63, 95% CI 0.46–0.85), Southern Africa (aRR 0.81, 95% CI 0.72–0.91), Central Africa (aRR 0.88, 95% CI 0.43–1.82), Western Africa (aRR 0.84, 95% CI 0.60–1.16) (**Figure 2**). Outcomes from the other three sub-group analyses (age, prevalence of a national VMMC campaign, and brothers) are shown in **Supplementary Table 4**. Male circumcision decreased the cumulative risk of HIV infection for both younger (≤34 years) and older men (≥35 years), but was significant in younger men (aRR 0.79, 95% CI 0.69–0.91) and not in older men (aRR 0.82, 95% CI 0.63–1.06). Male circumcision significantly reduced the cumulative risk of HIV infection

in country-years with VMMC campaigns in place (aRR 0.75, 95% CI 0.66–0.85), but did not significantly affect HIV infection risk in country-years without VMMC campaigns (aRR 0.98, 95% CI 0.83–1.15). In the sub-group analysis of brothers, the circumcision effect estimate was similar to the estimate in the main analysis (aRR 0.78, 95% CI 0.66–0.91).

We checked the representativeness of our sample by comparing men from circumcision status discordant households with men in the overall population (**Supplementary Table 5**).

DISCUSSION

In this quasi-experimental analysis using nationally-representative data from 48 surveys in 29 sub-Saharan African countries, male circumcision reduced the cumulative risk of HIV infection in men by one-fifth. Our findings provide robust causal evidence on the real-life long-term effect of male circumcision in the largest study of individual-level data on male circumcision effects to date. Our findings further emphasise the potential of male circumcision for reducing the long-term burden of HIV in sub-Saharan Africa, the world region where two-thirds of people living with HIV reside [29]. Importantly, the large real-life, long-term effect that our study establishes emerged during the scale-up of ART to very high levels of coverage in sub-Saharan African (2003-2018). Male circumcision could have strong complementary preventive effects to ART and thus remain an important preventive intervention in the context of treatment-as-prevention.

Our study is the first to empirically estimate the 'real-world' effect of male circumcision on the risk of HIV infection using extensive individual-level nationally-representative survey data from sub-Saharan Africa, and by applying modified Poisson regression models with household fixed-effects. Existing observational studies on the impact of male circumcision often determined the impact on HIV incidence instead of prevalence, and were often conducted at smaller geographical scales, using cross-sectional, case-control or cohort study designs [34–37]. An earlier meta-analysis, synthesising evidence from 27 observational studies that quantified the association between (traditional or medical) male circumcision and HIV status in sub-Saharan Africa, showed adjusted risk reductions of between 48% and 58% (depending on adjustment for possible confounders) [38]. The review showed that the association was much stronger among men at high risk of acquiring HIV—such as truck drivers, sex work clients, and STI clinic attendees—with an overall adjusted risk reduction of 71% (59%–80%), compared to 44% (30%–56%) among men in 'the general population' [38]. Mathematical modelling studies show that high coverage of antiretroviral therapy (ART) and male circumcision, the two main interventions intended to curb the spread of HIV, could substantially reduce HIV incidence and HIV prevalence could potentially even lead to elimi-

nation.[39,40] In Botswana and Kenya, two countries severely impact by the HIV pandemic, 80% uptake of male circumcision is predicted to reduce HIV prevalence by 45-67%, while 50% uptake would lead to 25-41% prevalence reductions [39].

Our analyses showed lower protective effects of male circumcision for Western and Central African countries and, generally, for countries without VMMC campaigns in place (at time of the survey being conducted). This may be attributed to a discrepancy in risk reduction from traditional male circumcision as compared to VMMC. Also, protective effects might be higher in settings with higher HIV incidence levels. Prospective cohort studies from rural Uganda [30] and rural Kenya [7,31], showed traditional male circumcision to be associated with an around 2-fold decrease in HIV acquisition, relative to the 3-fold decrease found in the randomised-controlled trials that implemented VMMC. However, similar studies from Central, Southern and Western Africa are lacking. Experimental and observational studies on the effectiveness of traditional male circumcision compared to VMMC on HIV incidence in different contexts outside of Eastern Africa should point out whether there is effect heterogeneity between studies from the different African regions. Although circumcision modality (traditional or medical) was available for some of the men included in our pooled data sample, missingness was very high (69.1%) and hence a household fixed-effect analysis not reliable due to the low number households with men who showed circumcision status discordance when selecting for traditional circumcision. Therefore, we cannot make definite conclusion on the effects of VMMC programmes on HIV prevalence. While there might be a real-life effect of male circumcision on HIV incidence, this might not (yet) be reflected in HIV prevalence levels, due to the relatively recent scale-up of VMMC programmes and young target population [32]. One of the major advantages of male circumcision, compared to other HIV prevention interventions, is that its effectiveness does not rely on repeated and consistent behaviours [33].

We confirm that male circumcision should be recognised as an important means to reduce the risk of HIV acquisition in men, and thereby indirectly also protecting women and children from HIV infection [41]. We recommend the continued promotion of VMMC as a public health intervention in sub-Saharan Africa, but want to underscore the importance of promoting VMMC alongside other effective behavioural and biomedical prevention interventions (*e.g.*, treatment-as-prevention and pre-exposure prophylaxis). Overall, medical male circumcision should primarily be rolled-out in communities with high HIV incidence and prevalence levels where male circumcision is not traditionally done, and could be targeted at men at higher risk of acquiring HIV such as truck drivers, sex work clients and men who have sex with men [42].

This study has a number of limitations. First, multivariable regression analyses with household fixed-effects can only provide hints on causal inference, but not claim causality with the same strength as randomised-controlled trials. Using this model, we control for all observed and unobserved household-level confounding), but there is limited control of individual-level confounding (*i.e.* unobserved individual-level confounding is not accounted for, but observed individual-level confounding is through the included model co-variates) [13,24]. Although fixed-effect models have been widely applied in econometrics and economics [25], the use in global health is relatively new, and findings should be interpreted in the light of existing evidence from traditional study designs. We believe that the use of household fixed-effect regression models on large (pooled) cross-sectional datasets forms a very promising complement to randomised-controlled trials (which are causally strong, but often conducted at small geographical scales and with weak external validity) and observational studies (which are often conducted at larger geographical scales, but associative rather than causal). Second, the sample represents a random selection of men 15 years or older with at least one other men in the same households in this age range with discordant circumcision status. Selection of households with discordant male circumcision status could have biased the circumcision effect estimates compared to the unobserved circumcision effect in the entire population. We checked the representativeness of our sample for all men 15 years or older in the surveys by comparing observed characteristics of the men included in our analyses with men in the overall population (**Supplementary Table 5**). As expected, due to likely higher rates in medical circumcision (as compared to traditional circumcision) in discordant households, men from discordant households were more often HIV-positive, younger, higher educated, and wealthier, but discrepancies were modest.

In conclusion, our findings indicate that male circumcision substantially reduces the risk of HIV infection among men in sub-Saharan Africa in the 'real-world' context of ART scale-up and treatment-as-prevention. These findings underpin the importance of scaling up VMMC, alongside other HIV prevention interventions, as an important element of HIV control and elimination strategies. Given overall low levels of male circumcision coverage in many countries in sub-Saharan Africa, the potential for impact of male circumcision on HIV burdens remains large.

Authors and contributions

CAB and TB initiated and conceptualised the study. CAB, XD, KO and TB wrote the first draft of the manuscript and verified the data and analyses. All authors reviewed, commented on, and approved the manuscript before submission for publication.

Declaration of interests

All authors are salaried employees of the institutions to which they are affiliated in the header. No specific funding was granted to support this study. All other authors declare no competing interests.

REFERENCES

1. Hallett TB, Singh K, Smith JA, White RG, Abu-Raddad LJ, Garnett GP. Understanding the impact of male circumcision interventions on the spread of HIV in southern Africa. PLOS ONE. 2008;3.
2. World Health Organization (WHO). WHO progress brief: voluntary medical male circumcision for HIV prevention in 14 priority countries in Eastern and Southern Africa, July 2017. 2017.
3. Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, *et al.* Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet. 2007; 643–656.
4. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, *et al.* Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007;369: 657–666. doi:10.1016/S0140-6736(07)60313-4
5. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 trial. PLOS Med. 2005;2: 1112–1122. doi:10.1371/journal.pmed.0020298
6. Newell M-L, Bärnighausen T. Male circumcision to cut HIV risk in the general population. Lancet. 2007;369: 617–619.
7. Shaffer DN, Bautista CT, Sateren WB, Sawe FK, Kiplangat SC, Miruka AO, *et al.* The protective effect of circumcision on HIV incidence in rural low-risk men circumcised predominantly by traditional circumcisers in Kenya: Two-year follow-up of the Kericho HIV Cohort Study. J Acquir Immune Defic Syndr. 2007;45: 371–379. doi:10.1097/QAI.0b013e318095a3da
8. Maffioli EM. Is traditional male circumcision effective as an HIV prevention strategy? Evidence from Lesotho. PLOS ONE. 2017;12: e0177076.
9. Organization WH, others. Traditional male circumcision among young people: a public health perspective in the context of HIV prevention. 2009.
10. World Health Organization (WHO), United Nations Joint Programme on HIV/AIDS (UNAIDS). A framework for voluntary medical male circumcision: effective HIV prevention and a gateway to improved adolescent boys' and men's health in eastern and southern Africa by 2021. Geneva World Heal Organ. 2016.
11. Stover J, Bollinger L, Antonio Izazola J, Loures L, DeLay P, Ghys PD, *et al.* What is required to end the AIDS epidemic as a public health threat by 2030? The cost and impact of the fast-track approach. PLOS ONE. 2016;11: 1–14. doi:10.1371/journal.pone.0154893
12. Strumpf EC, Harper S, Kaufman J. Fixed effects and difference in differences. Methods in Social Epidemiology. 2017.
13. Bärnighausen T, Oldenburg C, Tugwell P, Bommer C, Ebert C, Barreto M, *et al.* Quasi-experimental study designs series—paper 7: assessing the assumptions. J Clin Epidemiol. 2017;89: 53–66. doi:10.1016/j.jclinepi.2017.02.017
14. Bärnighausen T, Tugwell P, Røttingen J-A, Shemilt I, Rockers P, Geldsetzer P, *et al.* Quasi-experimental study designs series—paper 4: uses and value. J Clin Epidemiol. 2017;89: 21–29. doi:10.1016/j.jclinepi.2017.03.012
15. Huppert A, Katriel G. Mathematical modelling and prediction in infectious disease

epidemiology. Clin Microbiol Infect. 2013;19: 999–1005.

16. Vollmer S, Harttgen K, Subramanyam MA, Finlay J, Klasen S, Subramanian S V. Association between economic growth and early childhood undernutrition: evidence from 121 Demographic and Health Surveys from 36 low-income and middle-income countries. lancet Glob Heal. 2014;2: e225--e234.

17. Anekwe TD, Newell M-L, Tanser F, Pillay D, Bärnighausen T. The causal effect of childhood measles vaccination on educational attainment: a mother fixed-effects study in rural South Africa. Vaccine. 2015;33: 5020–5026.

18. Njeuhmeli E, Hatzold K, Gold E. Lessons Learned From Scale-Up of Voluntary Medical Male Circumcision Focusing on Adolescents: Benefits, Challenges, and Potential Opportunities for Linkages With Adolescent HIV, Sexual, and Reproductive Health Services. JAIDS. 2014;66: 193–199. Available: http://journals.lww.com/jAIDS/Abstract/2014/07011/Lessons_Learned_From_Scale_Up_of_Voluntary_Medical.7.aspx

19. Vandormael A, Akullian A, Siedner M, de Oliveira T, Bärnighausen T, Tanser F. Declines in HIV incidence among men and women in a South African population-based cohort. Nat Commun. 2019;10: 1–10.

20. Sgaier SK, Reed JB, Thomas A, Njeuhmeli E. Achieving the HIV prevention impact of voluntary medical male circumcision: lessons and challenges for managing programs. PLOS Med. 2014;11.

21. United Nations Joint Programme on HIV/AIDS (UNAIDS). UNAIDS Data 2019. 2019; 476. Available: https://www.unAIDS.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf_AIDSinfo.unAIDS.org.

22. Cork MA, Wilson KF, Perkins S, Collison ML, Deshpande A, Eaton JW, *et al.* Mapping male circumcision for HIV prevention efforts in sub-Saharan Africa. 2020; 1–15.

23. Sgaier SK, Reed JB, Thomas A, Njeuhmeli E. Achieving the HIV Prevention Impact of Voluntary Medical Male Circumcision : Lessons and Challenges for Managing Programs. PLOS Med. 2014;11. doi:10.1371/journal.pmed.1001641

24. Bärnighausen T, Røttingen J-A, Rockers P, Shemilt I, Tugwell P. Quasi-experimental study designs series—paper 1: introduction: two historical lineages. J Clin Epidemiol. 2017;89: 4–11.

25. Brüderl J, Ludwig V. Fixed-effects panel regression. The Sage handbook of regression analysis and causal inference. Sage Los Angeles; 2015. pp. 327–358.

26. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159: 702–706.

27. African Union. Regions African Union. 2017. Available: http://www.west-africa-brief.org/content/en/six-regions-african-union

28. WHO, UNAIDS. Voluntary medical male circumcision: Progress Report. 2019. Available: https://www.who.int/publications/i/item/voluntary-medical-male-circumcision-progress-brief-2019

29. United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS data 2021. 2021. Available: https://www.unAIDS.org/sites/default/files/media_asset/JC3032_AIDS_Data_book_2021_En.pdf

30. Gray RH, Kiwanuka N, Quinn TC, Sewankambo NK, Serwadda D, Mangen FW, *et al.* Male circumcision and HIV acquisition and transmission: Cohort studies in Rakai, Uganda. AIDS. 2000;14: 2371–2381. doi:10.1097/00002030-200010200-00019

31. Baeten JM, Richardson BA, Lavreys L, Rakwar JP, Mandaliya K, Bwayo JJ, *et al.* Female-to-male infectivity of HIV-1 among circumcised and uncircumcised Kenyan men. J Infect Dis. 2005;191: 546–553. doi:10.1086/427656

32. Grabowski MK, Serwadda DM, Gray RH, Nakigozi G, Kigozi G, Kagaayi J, *et al.* HIV prevention efforts and incidence of HIV in Uganda. N Engl J Med. 2017;377: 2154–2166.

33. Ortblad KF, Harling G, Chimbindi N, Tanser F, Salomon JA, Bärnighausen T. Does Incident Circumcision Lead to Risk Compensation? Evidence from a Population Cohort in KwaZulu-Natal, South Africa. J Acquir Immune Defic Syndr. 2019;80: 269–275. doi:10.1097/QAI.0000000000001912

34. Amusa L, Zewotir T, North D, Kharsany ABM, Lewis L. Medical male circumcision and HIV prevention among men in Kwazulu-Natal, South Africa: A propensity score analysis. Sci African. 2021;11: e00683.

35. Korenromp EL, Bershteyn A, Mudimu E, Weiner R, Bonecwe C, Loykissoonlal D, *et al.* The impact of the program for medical male circumcision on HIV in South Africa: analysis using three epidemiological models. Gates Open Res. 2021;5.

36. Hines JZ, Sachathep K, Pals S, Davis SM, Toledo C, Bronson M, *et al.* HIV incidence by male circumcision status from the Population-Based HIV Impact Assessment Surveys—Eight sub-Saharan African countries, 2015--2017. JAIDS J Acquir Immune Defic Syndr. 2021;87: S89--S96.

37. Davis S, Toledo C, Lewis L, Maughan-Brown B, Ayalew K, Kharsany ABM. Does voluntary medical male circumcision protect against sexually transmitted infections among men and women in real-world scale-up settings? Findings of a household survey in KwaZulu-Natal, South Africa. BMJ Glob Heal. 2019;4: e001389.

38. Weiss H a, Quigley M a, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. AIDS. 2000;14: 2361–2370. doi:10.1016/S1473-3099(09)70235-X

39. Nagelkerke NJD, Moses S, de Vlas SJ, Bailey RC. Modelling the public health impact of male circumcision for HIV prevention in high prevalence areas in Africa. BMC Infect Dis. 2007;7: 1–15.

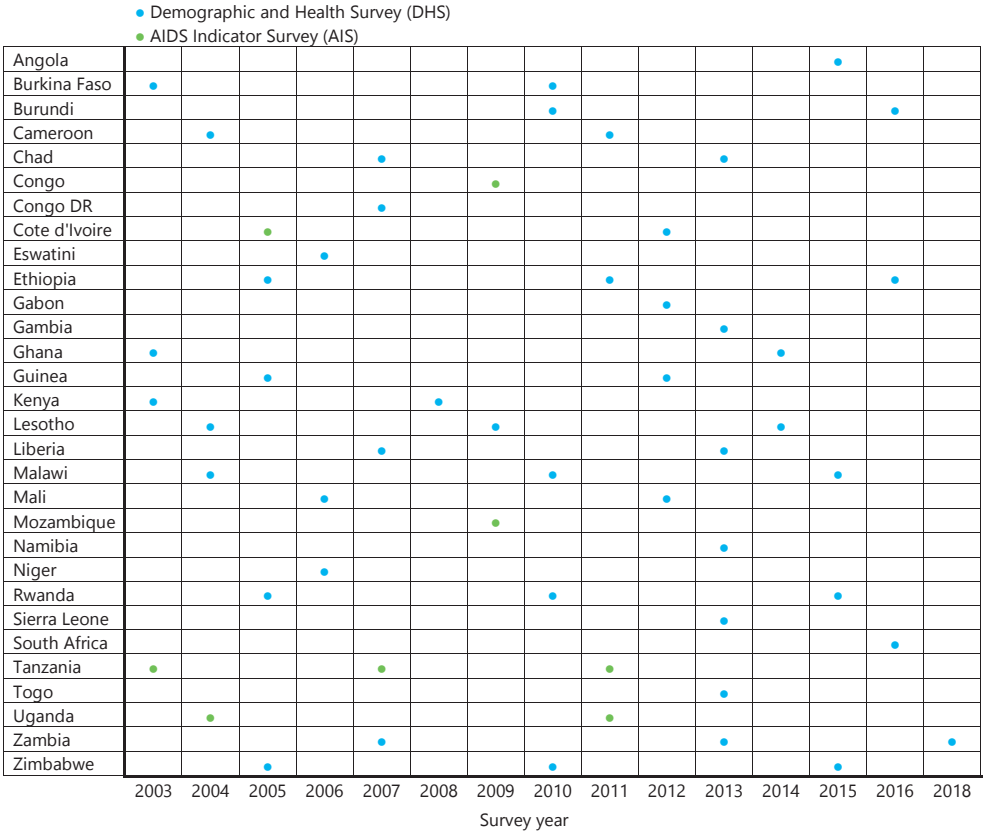
40. Hontelez JAC, Lurie MN, Bärnighausen T, Bakker R, Baltussen R, Tanser F, *et al.* Elimination of HIV in South Africa through expanded access to antiretroviral therapy: a model comparison study. PLOS Med. 2013;10: e1001534.

41. Weiss HA, Hankins CA, Dickson K. Male circumcision and risk of HIV infection in women: a systematic review and meta-analysis. Lancet Infect Dis. 2009;9: 669–677. doi:10.1016/S1473-3099(09)70235-X

42. UNAIDS. Blind Spot: Reaching out to men and boys. 2017. Available: https://www.unAIDS.org/sites/default/files/media_asset/blind_spot_en.pdf

SUPPORTING INFORMATION TO CHAPTER 3

Supplementary Figure 1. Data availability by country and year. Surveys were included when self-reported male circumcision status and HIV blood-test result were available for men between 15 years of age and 49 years or older.



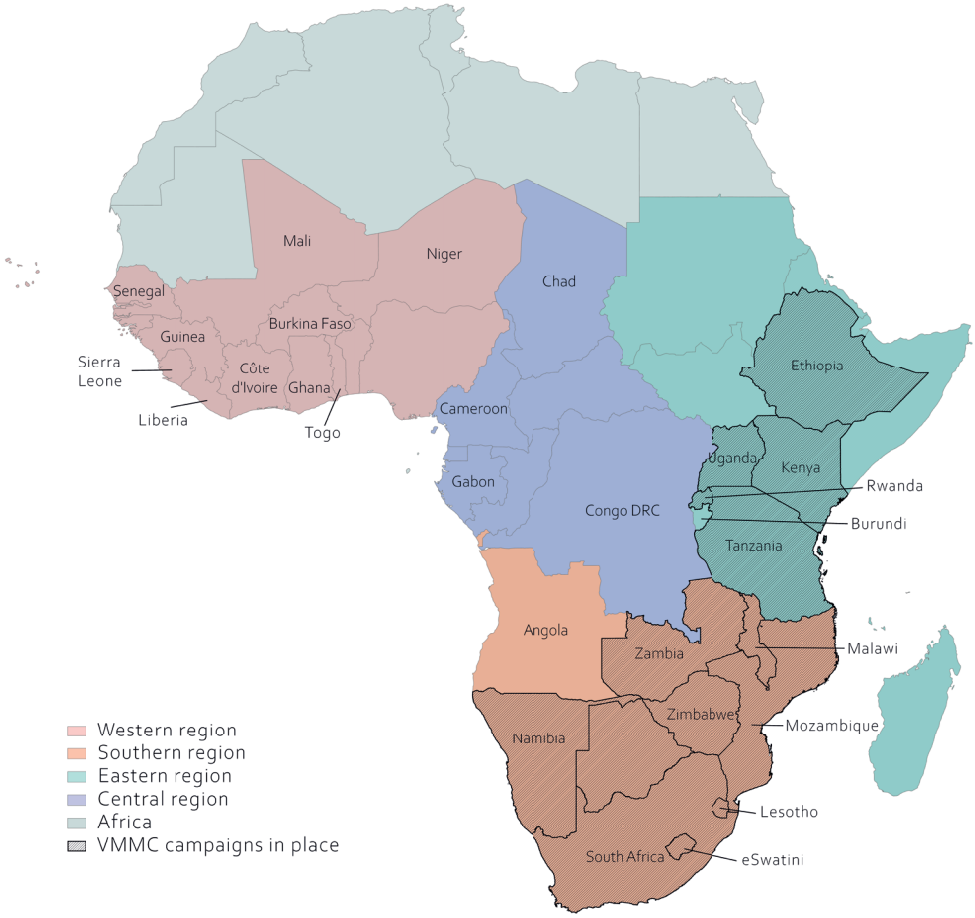
Supplementary Figure 2. Flow chart of the data selection.

Available **Demographic and Health Surveys** (DHS) and **AIDS Indicator Surveys** (AIS) conducted in **sub-Saharan Africa** between **2000 and 2020**	Sub-Saharan Africa, overall **38** countries, **107** surveys	Central Africa **7** countries, **14** surveys	Eastern Africa **13** countries, **44** surveys	Southern Africa **4** countries, **8** surveys	Western Africa **14** countries, **41** surveys
Surveys that include both **HIV and male circumcision indicators**	**31** countries, **61** surveys, **344,832** males	**5** countries, **7** surveys, **41,388** males	**5** countries, **12** surveys, **83,661** males	**9** countries, **18** surveys, **98,768** males	**12** countries, **24** surveys, **121,015** males
All men with known **HIV and circumcision status**	**279,351** males	**27,239** males	**63,687** males	**93,821** males	**94,604** males
Two or more adult men per household	**94,609** males	**10,600** males	**22,306** males	**33,208** males	**28,495** males
Two or more adult men per **household** where **at least one man is uncircumcised and one is circumcised** (discordant households)	**16,846** males	**2,763** males	**4,079** males	**7,963** males	**2,041** males

Supplementary Table 1. Start year of voluntary medical male circumcision (VMMC) campaigns Eastern and Southern Africa – for the countries that were included in this study. Source: WHO and UNAIDS VMMC progress report (https://www.who.int/publications/i/item/voluntary-medical-male-circumcision-progress-brief-2019).

Country	Start year of campaigns
Ethiopia	2009
Kenya	2008
Lesotho	2012
Malawi	2008
Mozambique	2009
Namibia	2009
Rwanda	2010
South Africa	2008
Eswatini	2008
Uganda	2010
Tanzania	2009
Zambia	2008
Zimbabwe	2009

Supplementary Figure 3. Maps show the African Regions and countries with national voluntary medical male circumcision (VMMC) campaigns.



Supplementary Table 2. Modified Poisson regression models of the effect of male circumcision on HIV status among men in sub-Saharan Africa. Adjusted risk ratios (aRR) are shown with 95% confidence intervals (CIs), which are adjusted for heterogeneity at the household-level using fixed-effects. Schooling levels are defined as the highest level of education attended. Previously married includes being divorced, separated, or widowed. The number of observations (N) includes men from all households where at least two circumcision discordant men (*i.e.,* at least one man circumcised and one uncircumcised) were included in the data. Residual degrees of freedom (DF) indicate the number of independent parameters estimated by the model. The pseudo R^2 represents the proportion of the total variability explained by the model.

	Model 1 – nested model		**Model 2 – adjusted for age**		**Model 3 – adjusted for age and educational level**		**Model 4 – adjusted for age, educational level and marital status**	
Variable	**aRR [95% CI]**	**p-value**	**aRR [95% CI]**	**p-value**	**aRR [95% CI]**	**p-value**	**aRR [95% CI]**	**p-value**
Male circumcision status								
Circumcised	0.83 [0.76–0.90]	<0.001	0.81 [0.74–0.88]	<0.001	0.81 [0.74–0.88]	<0.001	0.80 [0.73–0.88]	<0.001
Not circumcised	1 (ref)	-	1 (ref)	-	1 (ref)		1 (ref)	-
Age								
15-24			1 (ref)	-	1 (ref)	-	1 (ref)	-
25-34			3.32 [3.04–3.63]	<0.001	3.32 [3.04–3.64]	<0.001	2.57 [3.24–4.12]	<0.001
35-44			4.79 [4.39–5.23]	<0.001	4.81 [4.40–5.26]	<0.001	3.22 [5.13–6.60]	<0.001
45-54			5.19 [4.73–5.70]	<0.001	5.21 [4.74–5.73]	<0.001	3.42 [5.70–7.49]	<0.001
55+			3.68 [3.07–4.41]	<0.001	3.69 [3.07–4.42]	<0.001	2.29 [2.92–4.60]	<0.001
Highest education								
No education					1.04 [0.92–1.17]	0.541	1.06 [0.87–1.27]	0.612
Primary					1 (ref)	-	1 (ref)	-
Secondary					1.03 [0.95–1.12]	0.448	1.03 [0.96–1.18]	0.256
Post-secondary					0.98 [0.84–1.14]	0.796	0.98 [0.77–1.13]	0.476
Marital status								
Never married							1	-
Currently married							1.56 [1.40–1.72]	<0.001
Previously married							2.13 [1.88–2.40]	<0.001
Model summary								
N (observations)	19,911		19,911		19,910		18,836	19,910
Pseudo R^2	0.169		0.233		0.233		0.239	0.237

Supplementary Table 3. Modified Poisson regression model of the estimated effect of male circumcision on living with HIV among men (15 years and older) in sub-Saharan Africa, based on the sub-sample of men who live in the same household but differ in male circumcision status (discordant men).

	Model – adjusted for age, educational level, and marital status	
Variable	**aRR [95% CI]**	**p-value**
Male circumcision status		
Circumcised	0.80 [0.73–0.88]	<0.001
Not circumcised	1 (ref)	-
Age		
15-24	1 (ref)	-
25-34	2.34 [1.92–2.86]	<0.001
35-44	3.01 [2.39–3.79]	<0.001
45-54	3.19 [2.50–4.06]	<0.001
55+	2.01 [1.40–2.88]	<0.001
Highest education		
No education	1.05 [0.85–1.30]	0.651
Primary	1 (ref)	-
Secondary	0.96 [0.83–1.10]	0.536
Post-secondary	1.07 [0.82–1.40]	0.594
Marital status		
Never married	1	-
Currently married	1.53 [1.26–1.86]	<0.001
Previously married	1.86 [1.48–2.33]	<0.001
Model summary		
N (observations)	7,759	
Residual DF	6,669	
Pseudo R^2	0.277	

Supplementary Table 4. Outcomes for sub-group analyses. Adjusted risk ratios (aRR) are shown with 95% confidence intervals (CIs), which are adjusted for heterogeneity at the household-level using fixed-effects. The number of observations (N) includes men from all households where at least two circumcision discordant men (*i.e.,* at least one man circumcised and one uncircumcised) were included in the data. Residual degrees of freedom (DF) indicate the number of independent parameters estimated by the model. The pseudo R^2 represents the proportion of the total variability explained by the model.

	By African region				**By age**		**By presence VMMC campaigns**		**By family relatedness**
	Central	**Eastern**	**Southern**	**Western**	**34 or younger**	**35 or older**	**VMMC campaigns launched**	**No VMMC campaigns launched**	**Brothers**
Model estimates									
Risk ratio	0.88	0.63	0.81	0.84	0.79	0.82	0.75	0.98	0.78
95% CI	0.43–1.82	0.46–0.85	0.72–0.91	0.60–1.16	0.69–0.91	0.63–1.06	0.66–0.85	0.83–1.15	0.66–0.91
Robust SE	0.33	0.10	0.05	0.14	0.057	0.110	0.046	0.083	0.064
z-score	-0.35	-3.04	-3.60	-1.07	-3.28	-1.51	-4.69	-0.29	-3.07
p-value	0.727	0.002	<0.001	0.285	<0.001	0.130	<0.001	0.768	0.002
Model summary									
N (observations)	419	1,235	7,021	11,235	10,247	2,778	5,868	14,043	3,622
Residual df	251	729	4,065	10,663	8,590	2,415	3,410	12,329	2,111
Pseudo-R^2	0.168	0.159	0.158	0.170	0.208	0.176	0.151	0.230	0.100

Supplementary Table 5. Comparison of data characteristics for all men included in the surveys versus men from circumcision discordant households.

	All men N (%)	Discordant circumcision status - N (%)
Sample size	344,832	18,182
HIV status		
Positive	15,952 (4.7%)	1,078 (6.0%)
Negative	322,794 (95.3%)	16,855 (94.0%)
Male circumcision status		
Circumcised	183,460 (64.7%)	9,184 (53.8%)
Not circumcised	100,088 (35.3%)	7,904 (46.3%)
Sociodemographic characteristics		
Age (per 10-year age group)		
34 or younger	224,050 (65.0%)	13,065 (71.9%)
35 and older	120,782 (35.0%)	5,117 (28.1%)
Highest education		
No education	75,403 (21.9%)	2,117 (11.6%)
Primary	129,201 (37.5%)	7,138 (39.3%)
Secondary	120,958 (35.1%)	7,673 (42.2%)
Post-secondary	19,245 (5.6%)	1,253 (6.9%)
Socioeconomic status		
1 'Poorest'	66,980 (19.4%)	2,737 (15.1%)
2	66,485 (19.3%)	2,935 (16.1%)
3	65,708 (19.1%)	3,159 (17.4%)
4	67,275 (19.5%)	3,714 (20.4%)
5 'Wealthiest'	78,381 (22.7%)	5,637 (31.0%)
Marital status		
Never married	141,046 (41.6%)	10,771 (59.2%)
Currently married	184,183 (54.3%)	6,639 (36.5%)
Previously married	13,941 (4.1%)	772 (4.3%)
(Sexual) behavioural characteristics		
Lifetime sex partners		
None	97,150 (29.2%)	5,964 (33.7%)
1-2	89,459 (26.9%)	4,166 (23.6%)
3-6	88,331 (26.5%)	4,373 (24.7%)
7+	58,127 (17.5%)	3,179 (18.0%)
Had STI during past 12 months		
Yes	18,541 (5.4%)	1,072 (5.9%)
No	325,962 (94.6%)	17,096 (94.1%)
Ever engaged in transactional sex		
Yes	19,794 (11.1%)	994 (12.3%)
No	159,146 (88.9%)	7,066 (87.7%)
Survey characteristics		
Region		
Central Africa	41,388 (12.0%)	3,689 (20.3%)
Eastern Africa	83,661 (24.3%)	4,147 (22.8%)
Southern Africa	98,768 (28.6%)	8,197 (45.1%)
Western Africa	121,015 (35.1%)	2,149 (11.8%)

Supplementary Table 5. Comparison of data characteristics for all men included in the surveys versus men from circumcision discordant households. (*continued*)

	All men N (%)	Discordant circumcision status - N (%)
Time of survey		
Between 2000-2004	40,308 (11.7%)	1,390 (7.6%)
Between 2005-2009	106,046 (30.8%)	5,537 (30.45%)
Between 2010-2014	136,072 (39.5%)	6,068 (33.4%)
Between 2015-2019	62,406 (18.1%)	5,187 (28.5%)

Supplementary Table 6. Comparison of data characteristics for circumcised men from single-men households, circumcised men from multiple-men households, uncircumcised men from single-men households, and uncircumcised men from multiple-men households.

	Circumcised men from single-men households N (%)	Circumcised men from multiple-men households N (%)	Uncircumcised men from single-men households N (%)	Uncircumcised men from multiple-men households N (%)
Sample size	122,532	59,164	65,038	36,814
HIV status				
Positive	116,614 (3.6%)	1,462 (2.5%)	6,366 (10.0%)	2,459 (6.8%)
Negative	4,410 (96.4%)	57,016 (97.5%)	57,352 (90.0%)	33,672 (93.2%)
Sociodemographic characteristics				
Age (per 10-year age group)				
34 or younger	73,801 (60.2%)	42,644 (72.1%)	40,943 (63.0%)	26,801 (72.8%)
35 and older	48,731 (39.8%)	16,520 (27.9%)	24,095 (37.0%)	10,013 (27.2%)
Highest education				
No education	36,723 (30.0%)	12,016 (20.3%)	7,720 (11.9%)	3,043 (8.3%)
Primary	39,270 (32.1%)	19,569 (33.1%)	31,515 (48.5%)	17,414 (47.3%)
Secondary	38,887 (31.7%)	23,656 (40.0%)	22,563 (34.7%)	14,704 (39.9%)
Post-secondary	7,647 (6.2%)	3,920 (6.6%)	3,235 (5.0%)	1,652 (4.5%)
Socioeconomic status				
1 'Poorest'	25,748 (21.0%)	8,982 (15.2%)	13,919 (21.4%)	5,453 (14.8%)
2	24,519 (20.0%)	9,764 (16.5%)	13,444 (20.7%)	6,462 (17.6%)
3	22,748 (18.6%)	10,583 (17.9%)	13,035 (20.4%)	7,636 (20.7%)
4	22,084 (18.0%)	12,239 (20.7%)	13,008 (20.0%)	8,179 (22.2%)
5 'Wealthiest'	27,432 (22.4%)	17,596 (29.4%)	11,632 (17.9%)	9,082 (24.7%)
Marital status				
Never married	78,995 (64.5%)	21,469 (36.3%)	41,757 (64.2%)	12,172 (34.5%)
Currently married	38,031 (31.0%)	35,359 (59.8%)	20,407 (31.4%)	23,344 (63.4%)
Previously married	5,506 (4.5%)	2,335 (4.0%)	2,872 (4.4%)	1,298 (3.5%)
(Sexual) behavioural characteristics				
Lifetime sex partners				
None	27,562 (23.7%)	23,156 (40.7%)	12,916 (20.3%)	13,742 (38.0%)
1-2	31,506 (27.0%)	12,375 (21.7%)	20,840 (32.8%)	9,505 (26.3%)
3-6	32,508 (27.9%)	12,331 (21.7%)	20,417 (32.1%)	8,898 (24.6%)
7+	24,988 (21.4%)	9,089 (16.0%)	9,443 (14.8%)	4,056 (11.2%)
Had STI during past 12 months				
Yes	6,969 (5.7%)	2,893 (4.9%)	4,033 (6.2%)	1,801 (4.9%)
No	115,472 (94.3%)	56,233 (95.1%)	60,951 (93.8%)	34,976 (95.1%)
Ever engaged in transactional sex				
Yes	6,497 (9.9%)	2,895 (10.2%)	4,558 (12.2%)	2,028 (12.4%)
No	59,264 (90.1%)	25,640 (89.9%)	32,912 (87.8%)	14,280 (87.6%)

Supplementary Table 6. Comparison of data characteristics for circumcised men from single-men households, circumcised men from multiple-men households, uncircumcised men from single-men households, and uncircumcised men from multiple-men households. (*continued*)

	Circumcised men from single-men households N (%)	Circumcised men from multiple-men households N (%)	Uncircumcised men from single-men households N (%)	Uncircumcised men from multiple-men households N (%)
Survey characteristics				
Region				
Central Africa	12,192 (10.0%)	7,933 (13.4%)	4,459 (6.9%)	2,683 (7.3%)
Eastern Africa	25,896 (21.1%)	13,351 (22.6%)	15,943 (24.5%)	9,194 (25.0%)
Southern Africa	20,340 (16.6%)	10,423 (17.6%)	41,855 (64.4%)	23,555 (64.0%)
Western Africa	64,104 (52.3%)	27,457 (46.4%)	2,781 (4.3%)	1,382 (3.8%)
Time of survey				
Between 2000-2004	18,891 (15.4%)	9,962 (16.8%)	2,416 (3.7%)	1,499 (4.1%)
Between 2005-2009	50,256 (41.0%)	19,231 (32.5%)	15,420 (23.7%)	8,449 (23.0%)
Between 2010-2014	38,568 (31.5%)	21,790 (36.3%)	28,368 (43.6%)	16,578 (45.0%)
Between 2015-2019	14,817 (12.1%)	8,181 (13.8%)	18,834 (29.0%)	10,288 (28.0%)

Chapter 4

HIV prevalence among men who have sex with men, transgender women, and cisgender male sex workers in sub-Saharan Africa: a systematic review and meta-analysis

Mariëlle Kloek, Caroline A. Bulstra, Laura van Noord, Lina Al-Hassany, Frances M. Cowan, Jan A.C. Hontelez

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SUMMARY

Introduction: Developing effective targets, policies, and services for key populations requires estimations of population sizes and HIV prevalence across countries and regions. We estimated the relative and absolute HIV prevalence among men who have sex with men (MSM), transgender women and -men, and male and transgender sex workers (MSW and TGSW) in countries in sub-Saharan African.

Methods: We performed a systematic review of peer-reviewed studies assessing HIV prevalence in MSM, transgender-women and -men, MSW and TGSW in sub-Saharan Africa between 2010 and 2021, following PRISMA guidelines. We searched Embase, Medline Epub, Africa Index Medicus, Africa Journal Online, Web of Science and Google Scholar. We calculated HIV prevalence ratios (PRs) between the study prevalence, and the geospatial-, sex, time, and age-matched general population prevalence. We extrapolated results for MSM and transgender women to estimate the HIV prevalence and the number of people living with HIV for each country in sub-Saharan Africa using pooled review results, and regression approximations for countries with no peer-reviewed data.

Results and discussion: We found 44 articles assessing HIV prevalence in MSM, ten in transgender women, five in MSW, and zero in transgender men and TGSW. HIV prevalence among MSM and transgender women was significantly higher compared to the general population: PRs of 11.3 [CI: 9.9-12.9] for MSM and 8.1 [CI: 6.9-9.6] for transgender women in Western and Central Africa, and respectively 1.9 [CI: 1.7-2.0] and 2.1 [CI: 1.9-2.4] in Eastern and Southern Africa. HIV prevalence among MSW was significantly higher in both Nigeria (PR: 12.4 [CI: 7.3-21.0]) and Kenya (PR: 8.6 [CI: 4.6-15.6]). Extrapolating our findings for MSM and transgender women resulted in an estimated HIV prevalence of 15% or higher in MSM for about 60% of all sub-Saharan African countries, and for transgender women for all but two countries.

Conclusions: HIV prevalence among MSM and transgender women throughout sub-Saharan Africa is alarmingly high. This high prevalence, coupled with the specific risks and vulnerabilities faced by these populations, highlights the urgent need for risk-group tailored prevention and treatment interventions across the subcontinent. There is a clear gap in knowledge on HIV prevalence among transgender men, MSW, and TGSW in sub-Saharan Africa.

RESEARCH IN CONTEXT

Evidence before this study: Cisgender men who have sex with men (MSM), transgender people, cisgender men sex workers (MSW), and transgender sex workers (TGSW) are well established as people at higher risk for HIV. We searched PubMed for systematic reviews published between January 2010 and March 2021 that estimated the HIV prevalence among these key populations in sub-Saharan Africa, using the terms "HIV", "prevalence" or "burden", "sub-Saharan Africa", and "MSM", "transgender" or "sex worker" (or similar). One study, published in 2019, estimated the HIV prevalence among MSM in sub-Saharan Africa based on peer-reviewed studies that reported country-level HIV prevalence levels from a number of sub-Saharan African countries. However, this study did not match location and age composition when calculating risk ratios. We did not identify any reviews that assessed HIV prevalence among transgender people, MSW, and TGSW in sub-Saharan Africa. A study from 2012 estimated the worldwide HIV burden among transgender women, but did not include studies from sub-Saharan Africa. The Joint United Nations Programme on HIV/AIDS (UNAIDS) does report HIV prevalence in MSM and transgender people, yet, these estimates largely rely on country-reported numbers, which are often either missing, or based on a single population survey estimate.

Added value of this study: To our knowledge, this study is the first to provide a comprehensive overview and estimates of the HIV prevalence among MSM, transgender women, and MSW in sub-Saharan Africa. The data is derived from peer-reviewed literature, and provides a valuable addition to, and validation of, UNAIDS estimates for MSM, and is the first to provide such estimates for transgender women. Finally, we highlight a clear gap in knowledge on HIV burdens among transgender men, MSW, and TGSW on the subcontinent, as no peer-reviewed studies with primary data on HIV prevalence in these populations were found.

Implications of all the available evidence: Our results demonstrate that the HIV burden among MSM, transgender women and male sex workers in sub-Saharan Africa is alarmingly high, which re-enforces the pressing need to improve HIV treatment and prevention services for these high-risk populations and address structural barriers to health care and prevention. Our results provide important insights for policy makers that can help improve availability of- and access to HIV services for these high-risk populations.

INTRODUCTION

Sub-Saharan Africa is the epicentre of the HIV pandemic, with about 21 million people living with HIV [1]. Especially countries in Eastern and Southern Africa (ESA) are faced with so-called generalised epidemics, affecting large parts of the general population, while HIV prevalence in Western and Central African (WCA) countries is mostly concentrated amongst people at higher risk for HIV [1]. The successful roll-out of HIV treatment and prevention programmes across the subcontinent over the past decades has curbed transmission among the general population and female sex workers in many settings [2-4]. However, stigma and criminalisation cause barriers in access for other key populations, such as cisgender men who have sex with men (MSM), transgender people, and cisgender male and transgender sex workers (MSW and TGSW) [5-9]. Currently, an estimated 54% of all new HIV infections worldwide occur among key populations and their sex partners [10], and compared to the general population, the average risk for HIV infection is about 20 times higher for sex workers and MSM, and about 10 times higher for transgender people [10]. For MSM, particular risk factors include condomless anal sex, discrimination, and criminalisation in many sub-Saharan African settings [11, 12], while for transgender people, further HIV risks are added due to needle sharing for hormonal therapy, and transgender people are particularly vulnerable for social isolation and stigma in many countries [12, 13]. Male and transgender sex workers are additionally faced with the increased risks of being engaged in commercial sex, *i.e.*, having many sexual partners [8, 13].

Developing effective targets, policies and interventions requires estimations of population sizes and HIV prevalence across countries and regions [14]. Furthermore, such information could improve our understanding of the relative importance of these key populations in the HIV epidemic, thereby improving mathematical modelling projections on the impact of interventions for each key population and for the general epidemic. However, current population size and HIV prevalence estimates for MSM provided by UNAIDS largely rely on country-reported numbers from a single survey or expert opinion - and are potentially biased [15] - while estimates for transgender people, and MSW and TGSW are mostly completely absent. Summarising and extrapolating HIV prevalence estimates from recent scientific literature to estimate country-specific HIV prevalences for these key populations in sub-Saharan Africa could help fill this knowledge gap, by improving our understanding of the current HIV prevalence among these populations. While previous systematic reviews have included a limited number of studies from sub-Saharan Africa [11, 20-22], these reviews have been conducted almost a decade ago. Several studies have been published since then, and current prevalence is likely very different from the time those reviews were conducted, as the rapid scale-up of ART and other prevention interventions across the subcontinent has substantially changed HIV epidemiology over the past decade.

The aim of this study was to estimate the recent relative and absolute HIV prevalence for MSM, transgender-women and -men, MSW, and TGSW in sub-Saharan Africa. We first systematically reviewed peer-reviewed studies on the prevalence of HIV in each of these key populations, and then estimated the relative HIV prevalence by comparing prevalence estimates to geospatial-, sex, time, and age-matched estimates of HIV prevalence in the general population. We then applied pooled estimates of relative risk and prevalence to country specific HIV epidemics to estimate the country-specific HIV prevalence per risk group for each country in sub-Saharan Africa.

METHODS

Search strategy and selection criteria

We followed PRISMA guidelines for systematic reviews and meta-analyses [19]. We searched Embase, Medline Epub, Africa Index Medicus, Africa Journal Online, Web of Science and Google Scholar to identify studies that report HIV prevalence among MSM, transgender-women and -men, MSW and/or TGSW in sub-Saharan African countries, in peer reviewed literature reporting on data collected between January 1st 2010 and October 22th 2021. We choose this time period to strike a balance between the accuracy of our estimates of the current prevalence and relative risks in each key population versus the power to perform any meaningful meta-analyses. We constructed search strings in collaboration with a medical librarian (see **Supplementary File S1** for the complete search strategy). We used Medical Subject Headings (MeSH) terms and "all fields" terms comprising sex work ("sex worker", "prostitute"), LGBT people ("MSM", "transgender", "gay"), HIV/AIDS, prevalence ("cross-sectional study", "incidence", "odds ratio") and sub-Saharan Africa. After an initial search in June 2018, the search has been updated in July 2020 to include the most recent publications, and again in October 2021 to include more recent publications and the regional databases Africa Index Medicus and Africa Journal Online. In both cases, no changes were made to the search terms.

We included peer-reviewed studies that reported HIV prevalence or data from which HIV prevalence could be derived among MSM, transgender people, MSW and/or TGSW, of a site in at least one country in sub-Saharan Africa, had a cross-sectional or cohort study design, and were published in English or French. We excluded studies that: (1) were based on self-reported HIV status; (2) assessed subgroups of the study population (*i.e.*, prisoners, drug-using MSM, MSW among an MSM population), as estimates from such subgroups are likely biased towards higher HIV prevalence levels, making them not generalizable to the entire study population; (3) were a secondary analysis of previously collected data; (4) did not provide a prevalence estimate; (5) were based on data collected before 2010; and (6) failed to correctly define the different key populations (see **Supplementary Panel 1**).

Different studies conducted at the same location were included to maximise power, except if they were based on the same dataset. In that case, we included the study presenting the greatest total number of people tested.

Two independent reviewers (MK and LvN) performed screening of titles and abstracts of retrieved records. For those deemed eligible based on the set inclusion and exclusion criteria, full texts were examined to determine full eligibility. Any disagreements between the independent reviewers were resolved by consensus with the senior author (JACH).

Data extraction and meta-analyses

Two authors independently extracted the following study characteristics: population studied, study location, study year, study design, recruitment method, number of participants, age distribution, type of HIV test, and HIV prevalence with 95% confidence intervals (CIs). When the HIV prevalence and/or 95% CIs were not reported directly, we calculated these using the reported absolute numbers. The corresponding authors of studies were contacted if additional study information was required.

For each study, we calculated a prevalence ratio (PR) of HIV prevalence in the key population of interest, compared to the HIV prevalence in the general population. We derived general population HIV prevalence data from Demographic Health Surveys (DHSs) and AIDS Indicator Surveys (AISs), which are nationally-representative household surveys that often include voluntary HIV testing in adults, and have been systematically performed in many countries in sub-Saharan Africa [21]. Typically, a DHS or AIS is performed at around 350 randomly selected sample-locations in each country, and all members of about 25 households at each location are invited to participate [22]. These data were the only available general population HIV prevalence data that could be geospatially matched with locations of the studies in our review, and are generally assumed to be fairly representative of general population level HIV prevalence estimates [23, 24].

For each study in our review, we first geo-located the study site, and then selected DHSs/AISs sample locations from the survey conducted closest to the year of data collection in the study, with a maximum difference of three years. If, after contacting corresponding authors, year of data collection was still missing, the most reasonable DHS/AIS was selected based on the publication date of the study. We selected all sample locations within a five-kilometre radius from the study site, and calculated the general population HIV prevalence in the selected sample locations, standardised to the study population by age composition and gender (*i.e.*, only males when comparing to MSM and MSW prevalence, and males and females when comparing to transgender women).

For studies without DHS/AISs data collected within three years before or after the study, we extracted local HIV prevalence estimates from the study by Dwyer-Lindgren *et al.* [22]. They estimated yearly five by five-kilometre HIV prevalence for the whole of sub-Saharan Africa from 2000 to 2017, for females and males (15-49 years) combined. They estimated HIV prevalence based on a variety of data sources, including local studies, antenatal care surveys, and population-based surveys, and age- and sex- standardisation was not possible with these data.

We calculated the PR as the ratio between the prevalence among the key population in the study and the prevalence in the general population at that location. A pooled prevalence and PR, stratified by country and region (WCA and ESA) was calculated by summing absolute numbers of all studies and calculating a combined prevalence and PR. We stratified by region to control for potential effect modification, as PRs may differ for the more concentrated epidemics in WCA versus the mixed and generalised epidemics in ESA.

For MSM and transgender women, the total number of studies identified allowed us to extrapolate HIV prevalence derived from our review to crudely estimate the country-specific prevalence in five percentage point intervals (0 to 5%, 5% to 10%, 10% to 15%, 15% to 20%, and >20%) for all countries in sub-Saharan Africa. For the countries for which we had data and a sufficient number of people tested ($n \geq 80$ for MSM and $n \geq 50$ for transgender people), we divided them into the prevalence categories using the pooled country estimated prevalence. For the countries for which we had no data or an insufficient number of people tested ($n < 80$ for MSM and $n < 50$ for transgender people), we estimated the HIV prevalence in MSM and transgender women through a regression approximation. The cut-off value of 80 and 50 participants, respectively were arbitrarily chosen to ensure that studies with very small sample sizes would not dilute our regression analyses, and to ensure that countries would not be categorised based on a single study with a very small sample size.

The regression approximation was performed as follows. We first determined the relationship between the HIV prevalence in the study population and general HIV prevalence for all studies in our review by fitting a logistic Deming regression, with the HIV prevalence in the studies as the dependent variable, and corresponding HIV prevalence in the general population as the independent variable. We then applied this function to the country-level general urban population HIV prevalence for countries for which we had insufficient peer-reviewed data, as all peer-reviewed studies were conducted in urban settings. The general urban population HIV prevalence for each country was estimated by multiplying general population HIV prevalence estimates derived from UNAIDS 2020 [26] with a country-specific ratio of urban total HIV prevalence derived from DHS [21], and an average urban total HIV prevalence over all countries for countries without DHS data. The function for MSM is log odds(y)=-1.96 + 0.021x (p=0.07), and the function for transgender women is log odds(y)

= -1.64 + 0.059x (p=0.05), where y = HIV prevalence in the key population, and x = HIV prevalence in the general population. We did not stratify our regression approximation by region. Yet the regression models inherently capture prevalence heterogeneities across the regions, as the model is fitted using general population HIV prevalence as a predictor.

After estimating the relative HIV prevalence for each country, we roughly estimated the country-specific absolute HIV prevalence. We first applied estimates of the proportion of MSM (1.0% to 4.0%) and transgender women (0.5% to 1.0%) within populations [29] to the United Nations population size estimates [28] the develop rough population size estimates for the key populations. We then multiplied these with prevalence estimates for the key population, assuming rural and urban HIV prevalence levels to be the same. See **Appendix Panel 2** for a detailed description of the applied approach.

We performed several sensitivity and validation analyses on our prevalence estimations. First, we determined the impact of preferring DHS data over data from Dwyer-Lindgren *et al.* [27] as a source for HIV prevalence in the local general population by running our analyses using both DHS and Dwyer-Lindgren *et al.* [27] data for studies where this was possible and compared the resulting PRs. Second, we tested the validity of our regression approximation by applying the model to countries where we had used pooled peer-reviewed data to estimate country-level prevalence and compared the outcomes. Third, we tested whether the year of data collection, legal or illegal status of same-sex relationships and an indicator for the severity of anti-LGBT laws [31] could explain some of the observed heterogeneity in the relationship between key- and general population HIV prevalence by testing them as predictors in a logistic regression model. Fourth, we determined whether UNAIDS [26] reported point estimates of prevalence, based on grey literature, fell within the prevalence category assigned to each country based on our estimates.

All analyses were done using R version 4.0.0 and ArcGIS Pro version 2.5.0.

Role of funding source, interests and registration

The study's funder had no role in study design, data collection, data analysis, data interpretation, writing, or submitting of the report. Independent authors declare no competing interests. The review was not registered.

RESULTS

Our search identified 9,476 articles, of which 2,587 were unique records (**Figure 1**). Based on the screening of title and abstract, 207 full texts were retrieved, of which 48 met our inclusion criteria

[12, 32-78]. Most studies were excluded because they either only collected self-reported HIV status, re-analysed previously collected data that was already part of the review or provided data collected pre-2010. We did not find studies with conflated gender group definitions. A complete overview of each literature search is given in **Appendix Table 1**. Risk of bias was assessed using Joanna Briggs Institute (JBI) critical appraisal checklist (see **Appendix Table 1**) [20]. The majority of publications (91.7%, 44/48) provided HIV prevalence data on MSM (**Appendix Table S3**), compared to 20.8% (10/48) on transgender women (**Appendix Table S4**) and 10.4% (5/48) on MSW (**Appendix Table S5**). No articles were identified with relevant data on transgender men or TGSW. The 48 articles covered 21 of the 47 sub-Saharan African countries (44.7%); ten in WCA and 11 in ESA (**Figure 2**). The five studies that assessed HIV prevalence in MSW covered only two countries: Nigeria and Kenya [40, 51, 76-78]. All studies were performed in urban settings, and all were deemed of sufficient quality based on the JBI critical appraisal checklist (**Appendix Table 1**).

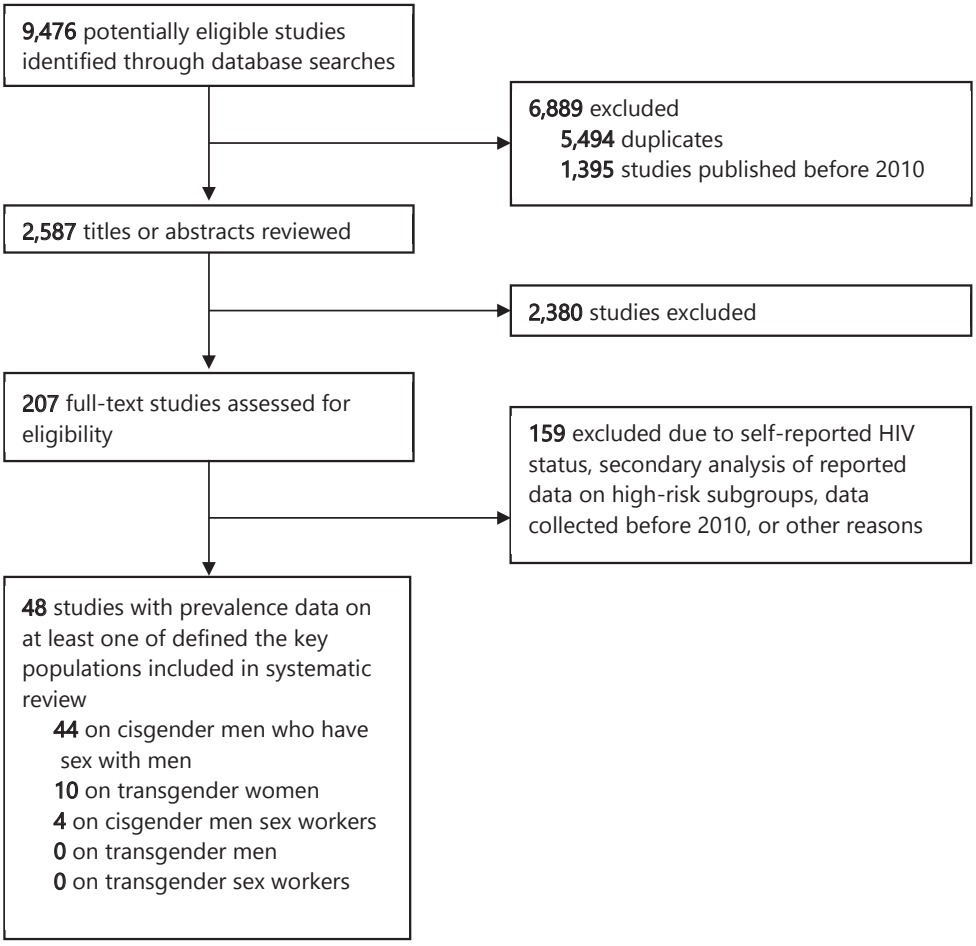

Figure 1. Flow chart of study selection disposition.

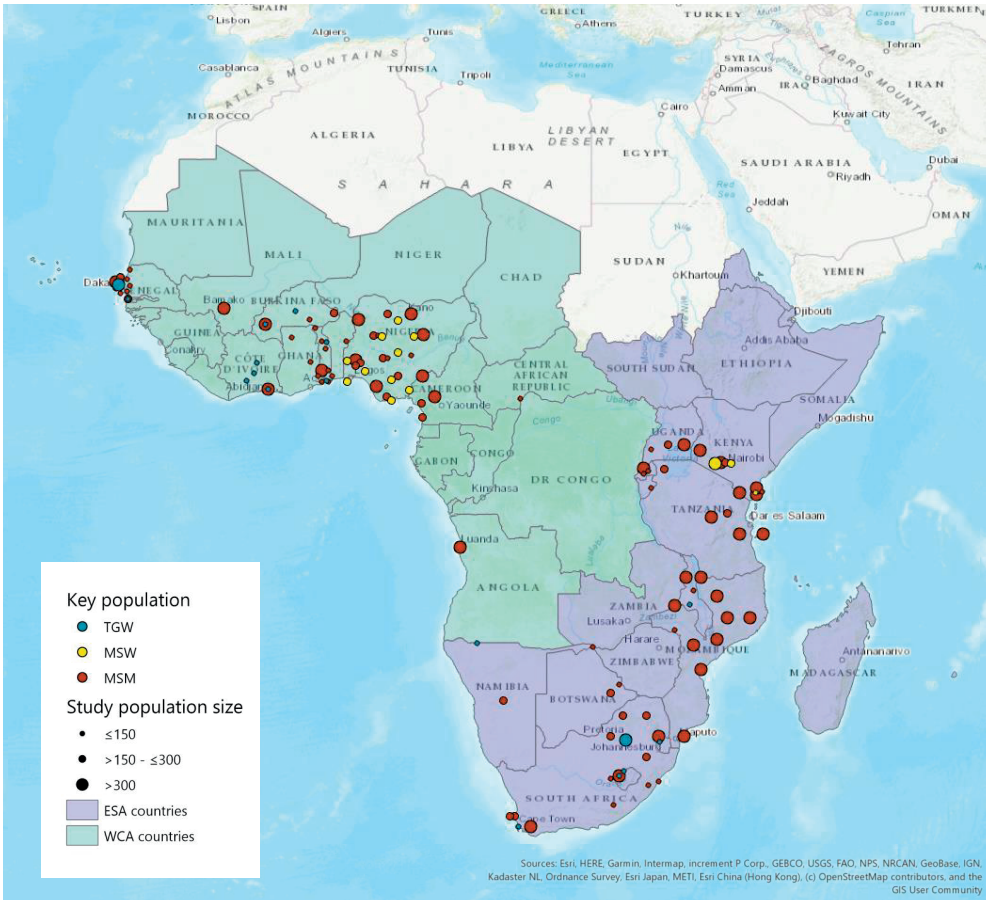

Figure 2. Locations of the included studies on HIV prevalence in men who have sex with men (MSM), transgender women (TGW), and male sex workers (MSW) in sub-Saharan Africa. ESA countries = eastern and southern African countries; WCA countries = western and central African countries.

Study-, country-, and region-specific PRs for HIV in MSM, compared to the general male population, are shown in **Figure 3** for WCA and in **Figure 4** for ESA. The reported HIV prevalence among MSM in WCA ranged between 4.3% in Angola to 51.0% in Senegal. Prevalence was significantly higher in 27 of the 29 study locations, with a weighted average PR of 11.3 (95% CI: 9.9–12.9). In ESA (**Figure 4**), the prevalence ranged from 7.5% in Mozambique to 36.0% in South Africa. Only 24 out of the 46 study locations showed a significantly higher HIV prevalence among MSM, with a weighted average PR of 1.9 (95% CI: 1.7–2.0).

Study- country- and region-specific PRs for transgender women are shown in Figure 5. In WCA, the prevalence ranged from 4.0 in Burkina Faso to 50.0 in the Gambia. Seven out of 9 study locations showed significantly higher HIV prevalence among transgender women, with PRs ranging from 1.6 to 86.7 (upper panel in **Figure 5**). The weighted average PR was

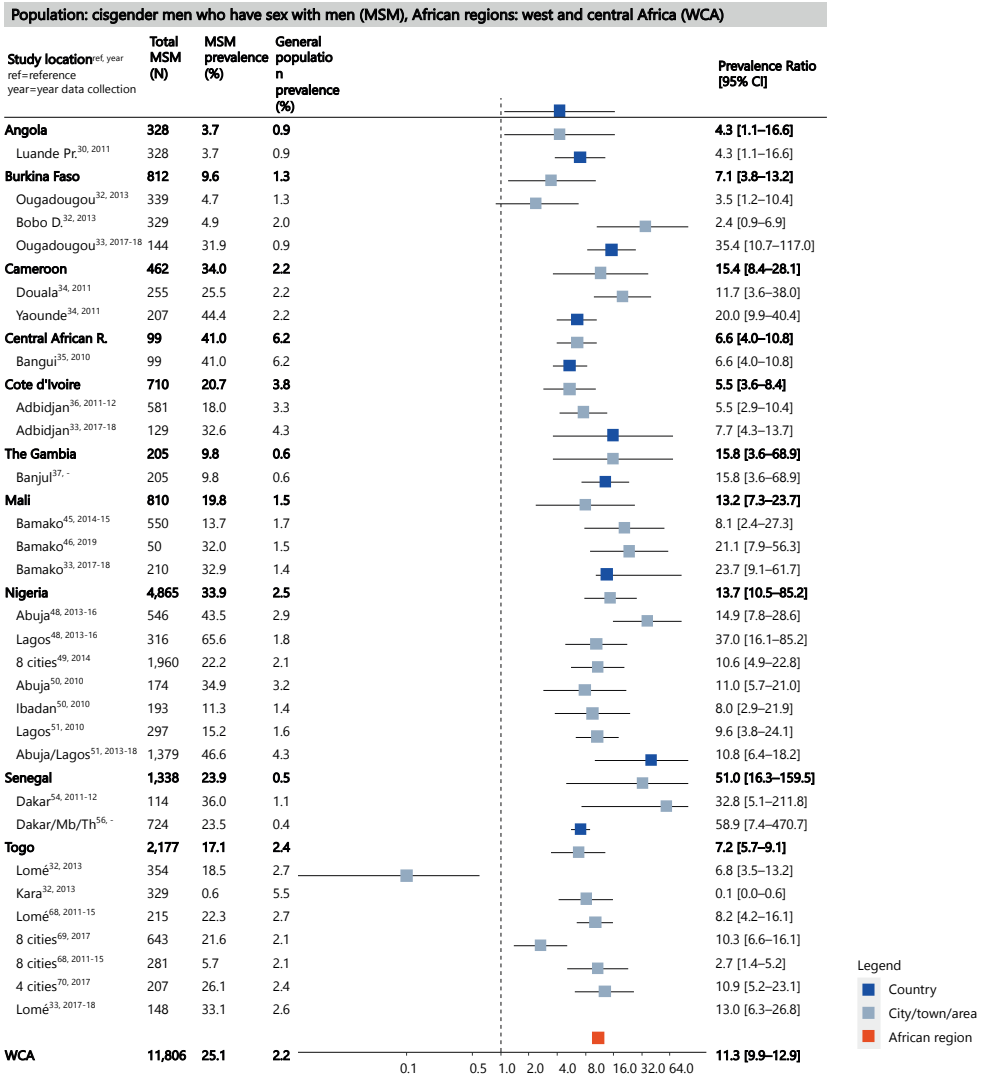

Figure 3. HIV prevalence and prevalence ratio (PR) for men who have sex with men (MSM) per study place, country, and region in west and central Africa (WCA). Grey squares represent individual study locations, and weighted averages for country and region level are in blue and red. PRs are relative risks compared to the geospatially matched general male population aged 15-49. MSM = men who have sex with men; 95% CI = 95% confidence interval.

8.1 (95% CI: 6.9–9.6). For ESA, the prevalence ranged from 9.4% in Rwanda to 63.5% in South Africa. Ten out of 14 study locations showed a significantly higher prevalence among transgender women, with PRs ranging from 0.5 to 4.7 and a weighted average PR of 2.1 (95% CI: 1.9–2.4; lower panel in **Figure 5**).

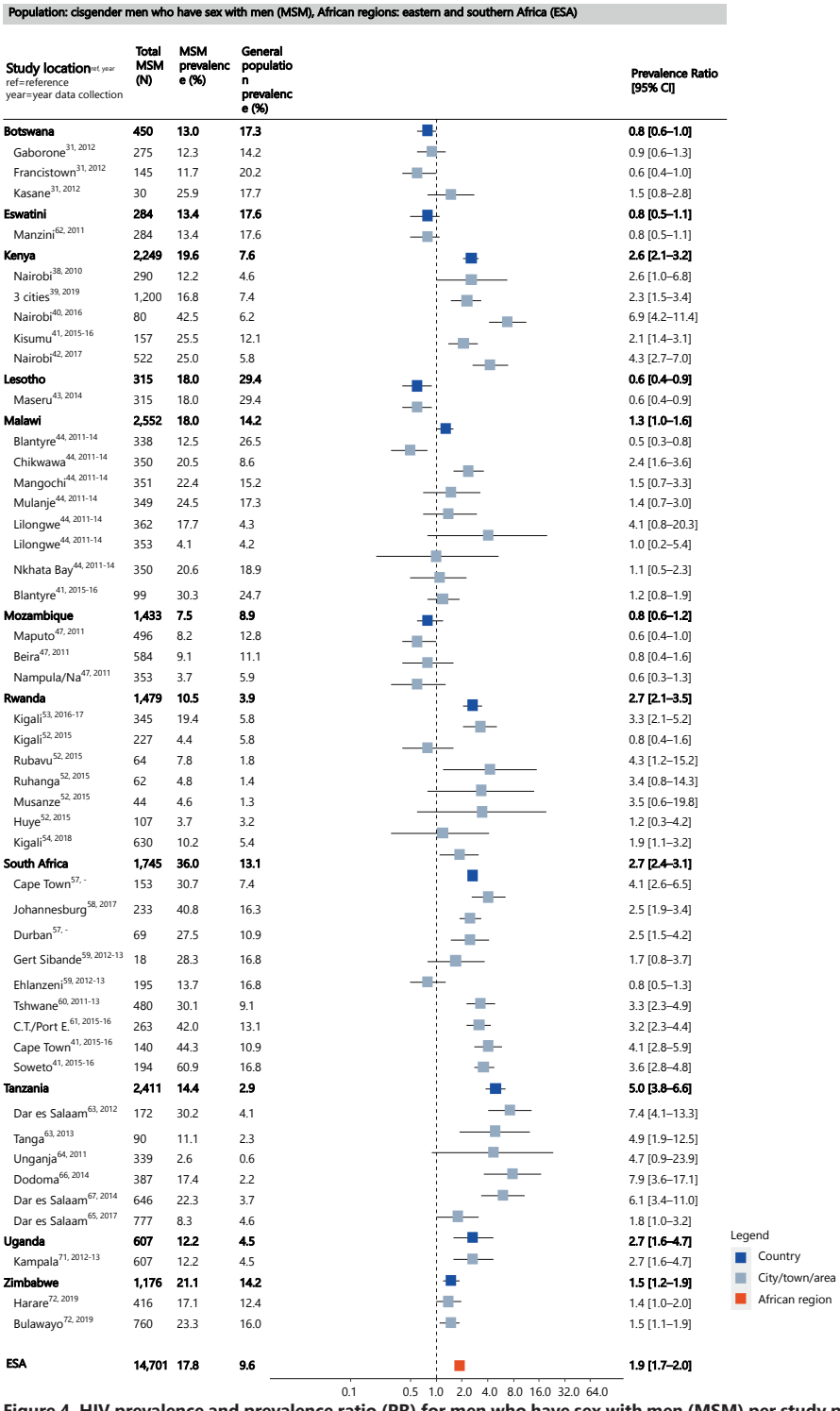

Figure 4. HIV prevalence and prevalence ratio (PR) for men who have sex with men (MSM) per study place, country, and region in eastern and southern Africa (ESA). Grey squares represent individual study locations, and weighted averages for country and region level are in blue and red. PRs are relative risks compared to the geospatially matched general male population aged 15-49. MSM = men who have sex with men; 95% CI = 95% confidence interval.

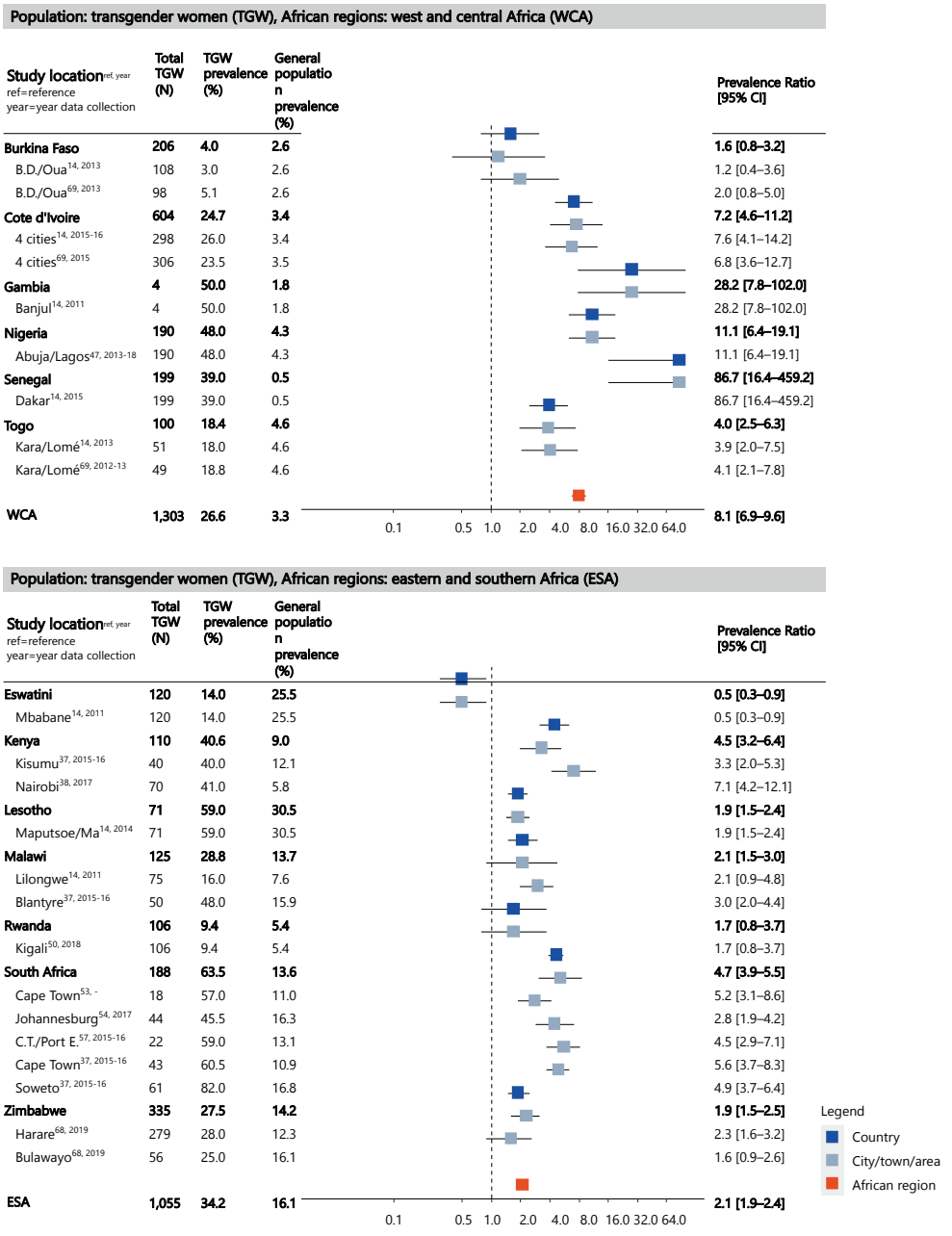

Figure 5. HIV prevalence and prevalence ratio (PR) for transgender women (TGW) per study place, country, and region in west and central Africa (WCA) and eastern and southern Africa (ESA). Grey squares represent individual study locations, and weighted averages for country and region level are in blue and red. PRs are relative risks compared to the geospatially matched general female population aged 15-49. TGW = transgender women; WCA = western and central Africa; ESA = eastern and southern Africa; 95% CI = 95% confidence interval.

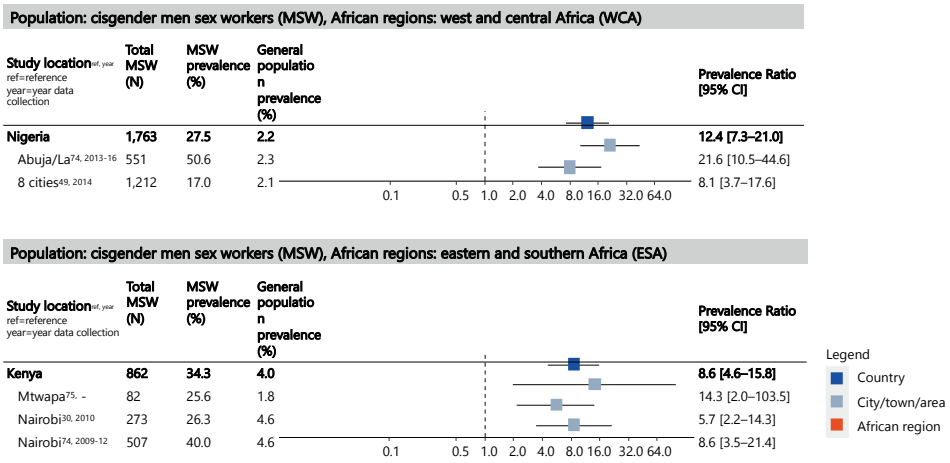

Figure 6. HIV prevalence and prevalence ratio (PR) for male sex workers (MSW) per study place, country, and region in west and central Africa (WCA) and eastern and southern Africa (ESA). Grey squares represent individual study locations, and weighted averages for country and region level are in blue and red. PRs are relative risks compared to the geospatially matched general male population aged 15-49. MSW = male sex worker; WCA = western and central Africa; ESA = eastern and southern Africa; 95% CI = 95% confidence interval.

Study-, country- and region-specific PRs for MSW are shown in Figure 6. For MSW, all five study locations showed a significantly higher prevalence compared to the general population, with an overall PR of 8.6 (95% CI 4.6; 15.8) for Nigeria (upper panel of Figure 6) and 12.4 (95% CI: 7.3–21.0) for Kenya (lower panel of **Figure 6**).

We had sufficient data points for both MSM and transgender women to extrapolate our findings to estimate HIV prevalence for the two populations in for countries in sub-Saharan Africa for which we found no studies, using a regression approximation (**Supplementary Figures 1 and 2**; **Supplementary Tables 6 to 9**). The resulting estimated country-specific HIV prevalence among MSM and transgender women for all countries in sub-Saharan Africa are presented in **Figure 7C** and **Figure 7F** and are compared to general population prevalence (Figure 7A and 7D) and UNAIDS estimations (**Figure 7B** and **Figure 7E**). For MSM, we estimated an HIV prevalence of 15-20% for 31 out of the 47 countries (66%) and a prevalence of ≥20% for seven countries (15%). For transgender women, the estimated HIV prevalence was above 15% for all but two countries and was ≥20% for 16 out of 47 countries (34%). For only 11 out of the 37 countries (30%), the UNAIDS point estimate fell within the prevalence categories assigned to those countries in our study (**Figure 7** and **Supplementary Table 12** and **Table 13**). For most countries (20 out of 37), our estimated HIV prevalence for MSM was higher than those published by UNAIDS. Two of the seven countries with UNAIDS reported prevalence data on transgender women. Two matched our estimates, three were higher, and two were lower. Our estimations roughly translate into about 600,000 to 2.2 million MSM

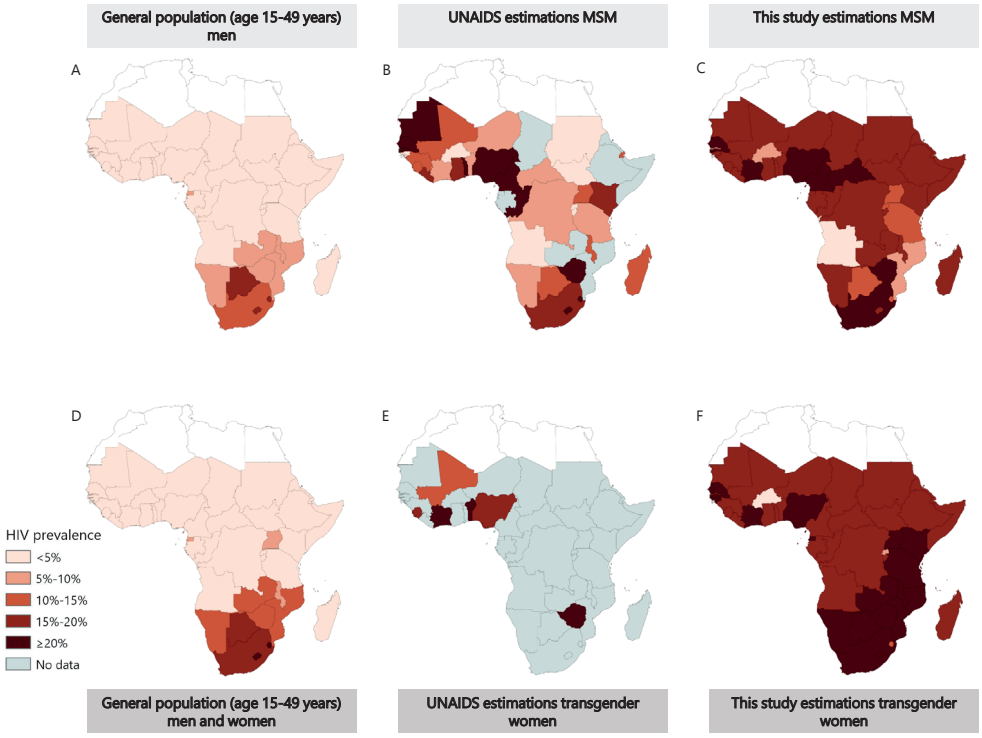

Figure 7. Maps of country level HIV prevalence levels for the general population (left column), UNAIDS reported prevalence in MSM and transgender women (middle column) and estimated HIV prevalence among MSM and transgender women based on peer-reviewed literature (right column). The peer-reviewed literature estimations are based on the country level weighted HIV prevalence derived from the included studies in the systematic literature search. For countries for which we did not find sufficient data, we estimated the country-level prevalence using a logistic Deming regression model fitted to the relationship between key-population and general population HIV prevalence in peer-reviewed literature.

and 400,000 to 800,000 transgender women currently living with HIV in sub-Saharan Africa (see **Supplementary Table 10** and **Table 11** for more details).

Our sensitivity analysis showed that the impact of choosing DHS data over data from Dwyer-Lindgren *et al.* had little impact on estimated PRs, as none were significantly different in settings where we could do both (see **Supplementary Table 16**). Furthermore, year of survey was borderline significantly associated with a higher HIV prevalence among MSM (p=0.04) and not significant for TGW (p=0.12), while legal status of same-sex relationships and severity of anti-LGBT laws were not significantly associated for both MSM (p=0.9 and 0.5 respectively) and TGW (p=0.08 and 0.3 respectively) (**Supplementary Table 7** and **Supplementary Table 9**). When validating regression approximations against data-based country prevalence estimates, we found that only about 20% of countries would end up in the same prevalence category (see **Supplementary Tables 14 and 15**).

DISCUSSION

Our systematic review identified 44 articles assessing HIV prevalence in MSM, ten in transgender women, five in MSW, and zero in transgender men and TGSW in sub-Saharan Africa since 2010. Prevalence among MSM and transgender women was significantly higher than the general population, with PRs for MSM and transgender women ranging from 11.3 and 8.1 respectively in Western and Central Africa, to 1.9 and 2.1 in Eastern and Southern Africa. Furthermore, the prevalence among MSW was also significantly higher in both Nigeria (PR: 12.4 [CI: 7.3-21.0]) and Kenya (PR: 8.6 [CI: 4.6-15.6]), the only two countries with data on MSW. Extrapolating our findings to country- and region-specific estimates resulted in an estimated HIV prevalence of 15-20% among MSM for roughly half of the sub-Saharan African countries and seven countries with an estimated HIV prevalence of ≥20%. For transgender women, we estimated an HIV prevalence of 15-20% or ≥20% for all but two countries. These estimates roughly translate into about 600,000 to 2.2 million MSM and 400,000 to 800,000 transgender women currently living with HIV in sub-Saharan Africa.

Our study is a major update of earlier reviews of studies on the HIV prevalence among MSM and transgender women in sub-Saharan Africa [11, 20-22]. In addition, we are the first to extrapolate geospatial, age, time and sex-matched associations with the general population HIV prevalence in each study to estimate the HIV prevalence among MSM and transgender women in all countries in sub-Saharan Africa. It is encouraging that our findings on the prevalence ratio in sub-Saharan Africa are consistent with those from Hessou *et al.* [80] for MSM (a PR for Western Central Africa of 14.5 versus 11.3 in our study, and 3.4 for Eastern Africa and 1.2 for Southern Africa versus 1.9 for Eastern Southern Africa in our study), and in line with global estimates on HIV prevalences among transgender people [21].

Our estimates and extrapolations are important when assessing country-level needs and targets for key-population-specific services, and estimating the required resources to meet those needs and targets. Annual HIV epidemic updates published by UNAIDS [26] provide HIV prevalence estimates for the majority of sub-Saharan African countries on MSM, usually based on country-reported results from a single survey that has not undergone peer-review, or even based on expert opinion alone. These estimates fitted within the same prevalence categories estimated by our study for only about 30% of all countries, highlighting the need to consider incorporating peer-reviewed evidence in the prevalence estimation exercise for these populations. UNAIDS estimates on the prevalence in transgender people are available for only a few countries, and no information exists on MSW and TGSW.

Even though it was not possible to extrapolate the findings of MSW to country- and region-specific estimates; the PR for MSW compared to MSM, was higher from Kenya (respectively

8.6 vs 2.6) and comparable for Nigeria (respectively 12.4 vs 13.7), suggesting similar or higher country- and region HIV levels for MSW. For TGSW and transgender men, we did not find any scientific literature showing how these groups are still highly underrepresented as a key population in HIV research and programming. We highly recommend more quantitative research into the population sizes, HIV prevalence, risks, service needs and uptake for MSW, transgender women and men, and TGSW throughout sub-Saharan Africa.

While our results do not cover access to services, limited data on access to services for MSM and transgender people suggests that access to treatment is extremely poor compared to the general population. A study that tested for antiretroviral adherence in 183 HIV-infected MSM and transgender women in several sub-Saharan African countries found that only 34% had antiretroviral residues in their blood, and 18% of those were not virally suppressed [81]. In addition, a systematic review by Stannah *et al.* [31] showed that, although HIV testing among MSM had increased significantly over the past decade, pooled estimates showed only about 23% of MSM living with HIV to be on treatment. A rough back-of-the-envelope calculation using these findings and our results shows that if treatment coverage for MSM is indeed only about 25%, about 500,000 to 1.7 million MSM in sub-Saharan Africa require treatment but are not receiving it. Likewise, effective pre-exposure prophylaxis (PrEP) services roll out remains challenging. While motivation to use PrEP seems high [79], Wahome *et al.* found low levels of PrEP adherence and the absence of an effect on HIV incidence among MSM in sub-Saharan Africa [80]. Despite a lack of peer-reviewed data, it seems reasonable to assume similar or even poorer access to HIV prevention and treatment for MSW, transgender people, and TGSW compared to MSM [84]. Failure to provide adequate services to these key populations could result in higher rates of morbidity, mortality, and onward transmission [82]. It is essential that these services are sensitive to the unique vulnerabilities and needs of each group [9], and should coincide with minimising structural barriers against LGBT+ people and sex workers at personal, societal and institutional level [9, 13, 21].

Our study has several limitations. First, we only incorporated peer-reviewed studies. We decided not to directly include grey literature in developing our estimates due to the likely heterogeneity in quality and large risk of bias in provided estimates. Our comparison between estimates derived from peer-reviewed literature (our review) and grey literature (UNAIDS estimates) confirms the high levels of heterogeneity between the two. Nevertheless, our peer-review-based estimates should also be cautiously interpreted in light of data limitations, selection biases and small sample sizes in the individual studies. Second, the majority of the included studies used respondent-driven sampling (RDS) as their recruitment method. RDS has been described as the preferred sampling method for populations without a readily available sampling frame, though it has potential limitations [66, 86-88]. For example, most studies did not report on additional important indicators, such as to which extent the sample

was part of the same social network [83]. People in a highly interconnected social network might not be representative of the population as a whole, as people who are not part of these networks may have different underlying characteristics and risks than those within the network. However, it is difficult to determine the direction of the potential bias, as we do not have a reliable gold standard from, *e.g.*, a population-based survey. Third, for some studies, we could not sex- and age-match general population level prevalence to calculate a PR, as no DHS surveys [21] were conducted within a three-year time window around the study. We used estimated HIV prevalence in all adults aged 15 to 49 years as published by Dwyer-Lindgren *et al.* [27] instead. However, it is reassuring that, for areas where we could use both, reverting to PRs using data from Dwyer-Lindgren *et al.* [27] did not result in any major deviations in estimated PRs (**Supplementary Table 16**). Fourth, age standardisation was often based on relatively broad age ranges (*e.g.*, interquartile ranges) reported by the individual studies. It is likely to assume that within broad standardisation categories, the age distribution among the key populations was relatively younger than the general population, resulting in an underestimation of the actual PRs. Fifth, our estimates for countries where we had no data are based on a statistical model derived from the systematic review. The sole independent predictor is HIV prevalence in the general population. These estimations should be interpreted with caution, as the regression approximation correctly predicted the data-based prevalence categories for countries with sufficient peer-reviewed data only 20% of the time (**Supplementary Table 14** and **Supplementary Table 15**). However, while we place higher confidence in estimates based on peer-reviewed directly, it should be noted that these can also be based on relatively sparse numbers of observations, making a predicted prevalence based on pooling estimates across countries in a regression approximation not necessarily less valid. Sixth, we did not control for the year of data collection in our main analysis. Yet we observed a borderline significant trend towards higher prevalence in later years for MSM in our sensitivity analysis (p=0.04) (**Supplementary Table 7**). This suggests that by pooling the ten years covered by our review, we may have slightly underestimated the current PRs and HIV prevalence among MSM in sub-Saharan Africa. However, whether this trend in time reflects an actual divergent trend in prevalence due to increased incidence and/or survival, or is caused by improved sampling approaches by which researchers are increasingly better at finding higher-risk individuals, is difficult to determine. Seventh, all study locations were urban settings, and our PRs and estimations are therefore based on HIV prevalences in urban settings. We, therefore, assumed HIV prevalence for MSM and transgender women to be the same for rural settings when extrapolating our findings to national-level estimates.

Conclusions

We show that the current HIV prevalence in MSM and transgender women in sub-Saharan Africa is alarmingly and consistently high across all African regions and countries. This

high prevalence, coupled with the specific risks and vulnerabilities that these populations face, highlights the urgent need for risk-group tailored prevention and treatment interventions across the subcontinent. The lack of studies on HIV prevalences in several countries, especially among transgender people and cisgender male- and transgender sex workers, highlights the need for more research.

Authors' contribution

MK and JACH conceptualised and designed the study, MK, LvN and LAH performed data collection and interpretation, MK, CAB, LvN, LAH and JACH performed all analyses, MK, CAB and JACH wrote the first draft of the manuscript, all authors contributed to writing and editing the final version of the manuscript. FMC provided overall supervision.

Conflicts of interest

None to declare.

Ethical committee approval

Not needed, no primary data collection or experiments on humans or animals were performed.

Data sharing statement

This study did not contain any primary data, only used secondary data from publicly accessible sources.

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REFERENCES

1. UNAIDS. Fact sheet - world AIDS day 2021. https://www.unAIDS.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf; 2020.
2. Bor J, Herbst AJ, Newell ML, Bärnighausen T. Increases in adult life expectancy in rural South Africa: valuing the scale-up of HIV treatment. Science. 2013;339(6122):961-5.
3. McNairy ML, El-Sadr WM. Antiretroviral therapy for the prevention of HIV transmission: what will it take? Clin Infect Dis. 2014;58(7):1003-11.
4. Chersich MF, Luchters S, Ntaganira I, Gerbase A, Lo YR, Scorgie F, *et al.* Priority interventions to reduce HIV transmission in sex work settings in sub-Saharan Africa and delivery of these services. J Int AIDS Soc. 2013;16:17980.
5. MacAllister J, Sherwood J, Galjour J, Robbins S, Zhao J, Dam K, *et al.* A comprehensive review of available epidemiologic and HIV service data for female sex workers, men who have sex with men, and people who inject drugs in select West and Central African countries. J Acquired Immune Defic Syndr. 2015;68:S83-S90. doi: 10.1097/qai.0000000000000457.
6. Beyrer C, Baral SD, Collins C, Richardson ET, Sullivan PS, Sanchez J, *et al.* The global response to HIV in men who have sex with men. Lancet. 2016;388(10040):198-206. doi: 10.1016/s0140-6736(16)30781-4.
7. Beyrer C, Baral SD, Griensven FV, Goodreau SM. Global epidemiology of HIV infection in men who have sex with men: Elsevier; 2012.
8. Baral SD, Friedman MR, Geibel S, Rebe K, Bozhinov B, Diouf D, *et al.* Male sex workers: practices, contexts, and vulnerabilities for HIV acquisition and transmission. Lancet. 2015;385(9964):260-73. PubMed PMID: WOS:000348044800030.
9. Poteat T, Reisner SL, Radix A. HIV epidemics among transgender women: ncbi.nlm.nih.gov; 2014. doi: 10.1097/COH.0000000000000030.
10. UNAIDS. UNAIDS data 2019. https://www.unAIDS.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf; 2019.
11. Baral SD, Grosso A, Holland C, Papworth E. The epidemiology of HIV among men who have sex with men in countries with generalised HIV epidemics. Curr Opin HIV AIDS. 2014;9(2):156-67. doi: 10.1097/coh.0000000000000037.
12. Poteat T, Ackerman B, Diouf D, Ceesay N, Mothopeng T, Odette KZ, *et al.* HIV prevalence and behavioural and psychosocial factors among transgender women and cisgender men who have sex with men in 8 African countries: A cross-sectional analysis. PLOS Med. 2017;14(11).
13. Poteat T, Wirtz AL, Radix A, Borquez A, Silva-Santisteban A, Deutsch MB, *et al.* HIV risk and preventive interventions in transgender women sex workers. Lancet. 2015;385(9964):274-86.
14. UNAIDS. Confronting inequalities. Lessons for pandemic responses from 40 years of AIDS. https://www.unAIDS.org/sites/default/files/media_asset/2021-global-AIDS-update_en.pdf; 2021.
15. UNAIDS. Estimating the size of populations at risk for HIV. https://data.unAIDS.org/publications/external-documents/estimatingpopsizes_en.pdf; 2003.
16. Baral S, Sifakis F, Cleghorn F, Beyrer C. Elevated risk for HIV infection among men who have sex with men in low- and middle-income countries 2000-2006: a systematic review. PLOS Med. 2007;4(12):e339.

17. Baral SD, Poteat T, Stromdahl S, Wirtz AL, Guadamuz TE, Beyrer C. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. Lancet Infect Dis. 2013;13(3):214-22.

18. Smith AD, Tapsoba P, Peshu N, Sanders EJ, Jaffe HW. Men who have sex with men and HIV/AIDS in sub-Saharan Africa. Lancet. 2009;374(9687):416-22.

19. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Bmj. 2009;339:b2700.

20. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc. 2015;13(3):147-53.

21. DHS. The DHS program STATcompiler. http://www.statcompiler.com (accessed 17 March 2022).

22. DHS. Methodology. https://www.dhsprogram.com/What-We-Do/Survey-Types/DHS.cfm (accessed 17 March 2022).

23. Bulstra CA, Hontelez JAC, Giardina F, Steen R, Nagelkerke NJD, Bärnighausen T, *et al.* Mapping and characterising areas with high levels of HIV transmission in sub-Saharan Africa: A geospatial analysis of national survey data. PLOS Med. 2020;17(3):e1003042.

24. Cuadros DF, Li J, Branscum AJ, Akullian A, Jia P, Mziray EN, *et al.* Mapping the spatial variability of HIV infection in Sub-Saharan Africa: Effective information for localized HIV prevention and control. Sci Rep. 2017;7(1):9093.

25. Dwyer-Lindgren L, Cork MA, Sligar A, Steuben KM, Wilson KF, Provost NR, *et al.* Mapping HIV prevalence in sub-Saharan Africa between 2000 and 2017. Nature. 2019;570(7760):189-93. PubMed PMID: 31092927.

26. UNAIDS. Countries: UNAIDS. https://www.unAIDS.org/en/regionscountries/countries; 2020.

27. Caceres CF, Konda K, Segura ER, Lyerla R. Epidemiology of male same-sex behaviour and associated sexual health indicators in low- and middle-income countries: 2003-2007 estimates. Sex Transm Infect. 2008;84 Suppl 1:i49-i56. PubMed PMID: 18647866; PubMed Central PMCID: PMC2569188.

28. United Nations. Population: United Nations department of social affairs. https://www.un.org/en/development/desa/population/publications/database/index.asp (accessed 17 March 2022).

29. Stannah J, Dale E, Elmes J, Staunton R, Beyrer C, Mitchell KM, *et al.* HIV testing and engagement with the HIV treatment cascade among men who have sex with men in Africa: a systematic review and meta-analysis. Lancet HIV. 2019;6(11):e769-e87. PubMed PMID: 31601542; PubMed Central PMCID: PMC6993044.

30. Kendall C, Kerr LRFS, Mota RMS, Cavalcante S, Macena RHM, Chen S, *et al.* Population size, HIV, and behaviour among MSM in Luanda, Angola: Challenges and findings in the first ever HIV and syphilis biological and behavioural survey. J Acquired Immune Defic Syndr. 2014;66(5):544-51. doi: 10.1097/qai.0000000000000213.

31. Tafuma TA, Merrigan MB, Okui LA, Lebelonyane R, Bolebantswe J, Mine M, *et al.* HIV/sexually transmitted infection prevalence and sexual behaviour of men who have sex with men in 3 districts of botswana: Results from the 2012 biobehavioural survey. Sex Transm Dis. 2014;41(8):480-5.

32. Holland CE, Kouanda S, Lougué M, Pitche VP, Schwartz S, Anato S, *et al.* Using population-size estimation and cross-sectional survey methods to evaluate HIV service coverage among key populations in Burkina Faso and Togo. Public Health Rep. 2016;131(6):773-82.

33. Yaya I, Boyer V, Ehlan PA, Coulibaly A, Agboyibor MK, Traoré I, *et al.* Heterogeneity in the prevalence of high-risk human papillomavirus infection in HIV-negative and HIV-positive men who have sex with men in West Africa. Clin Infect Dis. 2021.

34. Park JN, Papworth E, Kassegne S, Moukam L, Billong SC, Macauley I, *et al.* HIV prevalence and factors associated with HIV infection among men who have sex with men in Cameroon. J Int AIDS Soc. 2013;16 Suppl 3:18752.

35. Marcel MS, de Dieu LJ, Magloire CPS, Grésenguet G, Ralph-Sydney MB, Piette D, *et al.* Persistent high-risk behaviour and escalating HIV, syphilis and hepatitis b incidences among men who have sex with men living in Bangui, central African republic. Pan Afr Med J. 2018;29.

36. Hakim AJ, Aho J, Semde G, Diarrassouba M, Ehoussou K, Vuylsteke B, *et al.* The epidemiology of HIV and prevention needs of men who have sex with men in Abidjan, Cote d'Ivoire. PLOS ONE. 2015;10(4). doi: 10.1097/olq.0000000000000160.

37. Mason K, Ketende S, Peitzmeier S, Ceesay N, Diouf D, Loum J, *et al.* A cross-sectional analysis of population demographics, HIV knowledge and risk behaviours, and prevalence and associations of HIV among men who have sex with men in the gambia. AIDS Res Hum Retroviruses. 2013;29(12):1547-52.

38. Muraguri N, Tun W, Okal J, Broz D, Fisher Raymond H, Kellogg T, *et al.* HIV and STI prevalence and risk factors among male sex workers and other men who have sex with men in nairobi, kenya. J Acquired Immune Defic Syndr. 2015;68(1):91-6.

39. Bhattacharjee P, Isac S, Musyoki H, Emmanuel F, Olango K, Kuria S, *et al.* HIV prevalence, testing and treatment among men who have sex with men through engagement in virtual sexual networks in Kenya: a cross-sectional bio-behavioural study. J Int AIDS Soc. 2020;23(S2).

40. Gebrebrhan H, Kambaran C, Sivro A, Adhiambo W, Siele N, Becker MG, *et al.* Rectal microbiota diversity in Kenyan MSM is inversely associated with frequency of receptive anal sex, independent of HIV status. AIDS. 2021;35(7):1091-101.

41. Sandfort TGM, Dominguez K, Kayange N, Ogendo A. HIV testing and the HIV care continuum among sub-Saharan African men who have sex with men and transgender women screened for participation in HPTN 75. PLOS ONE. 2019.

42. Smith AD, Kimani J, Kabuti R, Weatherburn P, Fearon E, Bourne A. HIV burden and correlates of infection among transfeminine people and cisgender men who have sex with men in Nairobi, Kenya: an observational study. Lancet HIV. 2021;8(5):e274-e83. PubMed PMID: 33631101.

43. Stahlman S, Johnston LG, Yah C, Ketende S, Maziya S, Trapence G, *et al.* Respondent-driven sampling as a recruitment method for men who have sex with men in southern sub-Saharan Africa: a cross-sectional analysis by wave. Sex Transm Infect. 2016;92(4):292-8. doi: 10.1136/sextrans-2015-052184.

44. Wirtz AL, Trapence G, Kamba D, Gama V, Chalera R, Jumbe V, *et al.* Geographical disparities in HIV prevalence and care among men who have sex with men in Malawi: results from a multisite cross-sectional survey. Lancet HIV. 2017;4(6):e260-e9. doi: 10.1016/s2352-3018(17)30042-5.

45. Lahuerta M, Patnaik P, Ballo T, Telly N, Knox J, Traore B, *et al.* HIV Prevalence and Related Risk Factors in Men Who Have Sex with Men in Bamako, Mali: Findings from a Bio-behavioural Survey Using Respondent-Driven Sampling. 2017. PubMed PMID: 28516378.

46. Koyalta D, Mboumba Bouassa RS, Maiga A, Balde A, Bagendabanga JB, Alinity AA, *et al.* High Prevalence of Anal Oncogenic Human Papillomavirus Infection in Young Men Who Have Sex with Men Living in Bamako, Mali. Infect Agents Cancer. 2021;16(1). doi: 10.1186/s13027-021-00385-0.

47. Nalá R, Cummings B, Horth R, Inguane C, Benedetti M, Chissano M, *et al.* Men who have sex with men in Mozambique: identifying a hidden population at high-risk for HIV. AIDS Behav. 2015;19(2):393-404. doi: 10.1007/s10461-014-0895-8.

48. Keshinro B, Crowell TA, Nowak RG, Adebajo S, Peel S, Gaydos CA, *et al.* High prevalence of HIV, chlamydia and gonorrhoea among men who have sex with men and transgender women attending trusted community centres in Abuja and Lagos, Nigeria. J Int AIDS Soc. 2016;19(1). doi: 10.7448/ias.19.1.21270.

49. Bamgboye EA, Badru T, Bamgboye A. Transactional Sex between Men and Its Implications on HIV and Sexually Transmitted Infections in Nigeria. J Sex Transm Dis. 2017;2017:1810346. PubMed PMID: 28845320.

50. Vu L, Adebajo S, Tun W, Sheehy M, Karlyn A, Njab J, *et al.* High HIV prevalence among men who have sex with men in Nigeria: Implications for combination prevention. J Acquired Immune Defic Syndr. 2013;63(2):221-7. doi: 10.1097/QAI.0b013e31828a3e60.

51. Ramadhani HO, Crowell TA, Nowak RG, Ndembi N, Kayode BO, Kokogho A, *et al.* Association of age with healthcare needs and engagement among Nigerian men who have sex with men and transgender women: cross-sectional and longitudinal analyses from an observational cohort. J Int AIDS Soc. 2020;23 Suppl 6(Suppl 6):e25599. PubMed PMID: 33000907.

52. Ntale RS, Rutayisire G, Mujyarugamba P, Shema E, Greatorex J, Frost SDW, *et al.* HIV seroprevalence, self-reported STIs and associated risk factors among men who have sex with men: a cross-sectional study in Rwanda, 2015. 2018. PubMed PMID: 29680827.

53. Murenzi G, Kim HY, Munyaneza A, Tuyisenge P, Zawadi TM, Buteera AM, *et al.* Anogenital Human Papillomavirus and HIV Infection in Rwandan Men Who Have Sex With Men. J Acquir Immune Defic Syndr. 2020;84(5):463-9. PubMed PMID: 32692104.

54. Rwema JOT, Lyons CE. HIV infection and engagement in HIV care cascade among men who have sex with men and transgender women in Kigali, Rwanda: a cross-sectional study. Journal of the International AIDS Society 2020.

55. Drame FM, Crawford EE, Diouf D, Beyrer C, Baral SD. A pilot cohort study to assess the feasibility of HIV prevention science research among men who have sex with men in Dakar, Senegal. J Int AIDS Soc. 2013;16 Suppl 3:18753. PubMed PMID: 24321115.

56. Lyons CE, Ketende S, Diouf D, Drame FM, Liestman B, Coly K, *et al.* Potential impact of integrated stigma mitigation interventions in improving HIV/AIDS service delivery and uptake for key populations in senegal. J Acquired Immune Defic Syndr. 2017;74:S52-S9.

57. Jobson G, Tucker A, de Swardt G, Rebe K, Struthers H, McIntyre J, *et al.* Gender identity and HIV risk among men who have sex

with men in Cape Town, South Africa. AIDS Care Psychol Socio-Med Asp AIDS HIV. 2018:1-5.

58. Fearon E, Tenza S, Mokoena C, Moodley K, Smith AD, Bourne A, *et al.* HIV testing, care and viral suppression among men who have sex with men and transgender individuals in Johannesburg, South Africa. PLOS ONE. 2020;15(6).

59. Lane T, Osmand T, Marr A, Shade SB, Dunkle K, Sandfort T, *et al.* The mpumalanga men's study (MPMS): Results of a baseline biological and behavioural hiv surveillance survey in two msm communities in south africa. PLOS ONE. 2014;9(11).

60. Sandfort TG, Lane T, Dolezal C, Reddy V. Gender Expression and Risk of HIV Infection Among Black South African Men Who Have Sex with Men. AIDS Behav. 2015;19(12):2270-9.

61. Sullivan PS, Phaswana-Mafuya N, Baral SD, Valencia R, Zahn R, Dominguez K, *et al.* HIV prevalence and incidence in a cohort of South African men and transgender women who have sex with men: the Sibanye Methods for Prevention Packages Programme (MP3) project. J Int AIDS Soc. 2020;23(S6).

62. Baral SD, Ketende S, Mnisi Z, Mabuza X, Grosso A, Sithole B, *et al.* A cross-sectional assessment of the burden of HIV and associated individual- and structural-level characteristics among men who have sex with men in Swaziland. J Int AIDS Soc. 2013;16 Suppl 3:18768.

63. Ross MW, Nyoni J, Ahaneku HO, Mbwambo J, McClelland RS, McCurdy SA. High HIV seroprevalence, rectal STIs and riskxy sexual behaviour in men who have sex with men in Dar es Salaam and Tanga, Tanzania. BMJ Open. 2014;4(8).

64. Khatib A, Haji S, Khamis M, Said C, Khalid F, Dahoma M, *et al.* Reproducibility of Respondent-Driven Sampling (RDS) in Repeat Surveys of Men Who have Sex with Men, Unguja, Zanzibar. AIDS Behav. 2017;21(7):2180-7.

65. Ishungisa AM, Moen K, Leyna G, Makyao N, Ramadhan A, Lange T, *et al.* HIV prevalence among men who have sex with men following the implementation of the HIV preventive guideline in Tanzania: Respondent-driven sampling survey. BMJ Open. 2020;10(10).

66. Mmbaga EJ, Moen K, Makyao N, Mpembeni R, Leshabari MT. HIV and STI s among men who have sex with men in Dodoma municipality, Tanzania: A cross-sectional study. Sex Transm Infect. 2017;93(5):314-9.

67. Mmbaga EJ, Moen K, Leyna GH, Mpembeni R, Leshabari MT. HIV Prevalence and Associated Risk Factors Among Men Who Have Sex With Men in Dar es Salaam, Tanzania. J Acquir Immune Defic Syndr. 2018;77(3):243-9.

68. Teclessou JN, Akakpo SA, Ekouevi KD, Koumagnanou G, Singo-Tokofai A, Pitche PV. Evolution of HIV prevalence and behavioural factors among MSM in Togo between 2011 and 2015. Pan Afr Med J. 2017;28.

69. Tchankoni MK, Gbeasor-Komlanvi FA, Bitty-Anderson AM, Sewu EK, Zida-Compaore WIC, Alioum A, *et al.* Prevalence and factors associated with psychological distress among key populations in Togo, 2017. PLOS ONE. 2020;15(4).

70. Ferré VM, Gbeasor-Komlanvi FA. *et al.* Prevalence of human papillomavirus, human immunodeficiency virus and other sexually transmitted infections among female sex workers in Togo: a national cross-sectional survey. Clinical Microbiol Infect. 2019.

71. Hladik W, Sande E, Berry M, Ganafa S, Kiyingi H, Kusiima J, *et al.* Men Who Have

Sex with Men in Kampala, Uganda: Results from a Bio-Behavioural Respondent Driven Sampling Survey. AIDS Behav. 2017;21(5):1478-90.

72. Parmley LE, Chingombe I, Wu Y, Mapingure M, Mugurungi O, Samba C, *et al.* High burden of active syphilis and HIV/syphilis co-infection among men who have sex with men, transwomen, and genderqueer individuals in Zimbabwe. Sex Transm Dis. 2021.

73. Stahlman S, Liestman B, Ketende S, Kouanda S, Ky-Zerbo O, Lougue M, *et al.* Characterizing the HIV risks and potential pathways to HIV infection among transgender women in Cote d'Ivoire, Togo and Burkina Faso. J Int AIDS Soc. 2016;19.

74. McKinnon LR, Gakii G, Juno JA, Izulla P, Munyao J, Ireri N, *et al.* High HIV risk in a cohort of male sex workers from Nairobi, Kenya. Sex Transm Infect. 2014;90(3):237-42.

75. Smith AD, Muhaari AD, Agwanda C, Kowuor D, Van Der Elst E, Davies A, *et al.* Heterosexual behaviours among men who sell sex to men in coastal Kenya. AIDS. 2015;29:S201-S10.

76. Crowell TA, Keshinro B, Baral SD, Schwartz SR, Stahlman S, Nowak RG, *et al.* Stigma, access to healthcare, and HIV risks among men who sell sex to men in Nigeria. J Int AIDS Soc. 2017;20(1).

77. Hessou PHS, Glele-Ahanhanzo Y, Adekpedjou R, Ahouada C, Johnson RC, Boko M, *et al.* Comparison of the prevalence rates of HIV infection between men who have sex with men (MSM) and men in the general population in sub-Saharan Africa: a systematic review and meta-analysis. BMC Public Health. 2019;19(1):1634.

78. Zhang Y, Fogel JM, Guo X, Clarke W, Breaud A, Cummings V, *et al.* Antiretroviral drug use and HIV drug resistance among MSM and transgender women in sub-Saharan Africa. AIDS. 2018;32(10):1301-6.

79. Kimani M, van der Elst EM, Chiro O, Oduor C, Wahome E, Kazungu W, *et al.* PrEP interest and HIV-1 incidence among MSM and transgender women in coastal Kenya. J Int AIDS Soc. 2019;22(6):e25323.

80. Wahome EW, Graham SM, Thiong'o AN, Mohamed K, Oduor T, Gichuru E, *et al.* PrEP uptake and adherence in relation to HIV-1 incidence among Kenyan men who have sex with men. EClinicalMedicine. 2020;26:100541.

81. Poteat T, Malik M, Scheim A, Elliott A. HIV Prevention Among Transgender Populations: Knowledge Gaps and Evidence for Action. Curr HIV/AIDS Rep. 2017;14(4):141-52.

82. UNAIDS. Ending AIDS: progress towards the 90–90–90 targets. https://www.unAIDS.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf; 2017.

83. Malekinejad M, Johnston LG, Kendall C, Kerr LR, Rifkin MR, Rutherford GW. Using respondent-driven sampling methodology for HIV biological and behavioural surveillance in international settings: a systematic review. AIDS Behav. 2008;12(4 Suppl):S105-30.

84. Johnston LG, Khanam R, Reza M, Khan SI, Banu S, Alam MS, *et al.* The effectiveness of respondent driven sampling for recruiting males who have sex with males in Dhaka, Bangladesh. AIDS Behav. 2008;12(2):294-304.

85. Yeka W, Maibani-Michie G, Prybylski D, Colby D. Application of respondent driven sampling to collect baseline data on FSWs and MSM for HIV risk reduction interventions in two urban centres in Papua New Guinea. J Urban Health. 2006;83(6 Suppl):i60-72

SUPPORTING INFORMATION TO CHAPTER 4

Supplementary File 1. Systematic literature search

Date of searches

Initial search: 4 June 2018, updated search: 22 October 2021

Search terms

Search terms based on Embase format

('LGBT people'/exp OR 'sex worker'/de OR (LGBT* OR GLBT* OR transgender* OR transsexual* OR MSM OR sexwork* OR prostitute* OR ((sex OR escort) NEAR/4 (work* OR sell* OR money OR gift* OR surviv* OR transaction* OR men OR man)) OR ((money OR call) NEAR/3 (boy*)) OR gay OR ((cross) NEXT/1 (dress*)) OR ((drag) NEXT/1 (queen*)) OR genderqueer* OR ((gender) NEXT/1 (queer OR nonconforming)) OR homosexual* OR bisexual*):ab,ti,kw) AND ('Human immunodeficiency virus infection'/exp OR (HIV OR AIDS OR ((human) NEXT/1 (immunodeficiency) NEXT/1 (virus))):ab,ti,kw) AND ('prevalence'/exp OR 'cross-sectional study'/de OR 'incidence'/exp OR 'odds ratio'/de OR 'risk factor'/de OR (Prevalen* OR "cross-sectional" OR incidence* OR ((risk* OR odds) NEAR/1 (factor* OR relative OR ratio*))):ab,ti,kw) AND ('Africa south of the Sahara'/exp OR (((black OR Central OR South) NEAR/3 (Africa*)) OR 'sub-Saharan' OR subSaharan* OR Angola OR Benin OR Botswana OR 'Burkina Faso' OR Burundi OR Cameroon OR 'Cape Verde' OR Chad OR Comoro* OR Congo OR ((Cote) NEAR/3 (Ivoir*)) OR Djibouti OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mayotte OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Sahel OR Senegal OR 'Sierra Leone' OR Somalia OR Sudan OR Swaziland OR Tanzania OR Togo OR Uganda OR Zambia OR Zimbabwe):ab,ti,kw) NOT ('Conference Abstract' OR Editorial)/it

Supplementary Table 1. Overview of complete literature searches, including updates

	Search 2020	Search 2020 with new in-/ exclusion criteria 2021		Update 2021		Manual search African Journal Online 2021	
	Count	Number of added/ deleted studies	Total Count 2020	Number of studies from update 2021	Total Count 2021	Number of studies from manual search 2021	Final count 2021
Eligible studies	**5,376**		**5,376**	***6,863***	**9,315**	***161***	**9,476**
Excluded	3,420		3,420	*6,393*	6,889	*0*	6,889
Duplicates	2,152		2,152	*3,342*	5,494		5,494
Published before 2010	1,268		1,268	*127*	1,395		1,395
Already included in 2020 search				*2,924*			
Included for review title and abstract	**1,956**		**1,956**	***470***	**2,426**	***161***	**2,587**
Excluded	1,782		1,782	*438*	2,220	*160*	2,380
Included for review full text	**174**		**174**	***32***	**206**	***1***	**207**
Excluded	125	*12*	137	*21*	158	*1*	159
Final included	**49**	***37***	**37**	***11***	**48**	***0***	**48**
Cisgender men who have sex with men	44	*-11*	33	*11*	44	*0*	44
Transgender women	4	*0*	4	*6*	10	*0*	10
Cisgender men sex workers	5	*0*	5	*0*	5	*0*	5
Transgender men	0	*0*	0	*0*	0	*0*	0
Transgender sex workers	0	*0*	0	*0*	0	*0*	0

Supplementary Table 2. Bias assessment. Bias amongst the included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist for studies reporting prevalence data.[2] Answer options are Y = Yes or N = No.

Study	Was the sample frame appropriate to address the target population?	Were study participant sampled in an appropriate way?	Was the sample size adequate?	Were study subjects and the setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all participants?	Was there appropriate statistical analysis?	Was the response rate adequate, and if not, was the low response rate managed appropriate?
Kendall *et al.* (2014) [30]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Tafuma *et al.* (2014) [31]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Holland *et al.* (2016) [32]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Yaya *et al.* (2021) [33]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Park *et al.* (2013) [34]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Marcel *et al.* (2019) [35]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Hakim *et al.* (2015) [36]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Mason *et al.* (2013) [37]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Muraguri *et al.* (2015) [38]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Battacharjee *et al.* (2020) [39]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Gebrebrhan *et al.* (2020) [40]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sandfort *et al.* (2019) [41]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Smith *et al.* (2021) [42]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Stahlman *et al.* (2016) [43]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Wirtz *et al.* (2017) [44]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Lahuerta *et al.* (2017) [45]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Kayolta *et al.* (2021) [46]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Nalá *et al.* (2015) [47]	Y	Y	Y	Y	Y	Y	Y	Y	Y

Supplementary Table 2. Bias assessment. Bias amongst the included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist for studies reporting prevalence data.[2] Answer options are Y = Yes or N = No. (*continued*)

Study	Was the sample frame appropriate to address the target population?	Were study participant sampled in an appropriate way?	Was the sample size adequate?	Were study subjects and the setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all participants?	Was there appropriate statistical analysis?	Was the response rate adequate, and if not, was the low response rate managed appropriate?
Keshinro *et al.* (2016) [48]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Bamgboye *et al.* (2017) [49]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Vu *et al.* (2013) [50]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ramadhani *et al.* (2020) [51]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ntale *et al.* (2018) [52]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Murenzi *et al.* (2020) [53]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Rwema *et al.* (2020) [54]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Dramé *et al.* (2013) [55]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Lyons *et al.* (2017) [56]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Jobson *et al.* (2018) [57]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Fearon *et al.* (2017) [58]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Lane *et al.* (2014) [59]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sandfort *et al.* (2015) [60]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sullivan *et al.* (2020) [61]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Baral *et al.* (2013) [62]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ross *et al.* (2014) [63]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Khatib *et al.* (2017) [64]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ishungisa *et al.* (2020) [65]	Y	Y	Y	Y	Y	Y	Y	Y	Y

Supplementary Table 2. Bias assessment. Bias amongst the included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist for studies reporting prevalence data.[2] Answer options are Y = Yes or N = No. (*continued*)

Study	Was the sample frame appropriate to address the target population?	Were study participant sampled in an appropriate way?	Was the sample size adequate?	Were study subjects and the setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all participants?	Was there appropriate statistical analysis?	Was the response rate adequate, and if not, was the low response rate managed appropriate?
Mmbaga *et al.* (2017) [66]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Mmbaga *et al.* (2018) [67]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Teclessou *et al.* (2017) [68]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Tchankoni *et al.* (2020) [69]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ferré *et al.* (2019) [70]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Hladik *et al.* (2017) [71]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Parmley *et al.* (2021) [72]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Poteat *et al.* (2017) [12]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Stahlman *et al.* (2016) [73]	Y	Y	Y	Y	Y	Y	Y	Y	Y
McKinnon *et al.* (2014) [74]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Smith *et al.* (2015) [75]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Crowell *et al.* (2016) [76]	Y	Y	Y	Y	Y	Y	Y	Y	Y

All bias indicators were assessed based on the purpose of the data in our study and most indicators are part of the exclusion criteria. We graded Yes for all studies if the type of *sample frame* met our in-/exclusion criteria. Therefore, all included studies are graded Yes. Likewise, for whether *participants were sampled in an appropriate way*. If for example targeting a specific high risk MSM group, or subgroup amongst MSM (such as drug using MSM) we excluded the study. Regarding the *sample size* and whether the *data analysis conducted with sufficient coverage of the identified sample*, for the forest plots, country- and region prevalence and prevalence ratios were calculated weighted by study size. For the question whether *subjects and setting were described in detail*, for us it was important to know how MSM, transgender women and MSW were identified in the study. In some cases, we would find misclassification based on inappropriate classification of these groups (as described in panel S1 terminology). If aggregated data was not presented, we have contacted authors and retrieved aggregated data. *Setting details* were needed to retrieve the location of the study. We excluded studies with self-testing only, or based on self-reported HIV status. *Was there appropriate statistical analysis?* For each study, we checked the prevalence calculation based on the total number of people tested and number of people infected. Inconsistencies were discussed with the corresponding authors.

Supplementary Table 3. Overview of the prevalence of HIV infection in cisgender men who have sex with men (MSM) in the included studies and prevalence of HIV in the general male population at the study location.

Study	Country and location	Year(s) of study recruitment	Recruitment method	No. tested for HIV	Mean or median and IQR or range of age of the total population	HIV prevalence (%) (95% confidence interval)	HIV prevalence general male population in study recruitment year (%) (95% confidence interval)
	Angola						
Kendall *et al.* (2014) [30]	Luande Province	2011	RDS	328	> 18	3.7 (1.5-6.3) [c]	0.9 (0.5–1.2)
	Botswana						
Tafuma *et al.* (2014) [31]	Gaborone	2012	RDS	275	23.2 (18–53)	12.3 (8.4–16.3) [a]	14.2 (14.2–14.2)
	Francistown			145		11.7 (6.5–16.9) [a]	20.2 (20.1–20.2)
	Kasane			30		25.9 (9.0–42.8) [a]	17.7 (17.4–18.0)
	Burkina Faso						
Holland *et al.* (2016) [32]	Ouagadougou	2013	RDS	339	> 18	4.7 (2.8–7.7) [a]	1.3 (1.0–1.6)
	Bobo Dioulasso			329		4.9 (2.9–8.0) [a]	2.0 (1.5–2.5)
Yaya *et al.* (2021) [33]	Ouagadougou	2017-2018	RDS	144	Age group 18-24 40.1%, Age group 25-34 51.0%, Age group 35+ 8.9%	31.9 (24.3-39.6) [a]	0.9 (0.0-2.0)
	Cameroon						
Park *et al.* (2013) [34]	Douala	2011	RDS	255	23[†] (IQR 21–27)	25.5 (19.1–31.9) [b]	2.2 (1.4–3.0)
	Yaounde			207	25[†] (IQR 21–28)	44.4 (35.7–53.2) [b]	2.2 (1.7–2.8)
	Central African Republic						
Marcel *et al.* (2019) [35]	Bangui	2010	RDS	99	24	41.0 (31.4–51.3) [a]	6.2 (3.9–9.7)

Supplementary Table 3. Overview of the prevalence of HIV infection in cisgender men who have sex with men (MSM) in the included studies and prevalence of HIV in the general male population at the study location. (*continued*)

Study	Country and location	Year(s) of study recruitment	Recruitment method	No. tested for HIV	Mean or median and IQR or range of age of the total population	HIV prevalence (%) (95% confidence interval)	HIV prevalence general male population in study recruitment year (%) (95% confidence interval)
	Cote D'Ivoire						
Hakim *et al.* (2015) [36]	Abidjan	2011–2012	RDS	581	23[+] (IQR 18–51)	18.0 (13.0–23.1) [b]	3.3 (3.3–3.3)
Yaya *et al.* (2021) [33]	Abidjan	2017-2018	RDS	129	Age group 18-24 40.1%, Age group 25-34 51.0%, Age group 35+ 8.9%	32.6 (24.5-40.6) [a]	4.3 (2.0-6.5)
	Eswatini						
Baral *et al.* (2013) [62]	Manzini	2011	RDS	284	23.1 (18–43)	13.4 (7.9–19.7) [b]	17.6 (15.8–19.4)
	The Gambia						
Mason *et al.* (2013) [37]	Banjul	NR	Snowball sampling	205	22 (16–48)	9.8 (6.2–14.9) [b]	0.6 (0.6–0.6)
	Kenya						
Muraguri *et al.* (2015) [38]	Nairobi	2010	RDS	290	> 18	12.2 (7.6–17.5) [b]	4.6 (2.4–6.9)
Battacharjee *et al.* (2020) [39]	Kisumu Mombasa Kiambu	2019	RDS	1200	23	16.8 (14.6–18.9) [a]	7.4 (4.9–11.1)
Gebrebrhan *et al.* (2020) [40]	Nairobi	2016	RDS	80	25[+] (IQR 23–30)	42.5 (31.7-53.3) [a]	6.2 (3.5-8.9)
Sandfort *et al.* (2019) [41]	Kisumu	2015-2016	Sampling frame of MSM organisations	157	Age group 18-20 8.8%, Age group 21-25 41.8%, Age group 26-44 49.5%	25.5 (18.7-32.3)	12.1 (8.5-15.8)

Supplementary Table 3. Overview of the prevalence of HIV infection in cisgender men who have sex with men (MSM) in the included studies and prevalence of HIV in the general male population at the study location. (*continued*)

Study	Country and location	Year(s) of study recruitment	Recruitment method	No. tested for HIV	Mean or median and IQR or range of age of the total population	HIV prevalence (%) (95% confidence interval)	HIV prevalence general male population in study recruitment year (%) (95% confidence interval)
Smith *et al.* (2021) [42]	Nairobi	2017	RDS	522	Age group 18-22 39%, Age group 23-29 39%, Age group 30+ 23%	25.0 (21.3-28.7) [a]	5.8 (3.2-8.4)
	Lesotho						
Stahlman *et al.* (2016) [43]	Maseru	2014	RDS	315	22[†] (IQR 20–26)	18.0 (12.8–23.2) [b]	29.4 (26.1–32.8)
	Malawi						
Wirtz *et al.* (2017) [44]	Blantyre	2011–2014	RDS	338	24[†]	12.5 (8.5–18.7) [b]	26.5 (22.4–30.6)
	Chikwawa			350		20.5 (15.7–26.5) [b]	8.6 (8.5–8.7)
	Mangochi			351		22.4 (17.3–28.5) [b]	15.2 (8.3–22.1)
	Mulanje			349		24.5 (19.5–30.3) [b]	17.3 (14.8–19.8)
	Lilongwe			362		17.7 (10.6–28.1) [b]	4.3 (2.7–5.9)
	Mzuzu			353		4.1 (2.2–7.6) [b]	4.2 (2.2–6.1)
	Nkhata Bay			350		20.6 (16.3–25.6) [b]	18.9 (12.5–25.3)
Sandfort *et al.* (2019) [60]	Blantyre	2015-2016	Sampling frame of MSM organisations	99	Age group 18-20 5.5%, Age group 21-25 31.2%, Age group 26-44 63.3%	30.3 (21.2-39.4)	24.7 (17.4-31.9)
	Mali						
Lahuerta *et al.* (2017) [45]	Bamako	2014–2015	RDS	550	> 18	13.7 (9.2–18.1) [b]	1.7 (1.1–2.3)
Kayolta *et al.* (2021) [49]	Bamako	2019	RDS	50	24.2 (18-35)	32.0 (19.1-44.9) [a]	1.5 (0.2-2.9)

Supplementary Table 3. Overview of the prevalence of HIV infection in cisgender men who have sex with men (MSM) in the included studies and prevalence of HIV in the general male population at the study location. (*continued*)

Study	Country and location	Year(s) of study recruitment	Recruitment method	No. tested for HIV	Mean or median and IQR or range of age of the total population	HIV prevalence (%) (95% confidence interval)	HIV prevalence general male population in study recruitment year (%) (95% confidence interval)
Yaya *et al.* (2021) [33]	Bamako	2017-2018	RDS	210	Age group 18-24 40.1%, Age group 25-34 51.0%, Age group 35+ 8.9%	32.9 (26.5-39.2) [a]	1.4 (0.1-2.7)
	Mozambique						
Nalá *et al.* (2015) [47]	Maputo			496	22[†]	8.2 (4.7–12.6) [b]	12.8 (11.1–14.5)
	Beira	2011	RDS	584	21[†]	9.1 (5.8–12.6) [b]	11.1 (9.1–13.1)
	Nampula/ Nacala			353	21[†]	3.7 (1.1–7.1) [b]	Nampula: 5.9 (5.9–5.9)
	Nigeria						
Keshinro *et al.* (2016) [48]	Abuja	2013–2016	RDS	546	24[†] (IQR 21–27)	43.5 (37.3–49.6) [b]	2.9 (2.9–2.9)
	Lagos			316		65.6 (54.7–76.5) [b]	1.8 (1.8–1.8)
Bamgboye *et al.* (2017) [49]	Eight major cities	2014	RDS	1960	>15	22.2 (20.3–24.1) [a]	Kano: 0.6 (0.6–0.6) Lagos: 1.8 (1.8–1.8) Cross River: 2.9 (2.9–2.9) Enugu: 1.5 (1.5–1.5) Kaduna: 1.8 (1.7–1.8) Rivers: 4.3 (4.2–4.3) Oyo: 1.2 (1.2–1.2) Federal Capital Territory: 2.8 (2.8–2.8)
Vu *et al.* (2013) [50]	Abuja	2010	RDS	174	25[†] (18–52)	34.9 (25.5–45.9) [c]	3.2 (3.2–3.2)

Supplementary Table 3. Overview of the prevalence of HIV infection in cisgender men who have sex with men (MSM) in the included studies and prevalence of HIV in the general male population at the study location. (*continued*)

Study	Country and location	Year(s) of study recruitment	Recruitment method	No. tested for HIV	Mean or median and IQR or range of age of the total population	HIV prevalence (%) (95% confidence interval)	HIV prevalence general male population in study recruitment year (%) (95% confidence interval)
	Ibadan			193	23[†] (18–43)	11.3 (5.1–16.8) [c]	1.4 (1.4–1.4)
	Lagos			297	21 (18–45)	15.2 (9.7–21.2) [c]	1.6 (1.6–1.6)
Ramadhani *et al.* (2020) [51]	Abuja Lagos	2013-2018	Sampling frame of MSM organisation	1379	Age group 16-19 15.8%, Age group 20-24 42.6%, Age group 25+ 41.5%	47.6 (40.5-54.7)	4.3 (2.1-6.6)
	Rwanda						
Ntale *et al.* (2018) [52]	Kigali	2015	Snowball sampling	227	23[†] (IQR 21–26)	4.4 (2.3–8.2) [a]	5.8 (5.3–6.4)
	Rubavu			64		7.8 (2.9–18.0) [a]	1.8 (1.4–2.2)
	Ruhanga			62		4.8 (1.2–14.3) [a]	3.2 (3.2–3.2)
	Musanze			44		4.6 (0.8–16.8) [a]	1.3 (0.9–1.8)
	Huye			107		3.7 (5.6–18.2) [a]	3.2 (2.6–3.8)
Murenzi *et al.* (2020) [53]	Kigali	2016–2017	Sampling frame of MSM organisation	345	>18	19.4 (15.4–24.1)	5.8 (5.3–6.4)
Rwema *et al.* (2020) [54]	Kigali	2018	RDS	630	Age group 18-24 46.6%, Age group 25-34 38.4%, Age group 35+ 15.1%	10.2 (7.8-12.6) [b]	5.4 (2.9-7.9)
	Senegal						
Dramé *et al.* (2013) [55]	Dakar	2011–2012	Sampling frame of MSM organisations	114	28 (18–42)	36.0 (27.4–45.6) [a]	1.1 (0.3–1.9)
Lyons *et al.* (2017) [56]	Dakar Mbour Thies	NR	Combination of RDS and purposive sampling	724	> 18	23.5 (20.5–26.8) [b]	1.1 (0.3–1.9) 0.0 (0.0–0.0) 0.1 (0.1–0.1)

Supplementary Table 3. Overview of the prevalence of HIV infection in cisgender men who have sex with men (MSM) in the included studies and prevalence of HIV in the general male population at the study location. (*continued*)

Study	Country and location	Year(s) of study recruitment	Recruitment method	No. tested for HIV	Mean or median and IQR or range of age of the total population	HIV prevalence (%) (95% confidence interval)	HIV prevalence general male population in study recruitment year (%) (95% confidence interval)
	South Africa						
Jobson *et al.* (2018) [57]	Townships Cape Town	NR	Chain referral sampling	153	26[†] (IQR 11)	30.7 (23.6–38.7)	7.4 (7.4–7.5)
	Durban			69		27.5 (17.0–38.1)	10.9 (10.9–10.9)
Fearon *et al.* (2017) [58]	Johannesburg	2017	RDS	233	26	40.8 (34.5–47.4) [a]	16.3 (12.5–21.0)
Lane *et al.* (2014) [59]	Gert Sibande district	2012–2013	RDS	195	> 18	28.3 (21.1–35.3) [b]	16.8 (16.7–16.8)
	Ehlanzeni district			259	> 18	13.7 (9.1–19.6) [b]	16.8 (16.8–16.9)
Sandfort *et al.* (2015) [60]	Tshwane	2011–2013	RDS	480	24.5 (18–44)	30.1 (26.1–34.5) [b]	9.1 (9.0–9.1)
Sullivan *et al.* (2020) [61]	Cape Town Port Elizabeth	2015-2016	Sampling frame from MSM organisation	263	Age group 18-19 21.7% CT, 10.2% PE Age group 20-24 34.8% CT, 46.3% PE Age group 25+ 34.5% CT, 34.5% PE	42.0 (36.0-48.0)	13.1 (9.3-16.8)

Supplementary Table 3. Overview of the prevalence of HIV infection in cisgender men who have sex with men (MSM) in the included studies and prevalence of HIV in the general male population at the study location. (*continued*)

Study	Country and location	Year(s) of study recruitment	Recruitment method	No. tested for HIV	Mean or median and IQR or range of age of the total population	HIV prevalence (%) (95% confidence interval)	HIV prevalence general male population in study recruitment year (%) (95% confidence interval)
Sandfort *et al.* (2019) [60]	Cape Town (CT) Soweto (S)	2015-2016	Sampling frame from MSM organisation	140 194	Age group 18-20 23.6% CT, 12.1% S Age group 21-25 41.0% CT, 39.0% S Age group 26-44 35.4% CT, 48.9%	44.3 (36.1-52.5) 60.9 (54.0-67.8)	10.9 (7.4-14.4) 16.9 (12.6-21.0)
	Tanzania						
Ross *et al.* (2014) [63]	Dar es Salaam	2012	RDS	172	23† (IQR 21–28)	30.2 (23.6–37.7) [a]	4.1 (4.1–4.1)
	Tanga	2013		90	NR	11.1 (5.7–19.9) [c]	2.3 (2.3–2.3)
Khatib *et al.* (2017) [64]	Unganja, Zanzibar	2011	RDS	2011: 339	> 15	2011: 2.6 (1.0–4.7) [c]	0.6 (0.6–0.6)
Ishungisa *et al.* (2020) [65]	Dar es Salaam	2017	RDS	777	Age group 15-19 17.3%, Age group 20-24 34.8%, Age group 25-29 19.6%, Age group 30-34 13.5%, Age group 35+ 14.8%	8.3 (6.4-10.2) [b]	4.6 (2.2-6.9)
Mmbaga *et al.* (2017) [66]	Dodoma municipality	2014	RDS	387	27† (8–60)	17.4 (12.6–25.4) [b]	2.2 (2.2–2.2)
Mmbaga *et al.* (2018) [67]	Dar es Salaam	2014	RDS	646	26.5	22.3 (18.5–26.2) [b]	3.7 (3.7–3.7)

Supplementary Table 3. Overview of the prevalence of HIV infection in cisgender men who have sex with men (MSM) in the included studies and prevalence of HIV in the general male population at the study location. (*continued*)

Study	Country and location	Year(s) of study recruitment	Recruitment method	No. tested for HIV	Mean or median and IQR or range of age of the total population	HIV prevalence (%) (95% confidence interval)	HIV prevalence general male population in study recruitment year (%) (95% confidence interval)
	Togo						
Holland *et al.* (2016) [32]	Lomé	2013	RDS	354	> 18	18.5 (14.7–23.0) [a]	2.7 (2.1–3.3)
	Kara			329		0.6 (0.1–2.4) [a]	5.5 (4.3–6.7)
Teclessou *et al.* (2017) [68]	Lome	2011–2015	RDS	215	22[†] (IQR 21–26)	22.3 (17.0–28.6) [a]	2.72 (2.12–3.32)
	Eight cities			281	23[†] (IQR 21–28)	5.7 (3.4–9.3) [a]	Cinkasse: 2.0 (1.3–2.7) Dapaong: 0.0 (0.0–0.0) Kara: 5.5 (4.3–6.7) Sokode: 2.5 (1.9–3.1) Atakpame: 0.0 (0.0–0.0) Tsevie: 2.3 (2.3–2.3) Kpalime: 2.9 (1.7–4.1) Aneho: 1.5 (0.6–2.4)
Tchankoni *et al.* (2020) [69]	Eight cities	2017	RDS	643	23	21.6 (18.5–25.0) [b]	2.1 (1.5–2.7)
Ferre *et al.* (2019) [70]	Lome Kpalime Atakpama Tsevie	2017	RDS	207	22[†] (IQR 20–26)	26.1 (20.1-32.1) [a]	2.4 (0.7-4.1)
Yaya *et al.* (2021) [33]	Lome	2017-2018	RDS	148	Age group 18-24 40.1%, Age group 25-34 51.0%, Age group 35+ 8.9%	33.1 (25.5-40.7) [a]	2.6 (0.8-4.3)
	Uganda						

Supplementary Table 3. Overview of the prevalence of HIV infection in cisgender men who have sex with men (MSM) in the included studies and prevalence of HIV in the general male population at the study location. (*continued*)

Study	Country and location	Year(s) of study recruitment	Recruitment method	No. tested for HIV	Mean or median and IQR or range of age of the total population	HIV prevalence (%) (95% confidence interval)	HIV prevalence general male population in study recruitment year (%) (95% confidence interval)
Hladik *et al.* (2017) [71]	Kampala	2012–2013	RDS	607	23[†] (IQR 21–26)	12.2 (7.9–15.9) [b]	4.5 (4.5–4.5)
	Zimbabwe						
Parmley *et al.* (2021) [72]	Harare Bulawayo	2019	RDS and chain referral	416 760	Age group 18-24 46.9%, Age group 25-34 35.4%, Age group 35-44 12.2%, Age group 45+ 5.5%	17.1 (13.5-20.7) [b] 23.3 (20.3-26.3) [b]	12.4 (8.7-16.0) 16.0 (11.9-20.1)

For studies that used respondent driven sampling (RDS) to enrol participants, we preferred to retrieve the RDS adjusted prevalence data. If these were not presented, we retrieved crude prevalence estimates.

[†] Median

[a] Crude HIV prevalence

[b] Respondent driven sampling (RDS) adjusted HIV prevalence

[c] Respondent driven sampling analysis tool (RDSAT) adjusted HIV prevalence

Supplementary Table 4. Overview of the prevalence of HIV infection in transgender women in the included studies and prevalence of HIV in the general male and female population at the study location.

Study	Country and location	Year(s) of study	Recruitment method	No. tested for HIV	Mean or median and IQR or range of age of the total population	HIV prevalence (%) (95% confidence interval)	HIV prevalence general population (%) (95% confidence interval)
	Burkina Faso						
Poteat *et al.* (2017) [12]	Bobo-Dioulasso and Ouagadougou	2013	RDS	108	23.68 (16–56)	3 (0.7–9.2) [a]	Bobo-Dioulasso: 2.7 (2.5–2.9) Ouagadougou: 2.4 (2.2–2.6)
Stahlman *et al.* (2016) [43]	Bobo-Dioulasso Ouagandougou	2013	RDS	75 23	21[†] (IQR 20–24)	5.1 (1.9–12.1) [a]	Bobo-Dioulasso: 2.7 (2.5–2.9) Ouagadougou: 2.4 (2.2–2.6)
	Cote D'Ivoire						
Poteat *et al.* (2017) [12]	Abidjan, Bouake, Gagnoa, and Yamoussoukro	2015–2016	RDS	298	23.68 (16–56)	26 (21.2–31.4) [a]	Abidjan: 4.52 (4.5–4.5) Bouake: 3.3 (3.3–3.3) Gagnoa: 2.5 (2.5–2.5) Yamoussoukro: 3.4 (3.3–3.7)
Stahlman *et al.* (2016) [43]	Abidjan, Bouake, Gagnoa, Yamoussoukro	2015	RDS	306	23[†] (IQR 21–27)	23.5 (18.9–28.7) [a]	Abidjan: 4.63 (4.61–4.64) Bouake: 3.12 (3.12–3.11) Gagnoa: 2.63 (2.63–2.64) Yamoussoukro: 3.44 (3.43–3.45)
	Eswatini						
Poteat *et al.* (2017) [12]	Mbabane	2011	RDS	120	23.68 (16–56)	14.0 (8.6–21.8) [a]	25.5 (24.7–26.3)
	The Gambia						
Poteat *et al.* (2017) [12]	Banjul	2011	Snowball sampling	4	23.68 (16–56)	50.0 (9.2–90.8) [a]	1.8 (1.8–1.8)
	Kenya						
Sandfort *et al.* (2019) [41]	Kisumu	2015-2016	Samling frame of MSM organisation	40	Age group 18-20 2.3%, Age group 21-25 35.9%, Age group 26-44 61.5%	40.0 (24.8-55.2)	12.1 (8.5-15.8)

Supplementary Table 4. Overview of the prevalence of HIV infection in transgender women in the included studies and prevalence of HIV in the general male and female population at the study location. (*continued*)

Study	Country and location	Year(s) of study	Recruitment method	No. tested for HIV	Mean or median and IQR or range of age of the total population	HIV prevalence (%) (95% confidence interval)	HIV prevalence general population (%) (95% confidence interval)
Smith *et al.* (2021) [42]	Nairobi	2017	RDS	70	Age group 18-22 32.0%, Age group 23-29 49.0%, Age group 30+ 23.0%	41.0 (29.5-52.5) [a]	5.8 (3.2-8.4)
	Lesotho						
Poteat *et al.* (2017) [12]	Maputsoe Maseru	2014	RDS	71	23.68 (16–56)	59 (46.7–70.3) [a]	28.6 (27.2–30.1) 32.4 (30.6–34.3)
	Malawi						
Poteat *et al.* (2017) [12]	Lilongwe	2011–2012	RDS	75	23.68 (16–56)	16.0 (8.9–26.7) [a]	7.6 (6.3–8.9)
Sandfort *et al.* (2019) [41]	Blantyre	2015-2016	Sampling frame of MSM organisation	50	Age group 18-20 5.5%, Age group 21-25 31.2%, Age group 26-44 63.3%	48.0 (34.2-61.8)	15.9 (11.9-20.0)
	Nigeria						
Ramadhani *et al.* (2020) [51]	Abuja Lagos	2013-2018	Sampling frame of MSM organisation	190	Age group 16-19 15.8%, Age group 20-24 42.6%, Age group 25+ 41.5%	59.5 (56.9-62.1)	4.3 (2.1-6.6)
	Rwanda						
Rwema *et al.* (2020) [54]	Kigali	2018	RDS	106	Age group 18-24 39.6%, Age group 25-34 50.9%, Age group 35+ 9.5%	9.4 (3.8-15.0) [b]	5.4 (2.9-7.9)
	Senegal						
Poteat *et al.* (2017) [12]	Dakar	2015	RDS	199	23.68 (16–56)	39.0 (32.3–46.2) [a]	0.5 (0.0–2.3)
	South Africa						
Jobson *et al.* (2018) [57]	Cape Town	NR	Chain referral sampling	18	26 (IQR 15–37)	57.0 (32.6–78.7) [a]	11.0 (10.9–11.1)

Supplementary Table 4. Overview of the prevalence of HIV infection in transgender women in the included studies and prevalence of HIV in the general male and female population at the study location. (*continued*)

Study	Country and location	Year(s) of study	Recruitment method	No. tested for HIV	Mean or median and IQR or range of age of the total population	HIV prevalence (%) (95% confidence interval)	HIV prevalence general population (%) (95% confidence interval)
Fearon *et al.* (2020) [58]	Johannesburg	2017	RDS	44	26	45.5 (30.7–61.4) [a]	16.3 (12.5–21.0)
Sullivan *et al.* (2020) [61]	Cape Town (CT) Port Elizabeth (PE)	2015-2016	RDS	22	Age group 18-19 21.7% CT, 10.2% PE Age group 20-24 34.8% CT, 46.3% PE Age group 25+ 34.5% CT, 34.5% PE	59.0 (38.4-79.6) [a]	13.1 (9.3-16.8)
Sandfort *et al.* (2019) [41]	Cape Town (CT) Soweto (S)	2015-2016	Sampling frame of MSM organisation	43 61	Age group 18-20 23.7% CT, 15.7% S Age group 21-25 10.2% CT, 45.7% S Age group 26-44 66.1% CT, 38.6% S	60.5 (45.9-75.1) 82.0 (72.4-91.6)	10.9 (7.4-14.4) 16.8 (12.6-21.0)
	Togo						
Poteat *et al.* (2017) [12]	Kara Lomé	2013	RDS	51	23.68 (16–56)	18.0 (9.1–31.8) [a]	4.4 (3.8–5.1) 4.8 (3.2–6.4)
Stahlman *et al.* (2016) [43]	Kara Lomé	2012–2013	RDS	49	21[†] (IQR 20–25)	18.8 (9.6–33.0) [a]	4.4 (3.8–5.1) 4.8 (3.2–6.4)
	Zimbabwe						
Parmley *et al.* (2021) [72]	Harare Bulawayo	2019	RDS and chain referral	279 56	Age group 18-20 46.9%, Age group 21-25 35.4%, Age group 26-44 12.2%, Age group 45+ 5.5%	28.0 (22.7-33.3) [b] 25.0 (13.7-36.3) [b]	12.3 (8.6-15.9) 16.1 (12.0-20.1)

For studies that used respondent driven sampling (RDS) to enrol participants, we preferred to retrieve the RDS adjusted prevalence data. If these were not presented, we retrieved crude prevalence estimates.

[†] Median

[a] Crude HIV prevalence

[b] Respondent driven sampling (RDS) adjusted HIV prevalence

[c] Respondent driven sampling analysis tool (RDSAT) adjusted HIV prevalence

Supplementary Table 5. Overview of the prevalence of HIV infection in cisgender men sex workers (MSW) in the included studies and prevalence of HIV in the general male population at the study location.

Study	Country and location	Year(s) of study	Recruitment method	No. tested for HIV	Mean or median and IQR or range of age of the total population	HIV prevalence (%) (95% confidence interval)	HIV prevalence general male population (%) (95% confidence interval)
	Kenya						
Muraguri *et al.* (2015) [38]	Nairobi	2010	RDS	273	> 18	26.3 (17.8–35.6) [b]	4.6 (2.4–6.9)
McKinnon *et al.* (2014) [74]	Nairobi	2009–2012	Hotspot-based and snowball recruitment	507	27[†] (IQR 24–31)	40.0 (35.8–44.3) [a]	4.6 (2.4–6.9)
Smith *et al.* (2015) [42]	Mtwapa	NR	Peer referral	82	26[†]	25.6 (16.9–36.7)	1.8 (0.6–3.0)
	Nigeria						
Bamgboye *et al.* (2017) [49]	Eight major cities	2014	RDS	1212	> 15	17.0 (15.0-19.3) [a]	Kano: 0.6 (0.6–0.6) Lagos: 1.8 (1.8–1.8) Cross River: 2.9 (2.9–2.9) Enugu: 1.5 (1.5–1.5) Kaduna: 1.8 (1.7–1.8) Rivers: 4.3 (4.2–4.3) Oyo: 1.2 (1.2–1.2) Federal Capital Territory: 2.8 (2.8–2.8)
Crowell *et al.* (2016) [76]	Abuja Lagos	2013-2016	RDS	551	22[†] (IQR 20–25)	50.6 (46.3–54.8) [a]	2.9 (2.9–2.9) 1.8 (1.8–1.8)

For studies that used respondent driven sampling (RDS) to enrol participants, we preferred to retrieve the RDS adjusted prevalence data. If these were not presented, we retrieved crude prevalence estimates.

[†] Median

[a] Crude HIV prevalence

[b] Respondent driven sampling (RDS) adjusted HIV prevalence

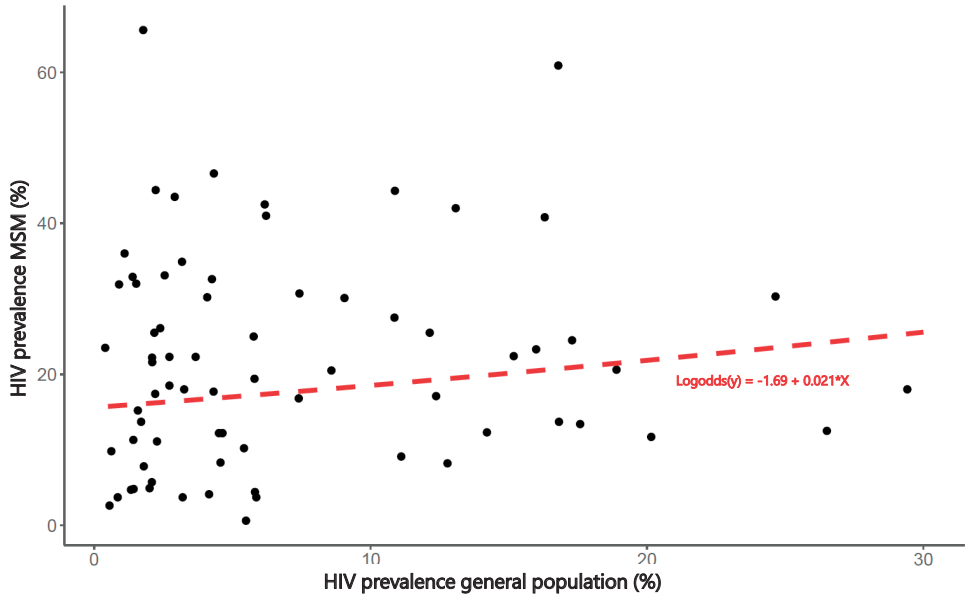
[c] Respondent driven sampling analysis tool (RDSAT) adjusted HIV prevalence

Supplementary Panel 1. Terminology; Men who have sex with men (MSM), transgender men and women and cisgender men and transgender sex workers (MSW and TGSW).

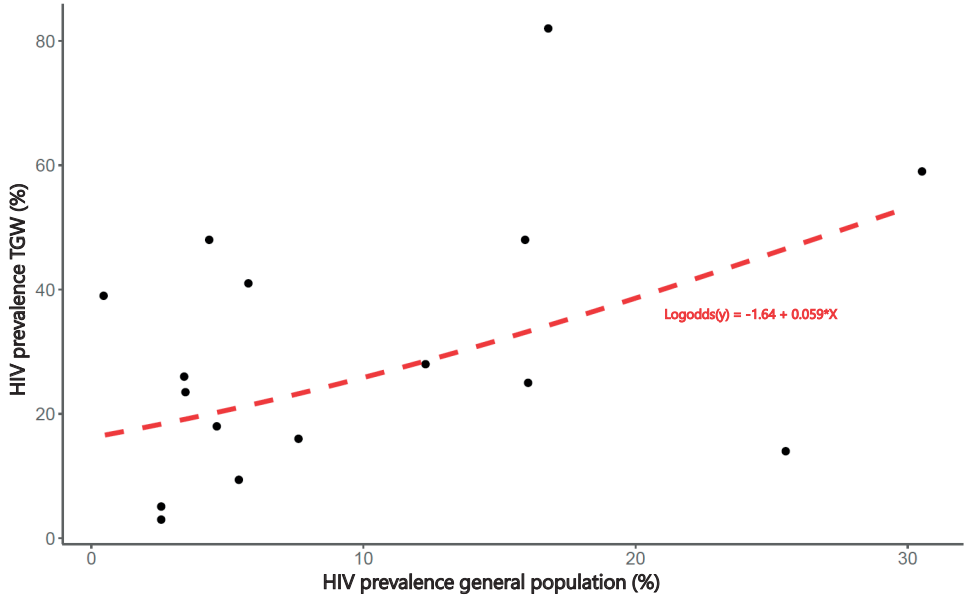
The terminology we used for the classifications and definitions of our study groups are derived from ILGA Europe (2), and consists of four concepts; sex, gender identity, sexual orientation, and type of sex partners. Sex is the biological sex assigned at birth (male or female). Gender identity refers to the combination of sex and gender of a person (how a person feels, *e.g.,* man, woman, or other), and can be cisgender (gender and sex at birth are typically aligned) or transgender (gender and sex at birth are not typically aligned), and is independent of gender affirming treatment or surgery. Sexual orientation describes a person's capacity for profound affection, emotional and sexual attraction to, and intimate and sexual relations with, individuals of a different gender or the same gender or more than one gender and the most common orientations are heterosexual (other gender), homosexual (same gender), bisexual (more than one gender). Queer is an umbrella term used to express a spectrum of gender identities and sexual orientations beyond the binary. Type of sex partners is about sexual behaviour and describes who a person has sex with, which does not have to be limited by sexual orientation. Besides sex assigned at birth, all concepts can naturally fluctuate over time on a personal level. In our study, we classified men who have sex with men (MSM) as cisgender men who have men sex partners, but may have other type of sex partners as well. Transgender men are people who identify as men and were female sex assigned at birth, and transgender women are people who identify as women and were male sex assigned at birth. Being transgender does not define a person's sexual orientation or sexual behaviour. Transgender men and -women can work as sex worker (transgender sex workers (TGSW)), and cisgender men can work as sex worker (cisgender male sex workers), regardless of their sexual orientation and type of sex partners. We here refer to "male" sex workers rather than "men" as this is the commonly accepted term for this group.

We have only included studies in this review based on these terms. For example, we assessed the HIV prevalence among the full spectrum of MSW, or cisgender men sex workers, meaning; male sex assigned at birth, identifying as man and offering sex. These MSW can have various sexual orientations (for example: heterosexual, homosexual or bisexual) and various types of clients (male, female or both). MSW in sub-population of MSM would therefore not be a representative sample of all MSW, and it is not possible assess to which extend and in which direction the HIV prevalence is influenced by the fact that a study only included MSW who are MSM. Future research should focus on clearly and appropriately defining the groups.

Supplementary Figure 1. Association between the HIV prevalence in the general population and in MSM. Each black dot represents a unique data point from peer-reviewed studies with at least 80 participants, red dashed line represents the fitted logistic Deming regression used for extrapolation.



Supplementary Figure 2. Association between the HIV prevalence in the general population and in transgender women (TGW). Each black dot represents a unique data point from peer-reviewed studies with at least 80 participants, red dashed line represents the fitted logistic Deming regression used for extrapolation.



Supplementary Table 6. Logistic Deming regression of the relationship between HIV prevalence in the general population and in MSM (used for extrapolation).

	Exponentiated coefficient	95% CI	p-value
Intercept	0.18	0.12; 0.27	<0.0001
HIV prevalence in general population (continuous)	1.02	0.99; 1.05	0.07

Supplementary Table 7: Univariate logistic regression on relationship between HIV prevalence in MSM and potential confounders.

	Exponentiated intercept	Exponentiated coefficient	95% CI	p-value
Year of data collection (continuous)	1.11 e-98	1.12	1.00; 1.23	0.04
Anti LGBT legislation index* (continuous)	0.25	0.97	0.91; 1.05	0.53
Legalisation of same-sex relations** (bivariate)	0.21	1.02	0.59; 1.76	0.92

* The anti LGBT legislation index is based on a score from 0-14, with 0 meaning low anti LGBT legislation and 14 meaning high anti-LGBT legislation. Values directly derived from Stannah *et al.* [54].
** Whether same sex relations are legal or illegal. The reference category is "illegal" Values directly derived from Stannah *et al.* (54).

Supplementary Table 8. Logistic Deming regression of the relationship between HIV prevalence in the general population and in transgender women (used for extrapolation).

	Exponentiated coefficient	95% CI	p-value
Intercept	0.19	0.07; 0.43	<0.0001
HIV prevalence in general population (continuous)	1.06	0.99; 1.18	0.05

Supplementary Table 9. Univariate logistic regression on relationship between HIV prevalence in transgender women and potential confounders.

	Exponentiated intercept	Exponentiated coefficient	95% CI	p-value
Year of data collection (continuous)	7.65e-137	1.17	0.88; 1.55	0.26
Anti LGBT legislation index* (continuous)	0.36	0.99	0.80; 1.23	0.95
Legalisation of same-sex relations** (bivariate)	0.27	2.19	0.53; 9.14	0.25

* The anti LGBT legislation index is based on a score from 0-14, with 0 meaning low anti LGBT legislation and 14 meaning high anti-LGBT legislation. Values directly derived from Stannah *et al.* (54).
** Whether same sex relations are legal or illegal. The reference category is "illegal" Values directly derived from Stannah *et al.* (54).

Supplementary Table 10. Review estimations for men who have sex with men (MSM).

Region / Country	General population males (age 15-49)				Men who have sex with men (MSM) Estimations	
	HIV prevalence (%)	Population size in thousand	Source of data for estimation	Urban prevalence factor for model	HIV prevalence MSM (%) (95% confidence interval)	Number of MSM living with HIV
Sub-Saharan Africa (SSA)					**20.5**	**600,000 – 2,200,000**
Western and central Africa (WCA)	**0.9**				**22.5**	**300,000 – 1,300,000**
Angola	1.3	7,343	Study		3.7 (1.7-5.7)	3,000 – 11,000
Benin	0.6	2,888	Model	1.44	15.8 (15.5-16.2)	5,000 – 18,000
Burkina Faso	0.5	4,939	Study		9.6 (7.6-11.6)	5,000 – 19,000
Cabo Verde	0.5	161	Model	1.44	15.8 (15.5-16.1)	<1,000
Cameroon	1.9	6,489	Study		34.0 (29.6-38.3)	22,000 – 88,000
Central African Republic	2.2	1,137	Study		41.0 (31.3-50.7)	5,000 – 19,000
Chad	0.8	3,750	Model	2.69	16.2 (15.4-17.2)	6,000 – 24,000
Congo	1.9	1,334	Model	1.03	16.1 (15.4-17.0)	2,000 – 9,000
Cote d'Ivoire	1.3	6,439	Study		20.7 (17.7-23.6)	13,000 – 53,000
Democratic Republic of the Congo	0.4	19,966	Model	1.33	15.7 (15.5-16.0)	31,000 – 126,000
Equatorial Guinea	5.6	460	Model	1.44	17.9 (15.0-22.3)	1,000 – 3,000
Gabon	1.6	591	Model	1.00	16.0 (15.5-16.8)	1,000 – 4,000
Gambia	1.3	561	Study		9.8 (5.7-13.9)	1,000 – 2,000
Ghana	1.0	8,030	Model	1.15	15.9 (15.5-16.4)	13,000 – 51,000
Guinea	0.9	3,025	Model	1.33	15.9 (15.5-16.5)	5,000 – 19,000
Guinea-Bissau	2.2	469	Model	1.44	16.5 (15.4-18.0)	1,000 – 3,000
Liberia	0.8	1,243	Model	1.37	15.9 (15.5-16.4)	2,000 – 8,000
Mali	0.7	4,560	Study		19.8 (17.1-22.6)	9,000 – 36,000
Mauritania	0.3	1,163	Model	1.44	15.7 (15.5-15.9)	2,000 – 7,000

Supplementary Table 10. Review estimations for men who have sex with men (MSM). (*continued*)

Region / Country	General population males (age 15-49)				Men who have sex with men (MSM) Estimations	
	HIV prevalence (%)	Population size in thousand	Source of data for estimation	Urban prevalence factor for model	HIV prevalence MSM (%) (95% confidence interval)	Number of MSM living with HIV
Niger	0.1	5,043	Model	2.00	15.6 (15.6-15.7)	8,000 – 32,000
Nigeria	1.0	48,935	Study		33.9 (32.6-35.3)	166,000 – 664,000
Sao Tome and Principe	0.3	52	Model	0.53	15.6 (15.6-15.7)	<1,000
Senegal	0.3	3,854	Study		25.2 (22.3-28.1)	10,000 – 39,000
Sierra Leone	1.1	2,004	Model	1.35	16.0 (15.5-16.7)	3,000 – 13,000
Sudan *(and South Sudan)*	0.2	13353	Model	1.44	15.7 (15.6-15.8)	21,000 – 84,000
Togo	1.3	2,035	Study		17.1 (15.6-18.7)	3,000 – 14,000
East and southern Africa (ESA)	**4.6**				**18.2**	**200,000 – 900,000**
Botswana	15.2	610	Study		13.0 (9.9-16.1)	1,000 – 3,000
Burundi	0.8	2,741	Model	2.78	16.2 (15.4-17.2)	4,000 – 18,000
Comoros	0.1	220	Model	1.44	15.6 (15.6-15.7)	<1,000
Djibouti	0.7	294	Model	1.44	15.9 (15.5-16.3)	0 – 2,000
Eritrea	0.4	846	Model	1.44	15.7 (15.5-16.0)	1,000 – 5,000
Eswatini	18.2	296	Study		13.4 (9.4-17.4)	0 – 2,000
Ethiopia	0.6	28,733	Model	3.22	16.1 (15.4-17.0)	46,000 – 185,000
Kenya	2.9	13,923	Study		19.6 (18.0-21.3)	27,000 – 109,000
Lesotho	16.0	588	Study		18.0 (13.8-22.2)	1,000 – 4,000
Madagascar	0.3	6,822	Model	1.44	15.7 (15.5-15.9)	11,000 – 43,000
Malawi	5.7	4,569	Study		18.0 (16.5-19.5)	8,000 – 33,000
Mauritius	2.3	327	Model	1.44	16.5 (15.4-18.1)	1,000 – 2,000
Mozambique	8.6	7,155	Study		7.5 (6.1-8.8)	5,000 – 21,000

Supplementary Table 10. Review estimations for men who have sex with men (MSM). (*continued*)

Region / Country	General population males (age 15-49)				Men who have sex with men (MSM) Estimations	
	HIV prevalence (%)	Population size in thousand	Source of data for estimation	Urban prevalence factor for model	HIV prevalence MSM (%) (95% confidence interval)	Number of MSM living with HIV
Namibia	8.3	642	Model	0.95	16.6 (15.1-22.1)	1,000 – 4,000
Rwanda	1.8	3,147	Study		10.5 (8.9-12.1)	3,000 – 13,000
Somalia	0.1	3,526	Model	1.44	15.6 (15.6-15.7)	6,000 – 22,000
South Africa	13.5	16,162	Study		36.0 (33.7-38.2)	58,000 – 233,000
Tanzania	3.3	14,151	Study		14.4 (13.0-15.8)	20,000 – 82,000
Uganda	3.9	10,425	Study		12.2 (9.6-14.8)	13,000 – 51,000
Zambia	8.0	4,394	Model	1.43	19.0 (14.8-25.7)	8,000 – 33,000
Zimbabwe	9.1	3,391	Study		21.1 (18.8-23.4)	7,000 – 29,000

Supplementary Table 11. Review estimations for transgender women (TGW).

Region / Country	General population (age 15-49)				Transgender women (TGW) Estimations	
	HIV prevalence (%) (males and females)	**Population size in thousand** (females)	**Source of data for estimation**	**Urban prevalence factor for model**	**HIV prevalence TGW (%) (95% confidence interval)**	**Number of TGW living with HIV**
Sub-Saharan Africa (SSA)					**28.6**	**400,000 – 800,000**
Western and central Africa (WCA)	**1.3**				**27.7**	**200,000 – 400,000**
Angola	1.8	7,608	Model	1.05	17.8 (16-21.0)	7,000 – 14,000
Benin	0.9	2,883	Model	1.44	17.3 (16.1-19.4)	2,000 – 5,000
Burkina Faso	0.7	4,891	Study		4.0 (1.3-6.7)	1,000 – 2,000
Cabo Verde	0.5	149	Model	1.44	16.8 (16.2-18.0)	<1,000
Cameroon	3.0	6,461	Model	1.07	19.0 (15.8-25.0)	6,000 – 12,000
Central African Republic	2.9	1,141	Model	1.44	19.9 (15.7-28.1)	1,000 – 2,000
Chad	1.1	3,739	Model	2.69	18.8 (15.9-24.1)	4,000 – 7,000
Congo	3.3	1,329	Model	1.03	19.2 (15.8-25.5)	1,000 – 3,000
Cote d'Ivoire	2.1	6,418	Study		24.7 (21.3-28.2)	8,000 – 16,000
Democratic Republic of the Congo	0.7	20,044	Model	1.33	17.0 (16.1-18.5)	17,000 – 34,000
Equatorial Guinea	7.3	312	Model	1.44	26.5 (14.9-53.0)	<1,000
Gabon	3.0	552	Model	1.00	18.8 (15.9-24.3)	<1,000
Gambia	1.8	582	Model	1.00	17.7 (16.0-20.8)	<1,000
Ghana	1.7	7,727	Model	1.15	17.9 (16.0-21.2)	7,000 – 14,000
Guinea	1.4	3,221	Model	1.33	17.8 (16.0-21.0)	3,000 – 6,000
Guinea-Bissau	3.0	492	Model	1.44	20.0 (15.7-28.5)	<1,000
Liberia	1.1	1,224	Model	1.37	17.5 (16.0-20.0)	1,000 – 2,000
Mali	0.9	4,541	Model	1.73	17.5 (16.0-20.1)	4,000 – 8,000
Mauritania	0.3	1,138	Model	1.44	16.6 (16.2-17.3)	1,000 – 2,000

Supplementary Table 11. Review estimations for transgender women (TGW). (*continued*)

Region / Country	General population (age 15-49)				Transgender women (TGW) Estimations	
	HIV prevalence (%) (males and females)	**Population size in thousand** (females)	**Source of data for estimation**	**Urban prevalence factor for model**	**HIV prevalence TGW (%) (95% confidence interval)**	**Number of TGW living with HIV**
Niger	0.2	5,097	Model	2.00	16.6 (16.2-17.2)	4,000 – 8,000
Nigeria	1.3	47,558	Study		48.0 (40.9-55.1)	114,000 – 228,000
Sao Tome and Principe	0.3	52	Model	0.53	16.4 (16.2-16.6)	<1,000
Senegal	0.3	4,118	Study		39.0 (32.2-45.8)	8,000 – 16,000
Sierra Leone	1.5	1,967	Model	1.35	17.9 (16.0-21.4)	2,000 – 4,000
Sudan *(and South Sudan)*	0.2	13,401	Model	1.44	16.5 (16.2-16.9)	11,000 – 22,000
Togo	2.0	2,040	Study		18.4 (10.8-26.0)	2,000 – 4,000
East and southern Africa (ESA)	**6.5**				**29.7**	**200,000 – 400,000**
Botswana	19.9	644	Model	1.44	51.3 (12.8-95.9)	2,000 – 3,000
Burundi	1	2,793	Model	2.78	18.6 (15.9-23.6)	3,000 – 5,000
Comoros	0.1	215	Model	1.44	16.4 (16.2-16.6)	<1,000
Djibouti	0.8	257	Model	1.44	17.2 (16.1-19.0)	<1,000
Eritrea	0.5	842	Model	1.44	16.8 (16.2-18.0)	<1,000
Eswatini	26.8	312	Study		14.0 (7.8-20.2)	<1,000
Ethiopia	0.9	28,513	Model	3.22	18.7 (15.9-24.0)	27,000 – 53,000
Kenya	4.2	14,055	Study		40.6 (31.5-49.8)	29,000 – 57,000
Lesotho	21.1	562	Model	1.22	47.0 (13.1-93.5)	1,000 – 3,000
Madagascar	0.3	6,848	Model	1.44	16.6 (16.2-17.3)	6,000 – 11,000
Malawi	8.1	4,707	Study		28.8 (20.9-36.7)	7,000 – 14,000
Mauritius	1.7	322	Model	1.44	18.3 (15.9-22.6)	<1,000
Mozambique	11.5	7,559	Model	1.27	31.5 (14.4-69.2)	12,000 – 24,000

Supplementary Table 11. Review estimations for transgender women (TGW). (*continued*)

Region / Country	General population (age 15-49)				Transgender women (TGW) Estimations	
	HIV prevalence (%) (males and females)	**Population size in thousand** (females)	**Source of data for estimation**	**Urban prevalence factor for model**	**HIV prevalence TGW (%) (95% confidence interval)**	**Number of TGW living with HIV**
Namibia	11.6	670	Model	0.95	27.1 (14.9-55.1)	1,000 – 2,000
Rwanda	2.5	3,300	Study		9.4 (3.8-15.0)	2,000 – 3,000
Somalia	0.1	3,575	Model	1.44	16.4 (16.2-16.6)	3,000 – 6,000
South Africa	19.1	16,091	Study		63.5 (56.6-70.3)	51,000 – 102,000
Tanzania	4.7	14,113	Model	1.41	22.3 (15.4-37.0)	16,000 – 31,000
Uganda	5.4	10,939	Model	1.59	24.4 (15.2-44.9)	13,000 – 27,000
Zambia	11.1	4,507	Model	1.43	33.1 (14.3-73.5)	7,000 – 15,000
Zimbabwe	11.9	3,857	Study		27.5 (22.7-32.3)	5,000 – 11,000

Supplementary Table 12. Comparison of UNAIDS estimations versus estimations from this study for men who have sex with men (MSM). An assessment of whether the point estimate of the HIV prevalence from UNAIDS falls within the HIV prevalence range derived from our study.

Men who have sex with men (MSM)	**HIV prevalence UNAIDS (%)** point estimate	**HIV prevalence from this study** category	**Source of data for estimation from this study**	**Comparison** UNAIDS is lower/ equal/ higher compared our study
Region / Country				
Western and central Africa (WCA)				
Angola	2.0	<5%	Study	Equal
Benin	7.0	15% - 20%	Model	Lower
Burkina Faso	1.9	5% - 10%	Study	Lower
Cabo Verde		15% - 20%	Model	
Cameroon	20.6	≥20%	Study	Equal
Central African Republic	6.5	≥20%	Study	Lower
Chad		15% - 20%	Model	
Congo	41.2	15% - 20%	Model	Higher
Cote d'Ivoire	7.7	≥20%	Study	Lower
Democratic Republic of the Congo	7.1	15% - 20%	Model	Lower
Equatorial Guinea		15% - 20%	Model	
Gabon		15% - 20%	Model	
Gambia	34.4	5% - 10%	Study	Higher
Ghana	18.0	15% - 20%	Model	Equal
Guinea	11.4	15% - 20%	Model	Lower
Guinea-Bissau	3.0	15% - 20%	Model	Lower
Liberia	19.8	15% - 20%	Model	Equal
Mali	12.6	15% - 20%	Study	Lower
Mauritania	23.4	15% - 20%	Model	Higher
Niger	6.4	15% - 20%	Model	Lower
Nigeria	20.9	≥20%	Study	Equal
Sao Tome and Principe	3.2	15% - 20%	Model	Lower
Senegal	27.6	≥20%	Study	Equal
Sierra Leone	14.0	15% - 20%	Model	Lower
Sudan *(and South Sudan)*	0.8	15% - 20%	Model	Lower
Togo	22.0	15% - 20%	Study	Higher
East and southern Africa (ESA)				
Botswana	14.8	10% - 15%	Study	Equal
Burundi	4.8	15% - 20%	Model	Lower
Comoros		15% - 20%	Model	

Supplementary Table 12. Comparison of UNAIDS estimations versus estimations from this study for men who have sex with men (MSM). An assessment of whether the point estimate of the HIV prevalence from UNAIDS falls within the HIV prevalence range derived from our study. (*continued*)

Men who have sex with men (MSM)	**HIV prevalence UNAIDS (%)** point estimate	**HIV prevalence from this study** category	**Source of data for estimation from this study**	**Comparison** UNAIDS is lower/ equal/ higher compared our study
Djibouti	14.2	15% - 20%	Model	Lower
Eritrea		15% - 20%	Model	
Eswatini	27.2	10% - 15%	Study	Higher
Ethiopia		15% - 20%	Model	
Kenya	18.2	15% - 20%	Study	Equal
Lesotho	32.9	15% - 20%	Study	Higher
Madagascar	14.9	15% - 20%	Model	Lower
Malawi	12.9	15% - 20%	Study	Lower
Mauritius	17.2	15% - 20%	Model	Equal
Mozambique		5% - 10%	Study	
Namibia	7.8	15% - 20%	Model	Lower
Rwanda	4.0	10% - 15%	Study	Lower
Somalia		15% - 20%	Model	
South Africa	18.1	≥20%	Study	Lower
Tanzania	8.4	10% - 15%	Study	Lower
Uganda	13.2	10% - 15%	Study	Equal
Zambia		15% - 20%	Model	
Zimbabwe	21.1	≥20%	Study	Equal

Supplementary Table 13. Comparison of UNAIDS estimations versus estimations from this study for transgender women. An assessment of whether the point estimate of the HIV prevalence from UNAIDS falls within the HIV prevalence range derived from our study.

Transgender women	**HIV prevalence UNAIDS (%)** point estimate	**HIV prevalence from this study** category	**Source of data for estimation from this study**	**Comparison** UNAIDS is lower/ equal/ higher compared our study
Region / Country				
Western and central Africa (WCA)				
Angola		15% - 20%	Model	
Benin	26.4	15% - 20%	Model	Higher
Burkina Faso		0% - 5%	Study	
Cabo Verde		15% - 20%	Model	
Cameroon		15% - 20%	Model	
Central African Republic		15% - 20%	Model	
Chad		15% - 20%	Model	
Congo		15% - 20%	Model	
Cote d'Ivoire	24.7	≥20%	Study	Equal
Democratic Republic of the Congo		15% - 20%	Model	
Equatorial Guinea		≥20%	Model	
Gabon		15% - 20%	Model	
Gambia		15% - 20%	Model	
Ghana		15% - 20%	Model	
Guinea		15% - 20%	Model	
Guinea-Bissau		≥20%	Model	
Liberia		15% - 20%	Model	
Mali	14.6	15% - 20%	Model	Lower
Mauritania		15% - 20%	Model	
Niger		15% - 20%	Model	
Nigeria	19.8	≥20%	Study	Lower
Sao Tome and Principe		15% - 20%	Model	
Senegal		≥20%	Study	
Sierra Leone	22.4	15% - 20%	Model	Higher
Sudan *(and South Sudan)*		15% - 20%	Model	
Togo		15% - 20%	Study	
East and southern Africa (ESA)				
Botswana		≥20%	Model	
Burundi		15% - 20%	Model	

Supplementary Table 13. Comparison of UNAIDS estimations versus estimations from this study for transgender women. An assessment of whether the point estimate of the HIV prevalence from UNAIDS falls within the HIV prevalence range derived from our study. (*continued*)

Transgender women	**HIV prevalence UNAIDS (%)** point estimate	**HIV prevalence from this study** category	**Source of data for estimation from this study**	**Comparison** UNAIDS is lower/ equal/ higher compared our study
Comoros		15% - 20%	Model	
Djibouti		15% - 20%	Model	
Eritrea		15% - 20%	Model	
Eswatini		10% - 15%	Study	
Ethiopia		15% - 20%	Model	
Kenya		≥20%	Study	
Lesotho		≥20%	Model	
Madagascar		15% - 20%	Model	
Malawi		≥20%	Study	
Mauritius	28.4	15% - 20%	Model	Higher
Mozambique		≥20%	Model	
Namibia		≥20%	Model	
Rwanda		5% - 10%	Study	
Somalia		15% - 20%	Model	
South Africa		≥20%	Study	
Tanzania		≥20%	Model	
Uganda		≥20%	Model	
Zambia		≥20%	Model	
Zimbabwe	27.5	≥20%	Study	Equal

Supplementary Table 14. Comparison of estimations derived from study data to estimations derived regression model for men who have sex with men (MSM). An assessment of the use of the regression model for studies for which we have study data and whether the estimation from the regression model still falls within the HIV prevalence category range.

Men who have sex with men (MSM)	**HIV prevalence regression model (%)** point estimate	**HIV prevalence derived from studies** category	**Comparison** regression model is lower/ equal/ higher compared data derived from studies
Region / Country			
Western and central Africa (WCA)			
Angola	16.0	<5%	Higher
Benin			
Burkina Faso	15.9	5% - 10%	Higher
Cabo Verde			
Cameroon	16.1	≥20%	Lower
Central African Republic	16.5	≥20%	Lower
Chad			
Congo			
Cote d'Ivoire	16.0	≥20%	Lower
Democratic Republic of the Congo			
Equatorial Guinea			
Gabon			
Gambia	15.9	5% - 10%	Higher
Ghana			
Guinea			
Guinea-Bissau			
Liberia			
Mali	15.9	15% - 20%	Equal
Mauritania			
Niger			
Nigeria	16.0	≥20%	Lower
Sao Tome and Principe			
Senegal	15.6	≥20%	Lower
Sierra Leone			
Sudan *(and South Sudan)*			
Togo	16.1	15% - 20%	Equal
East and southern Africa (ESA)			
Botswana	22.6	10% - 15%	Higher
Burundi			

Supplementary Table 14. Comparison of estimations derived from study data to estimations derived regression model for men who have sex with men (MSM). An assessment of the use of the regression model for studies for which we have study data and whether the estimation from the regression model still falls within the HIV prevalence category range. (*continued*)

Men who have sex with men (MSM)	**HIV prevalence regression model (%)** point estimate	**HIV prevalence derived from studies** category	**Comparison** regression model is lower/ equal/ higher compared data derived from studies
Comoros			
Djibouti			
Eritrea			
Eswatini	22.7	10% - 15%	Higher
Ethiopia			
Kenya	16.5	15% - 20%	Equal
Lesotho	21.8	15% - 20%	Higher
Madagascar			
Malawi	18.4	15% - 20%	Equal
Mauritius			
Mozambique	18.8	5% - 10%	Higher
Namibia			
Rwanda	16.6	10% - 15%	Higher
Somalia			
South Africa	19.8	≥20%	Lower
Tanzania	16.9	10% - 15%	Higher
Uganda	17.4	10% - 15%	Higher
Zambia			
Zimbabwe	18.4	≥20%	Lower

Supplementary Table 15. Comparison of estimations derived from study data to estimations derived regression model for transgender women. An assessment of the use of the regression model for studies for which we have study data and whether the estimation from the regression model still falls within the HIV prevalence category range.

Men who have sex with men (MSM)	**HIV prevalence regression model (%)** point estimate	**HIV prevalence derived from studies** category	**Comparison** regression model is lower/ equal/ higher compared data derived from studies
Region / Country			
Western and central Africa (WCA)			
Angola			
Benin			
Burkina Faso	17.4	0% - 5%	Higher
Cabo Verde			
Cameroon			
Central African Republic			
Chad			
Congo			
Cote d'Ivoire	18.3	≥20%	Lower
Democratic Republic of the Congo			
Equatorial Guinea			
Gabon			
Gambia			
Ghana			
Guinea			
Guinea-Bissau			
Liberia			
Mali			
Mauritania			
Niger			
Nigeria	17.8	≥20%	Lower
Sao Tome and Principe			
Senegal	16.4	≥20%	Lower
Sierra Leone			
Sudan *(and South Sudan)*			
Togo	18.7	15% - 20%	Equal
East and southern Africa (ESA)			
Botswana			
Burundi			
Comoros			
Djibouti			

Supplementary Table 15. Comparison of estimations derived from study data to estimations derived regression model for transgender women. An assessment of the use of the regression model for studies for which we have study data and whether the estimation from the regression model still falls within the HIV prevalence category range. (*continued*)

Men who have sex with men (MSM)	**HIV prevalence regression model (%)** point estimate	**HIV prevalence derived from studies** category	**Comparison** regression model is lower/ equal/ higher compared data derived from studies
Eritrea			
Eswatini	56.9	10% - 15%	Higher
Ethiopia			
Kenya	20.5	≥20%	Equal
Lesotho			
Madagascar			
Malawi	30.0	≥20%	Equal
Mauritius			
Mozambique			
Namibia			
Rwanda	20.8	5% - 10%	Higher
Somalia			
South Africa	38.1	≥20%	Equal
Tanzania			
Uganda			
Zambia			
Zimbabwe	28.6	≥20%	Equal

Supplementary Table 16. Assessment of the impact of the use of geospatially matched Demographic Health Surveys (DHS)[53] data versus Dwyer-Lindgren *et al.*[56] (DL) data. An assessment of the use of DL data instead of DHS data on the Prevalence Ratio (PR). Key pop = key population. Gen pop = general population. * Multiple locations and all are included in the analysis, but for overview purposes only the first location is added in this Table. See Table S3-5 for full study description.

Study ID	**Population**	**Country**	**Location***	**HIV prevalence** Study key pop	**HIV prevalence** DHS gen pop	**HIV prevalence** DL gen pop	**PR [CI]** Study **vs** DHS	**PR** Study vs DL	**Impact** Using DL data results in a higher/ equal/ lower PR compared to DHS data
Smith *et al.* (2015) [42]	MSW ESA	Kenya	Mtwapa	25.6	1.8	5.8	14.3 [2.0-103.5]	4.4	Equal
Muraguri *et al.* (2015) [38]	MSW ESA	Kenya	Nairobi	26.3	4.6	6.9	5.7 [2.2-14.3]	3.8	Equal
McKinnon *et al.* (2014) [74]	MSW ESA	Kenya	Nairobi	40.0	4.6	6.2	8.6 [3.5-21.4]	6.5	Equal
Poteat *et al.* (2017) [12]	TGW ESA	Eswatini	Mbabane	14.0	25.5	30.1	0.5 [0.3-0.9]	0.5	Equal
Poteat *et al.* (2017) [12]	TGW ESA	Lesotho	Maputsoe*	59.0	30.5	27.1	1.9 [1.5-2.4]	2.2	Equal
Poteat *et al.* (2017) [12]	TGW ESA	Malawi	Lilongwe	16.0	7.6	10.9	2.1 [0.9-4.8]	1.5	Equal
Poteat *et al.* (2017) [12]	TGW WCA	Burkina Faso	Bobo-Dioulasso*	3.0	2.6	1.6	1.2 [0.4-3.6]	1.9	Equal
Stahlman *et al.* (2016) [43]	TGW WCA	Burkina Faso	Bobo-Dioulasso*	5.1	2.6	1.6	2.0 [0.8-5.0]	3.2	Equal
Poteat *et al.* (2017) [12]	TGW WCA	Togo	Kara*	18.0	4.6	3.1	3.9 [2.0-7.5]	5.9	Equal
Stahlman *et al.* (2016) [73]	TGW WCA	Togo	Kara*	18.8	4.6	3.1	4.1 [2.1-7.8]	6.1	Equal
Baral *et al.* (2013) [62]	MSM ESA	Eswatini	Manzini	13.4	17.6	29.0	0.8 [0.5-1.1]	0.5	Equal
Muraguri *et al.* (2015) [38]	MSM ESA	Kenya	Nairobi	12.2	4.6	6.9	2.6 [1.0-6.8]	1.8	Equal
Stahlman *et al.* (2016) [73]	MSM ESA	Lesotho	Maseru	18.0	29.4	27.2	0.6 [0.4-0.9]	0.7	Equal
Wirtz *et al.* (2017) [44]	MSM ESA	Malawi	Blantyre	12.5	26.5	18.7	0.5 [0.3-0.8]	0.7	Equal
Wirtz *et al.* (2017) [44]	MSM ESA	Malawi	Mangochi	22.4	15.2	13.7	1.5 [0.7-3.3]	1.6	Equal
Wirtz *et al.* (2017) [44]	MSM ESA	Malawi	Mulanje	24.5	17.3	20.4	1.4 [0.7-3.0]	1.2	Equal
Wirtz *et al.* (2017) [44]	MSM ESA	Malawi	Lilongwe	17.7	4.3	10.2	4.1 [0.8-20.3]	1.7	Equal
Wirtz *et al.* (2017) [44]	MSM ESA	Malawi	Mzuzu	4.1	4.2	8.6	1.0 [0.2-5.4]	0.5	Equal
Wirtz *et al.* (2017) [44]	MSM ESA	Malawi	Nkhata Bay	20.6	18.9	11.2	1.1 [0.5-2.3]	1.8	Equal
Sandfort *et al.* (2019) [73]	MSM ESA	Malawi	Blantyre	30.3	24.7	18.7	1.2 [0.8-1.9]	1.6	Equal
Nalá *et al.* (2015) [47]	MSM ESA	Mozambique	Maputo	8.2	12.8	18.3	0.6 [0.4-1.0]	0.4	Equal

Supplementary Table 16. Assessment of the impact of the use of geospatially matched Demographic Health Surveys (DHS)[53] data versus Dwyer-Lindgren *et al.*[56] (DL) data. An assessment of the use of DL data instead of DHS data on the Prevalence Ratio (PR). Key pop = key population. Gen pop = general population. * Multiple locations and all are included in the analysis, but for overview purposes only the first location is added in this Table. See Table S3-5 for full study description. (*continued*)

Study ID	**Population**	**Country**	**Location***	**HIV prevalence** Study key pop	**HIV prevalence** DHS gen pop	**HIV prevalence** DL gen pop	**PR [CI]** Study **vs** DHS	**PR** Study vs DL	**Impact** Using DL data results in a higher/ equal/ lower PR compared to DHS data
Nalá *et al.* (2015) [47]	MSM ESA	Mozambique	Beira	9.1	11.1	19.4	0.8 [0.4-1.6]	0.5	Equal
Murenzi *et al.* (2020) [53]	MSM ESA	Rwanda	Kigali	19.4	5.8	5.4	3.3 [2.1-5.2]	3.6	Equal
Ntale *et al.* (2018) [52]	MSM ESA	Rwanda	Kigali	4.4	5.8	5.6	0.8 [0.4-1.6]	0.8	Equal
Ntale *et al.* (2018) [52]	MSM ESA	Rwanda	Rubavu	7.8	1.8	2.8	4.3 [1.2-15.2]	2.8	Equal
Ntale *et al.* (2018) [52]	MSM ESA	Rwanda	Musanze	4.6	1.3	2.6	3.5 [0.6-19.8]	1.8	Equal
Ntale *et al.* (2018) [52]	MSM ESA	Rwanda	Huye	3.7	3.2	1.9	1.2 [0.3-4.2]	1.9	Equal
Kendall *et al.* (2014) [30]	MSM WCA	Angola	Luande Province	3.7	0.9	1.8	4.3 [1.1-16.6]	2.1	Equal
Holland *et al.* (2016) [32]	MSM WCA	Burkina Faso	Ougadougou	4.7	1.3	1.4	3.5 [1.2-10.4]	3.5	Equal
Holland *et al.* (2016) [32]	MSM WCA	Burkina Faso	Bobo Dioulasso	4.9	2.0	1.9	2.4 [0.9-6.9]	2.6	Equal
Park *et al.* (2013) [34]	MSM WCA	Cameroon	Douala	25.5	2.2	4.5	11.7 [3.6-38.0]	5.7	Equal
Park *et al.* (2013) [34]	MSM WCA	Cameroon	Yaounde	44.4	2.2	6.1	20.0 [9.9-40.4]	7.3	Lower
Lahuerta *et al.* (2017) [45]	MSM WCA	Mali	Bamako	13.7	1.7	1.6	8.1 [2.4-27.3]	8.8	Equal
Dramé *et al.* (2013) [55]	MSM WCA	Senegal	Dakar	36.0	1.1	0.5	32.8 [5.1-211.8]	72.4	Equal
Lyons *et al.* (2017) [56]	MSM WCA	Senegal	Dakar*	23.5	0.4	0.4	58.9 [7.4-470.7]	60.8	Equal
Holland *et al.* (2016) [32]	MSM WCA	Togo	Lome	18.5	2.7	3.4	6.8 [3.5-13.2]	5.5	Equal
Holland *et al.* (2016) [32]	MSM WCA	Togo	Kara	0.6	5.5	2.8	0.1 [0.0-0.6]	0.2	Equal
Teclessou *et al.* (2017) [68]	MSM WCA	Togo	Lome	22.3	2.7	3.4	8.2 [4.2-16.1]	6.6	Equal
Tchankoni *et al.* (2020) [69]	MSM WCA	Togo	Cinkassé*	21.6	2.1	2.0	10.3 [6.6-16.1]	10.7	Equal
Teclessou *et al.* (2017) [68]	MSM WCA	Togo	Cinkassé*	5.7	2.1	2.6	2.7 [1.4-5.2]	2.2	Equal
Overall average PR							**6.1**	**6.2**	

Supplementary Panel 2. Association between the HIV prevalence in the general population and in key populations.

For MSM (men who have sex with men) and transgender women (TGW), the total number of studies identified allowed us to extrapolate country and regional specific RRs derived from our meta-analyses to crudely estimate the country specific prevalence and number of people living with HIV aged 15-49 years for both populations for each country in sub-Saharan Africa. We first determined the relationship between the study prevalence and general population HIV prevalence for the two populations by fitting a logistic Deming regression, weighted by study size, through all data points, *i.e.*, log odds(y) = $\alpha + \beta x$, with x = HIV prevalence in the general population and y = prevalence in MSM or TGW. Only studies with a sample size >80 were included. The resulting regression functions are presented in **Supplementary Figure 1** (MSM) and **Supplementary Figure 2** (TGW). For MSM and TGW the β coefficient appeared borderline significant ($p<0.1$) with, $p=0.07$ and $p=0.05$. The resulting the functions were: log odds(y) = -1.96 + 0.021x (for MSM), and log odds(y) = -1.64 + 0.059x (for TGW).

In addition, we tested whether year of data collection, legal or illegal status of same sex relationships, and an indicator for the severity of anti LGBT laws could explain some of the observed heterogeneity in the relationship between key- and general population HIV prevalence by testing them as predictors in a logistic regression model.

To estimate the HIV prevalence for MSM and TGW for each country for which we did not have data or did not have sufficient data (number of people tested <80) we then applied the functions to the urban general population HIV prevalence (we used the urban prevalence because all studies were derived from urban areas and thus compared to local urban DHS prevalence). For MSM we used the general population prevalence amongst males aged 15-49, and for transgender women we used the general population prevalence amongst males and females aged 15-49, derived from UNAIDS 2020. The general population prevalence was then multiplied by an urban prevalence factor based on the ratio between the general population prevalence and the urban general population prevalence derived from DHS/AIS surveys, and for countries without DHS/AIS surveys an average of 1.44 was used, which is the average from all available sub-Saharan African countries. For the countries for which we had sufficient data, we used the country estimated prevalence in MSM and TGW as presented in the forest plots (**Manuscript Figure 3-5**).

Next, we estimated total country-specific population sizes by applying estimates of the proportion of MSM (range: 1%-4%) and transgender women (range: 0.5%-1%) within populations to the United Nations population size estimates, and determined country-specific absolute HIV burden among by multiplying prevalence estimates with population size estimates.

Chapter 5

No increased HIV risk in general population near sex work sites: a nationally representative cross-sectional study in Zimbabwe

Marielle Kloek[‡], Caroline A. Bulstra[‡], Sungai T. Chabata, Elizabeth Fearon, Isaac Taramusi, Sake J. de Vlas, Frances M. Cowan, Jan A.C. Hontelez

[‡] *Shared first co-authorship*

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ABSTRACT

Objective: Sex work sites have been hypothesised to be at the root of the observed heterogeneity in HIV prevalence in sub-Saharan Africa. We determined if proximity to sex work sites is associated with HIV prevalence among the general population in Zimbabwe, a country with one of the highest HIV prevalence in the world.

Methods: In this cross-sectional study we use a unique combination of nationally representative geolocated individual-level data from 16,121 adults (age 15–49 years) from 400 sample locations and the locations of 55 sex work sites throughout Zimbabwe; covering an estimated 95% of all female sex workers in the country. We calculated the shortest distance by road from each survey sample location to the nearest sex work site, for all sites and by type of sex work site, and conducted univariate and multivariate multilevel logistic regressions to determine the association between distance to sex work sites and HIV seropositivity, controlling for age, sex, male circumcision status, number of lifetime sex partners, being a client of female sex workers or being a stable partner of a client of female sex workers.

Results: We found no significant association between HIV seroprevalence and proximity to the nearest sex work site among the general population in Zimbabwe, regardless of which type of site is closest (city site adjusted odds ratio {aOR} 1.010 [95% confidence interval {CI} 0.992–1.028]; economic growth point site aOR 0.982 [95% CI 0.962–1.002]; international site aOR 0.995 [95% CI 0.979–1.012]; seasonal site aOR 0.987 [95% CI 0.968–1.006] and transport site aOR 1.007 [95% CI 0.987–1.028]). Individual-level indicators of sex work were significantly associated with HIV seropositivity: being a client of female sex workers (aOR 1.445 [95% CI 1.188–1.745]); nine or more partners versus having one to three lifetime partners (aOR 2.072 [95% CI 1.654–2.596]).

Conclusions: Sex work sites do not seem to directly affect HIV prevalence among the general population in surrounding areas. Prevention and control interventions for HIV at these locations should primarily focus on sex workers and their clients, with special emphasis on including and retaining mobile sex workers and clients into services.

INTRODUCTION

About two thirds of people living with HIV worldwide reside in sub-Saharan Africa [1], with many countries still experiencing high incidence and prevalence levels in the general population. Throughout the subcontinent, the epidemic is geographically heterogeneous with localised areas of high transmission around big cities, truck route pit-stops and locations with high levels of economic activity [2]. Sex work has often been hypothesised to be at the root of the observed geographical heterogeneity [3,4], as sites where sex workers offer their services, here called 'sex work sites', are oftentimes also situated at locations with high economic activity. However, whether the presence of sex work sites is associated with higher HIV prevalence in the general population, and thus can directly explain the observed geographical heterogeneity in the epidemic, has never been empirically tested.

Zimbabwe is one of the countries with the highest HIV burden worldwide. Although incidence levels have decreased by 44% over the past decade [1,5], the decline seems to have stalled in recent years [6]. HIV prevalence among female sex workers is over 50% according to the latest estimates (2018–2020) by the Centre for Sexual Health and HIV/AIDS Research (CeSHHAR) Zimbabwe [7], an organisation focused on HIV implementation research and responsible for running Zimbabwe's nationally scaled healthcare programme for female sex workers on behalf of the Zimbabwean government (www.ceshhar.org). CeSHHAR runs (mobile) clinics throughout Zimbabwe, offering services at 36 sex work sites [7]. Data on the locations and typology of sex work sites, together with nationally representative geolocated survey data from the Demographic and Health Survey (DHS) on HIV prevalence and risk behaviour in the general population [2,8] create the unique opportunity to test whether the HIV prevalence in the general population of Zimbabwe is higher among those living in close proximity to sex work sites.

We determined if geospatial heterogeneity in HIV prevalence in the general population in Zimbabwe is associated with proximity to sex work sites. We first calculated travel distance between DHS sample locations and known sex work sites, and used univariate and multivariate logistic regression models to determine the association between distance to the nearest sex work site and HIV prevalence, controlling for demographic and sexual behavioural factors.

METHODS

Data - CeSHHAR

CeSHHAR has registered the locations and characteristics of 55 sex work sites throughout Zimbabwe, from 2015 to 2017 [7], and GPS coordinates of each site were collected via Google Maps Coordinates [9]. Sex work sites are described as 'hotspots' for sex work, and one sex work site can consist of multiple venues where sex work takes place, such as bars, shebeens, streets, brothels, beer halls, sport bars, nightclubs, parking lots at border crossings, truck stops, mining areas or marketplaces. For example, the city Harare is identified as one sex work site but consists of a huge variety of sex work venues throughout the city, from parking lots to hotels. The sex work sites are originally identified based on expert opinion and reported by Fearon *et al.* [7]. They include 36 CeSHHAR sites, as well as 19 additional sex work locations identified in a structured workshop with experts, based on reached consensus on the presence of each of those sex work locations per province. The identified sex work sites cover an estimated 95% of all female sex workers, based on the calculations by Fearon *et al.* [7], who counted the numbers of female sex workers at the different CeSHHAR sites during various times to calculate the proportion of female sex workers among the general population at each site (using existing size population size data), which were then used to estimate the number of female sex workers at non-CeSHHAR sites [7]. All 55 sex work sites were primarily identified as locations where female sex workers provide their services, but the sites might also be utilised by male and transgender sex workers. As different sex work sites might attract different types of clients with a different connection to the surrounding general population, we added a stratified analysis using five sex work site categories, based on expert opinion: city (city or regional capital), economic growth point (rural area with rapid economic growth), international (tourism, international business and border crossing), seasonal (mining, farming, fishing, university or army base) or transport (truck stop, transport hub or border crossing) [7]. Sites that fitted in multiple classifications were included in each relevant category up to a maximum of three categories per site. This way, a sex work site that was classified as, for example, truck stop and mining area was included as both a transport site and a seasonal site.

Data - DHS

We used the 2015 DHS from Zimbabwe, which includes voluntary HIV testing in the general population, and overlaps with the timeframes in which sex work sites were identified, classified and localised. The survey was conducted using standard DHS methodology; 400 locations (primary sampling units) were randomly sampled throughout the country, weighted by the population density per area, and about 25 randomly selected households were included at each sample location. HIV status was determined in the DHS by testing a blood sample from a finger prick using enzyme-linked immunosorbent assay. GPS coordinates of sample

locations were randomly displaced up to 2 km for urban and up to 5 km for rural locations, to ensure confidentiality of participants. All males and females aged 15–49 years with available HIV test results were included in our analysis.

Besides HIV status and GPS data, we included several demographic and (sexual) behavioural variables in our analyses: age, sex, male circumcision, number of lifetime sex partners, being a client of female sex workers or being a stable partner of someone who reported to be a client of female sex workers. Clients of female sex workers were defined based on whether a man had ever, or in the last year, paid for sexual intercourse. Men who reported to have offered gifts and goods in exchange for sex, instead of money, were not defined as clients of female sex workers in our analysis, due to lack of coherency comparing those answers to the other female sex work-related questions. Missing values for lifetime sex partners (136 values, 0.84% of all values) were imputed using multiple imputation [10].

In addition to the variables directly extracted from the DHS, for each sample location we estimated the proportion of all men being a client of female sex workers, the proportion of all women being a female sex worker within 50 km radius around the sample location, and the human mobility level of people at each sample location. The proportions were determined to indicate the proportion of people directly engaging in sex work among the general population, as the relative size (*i.e.*, number of sex workers relative to the population density of the area) is likely more important than absolute size (*i.e.*, the estimated number of sex workers) [7,11]. We calculated the proportion of clients of female sex workers as the fraction of all 15- to 49-year-old men at each sample location, as proxy for utility of commercial sex work among men at the sample location. We estimated the proportion of female sex workers among the female population around each DHS sample location (in a 50-km radius) by dividing the number of female sex workers in the area, based on sex work site size estimates from the CeSHHAR database [7], by the total female population in the area, based on population estimates provided by the WorldPop project [12] and ZimStat [13]. The estimates are provided in **Supplementary Figure 1**. We hypothesised that human mobility might influence the association between distance to a sex work site and HIV prevalence, as human mobility is often associated with higher HIV risk and mobile individuals might engage in sex work at different locations than where they (or their families) live long-term [3,14,15]. We therefore estimated the human mobility level of individuals in the DHS data based on combining three DHS variables; whether an individual was identified as being mobile in the past year through either being a seasonal worker; being away from home for at least 1 month; or being away from home more than two times in the past 12 months, with an individual being identified as 'mobile' when at least one out of three were answered with 'yes'. The prevalence of human mobility was then aggregated per DHS sample location, where sample locations with a human mobility prevalence of 50% or more were marked as

locations with high human mobility, and sample locations with less than 50% were marked as locations with low human mobility. More details on survey protocols and questionnaires can be found on the DHS website (https://dhsprogram.com/).

Statistical analysis

We applied Ordinary Kriging to predict and visualise geospatial heterogeneity in HIV prevalence among adults throughout Zimbabwe. This is a commonly used geospatial method that could be used to estimate the best linear unbiased prediction of HIV prevalence at unsampled locations, based on HIV prevalence levels from known data points, which in our study were the sample locations from the DHS data [16]. Using this method, an HIV prevalence estimate was predicted for every 5-by-5 km grid cell in Zimbabwe. The method is described in more detail elsewhere [2].

Next, we determined the distance between DHS sample locations and sex work sites, calculated as the shortest distance from each DHS sample location to the nearest sex work site via paved and unpaved roads in kilometres (roads available via Open Street Map [17]). We applied these distances to each individual in the DHS data based on their sample location. The proximity calculation is illustrated in **Supplementary Figure 2**.

To determine the association between HIV prevalence among the general population and proximity to sex work sites, we performed individual-level and multilevel logistic regression analyses with HIV status (positive or negative) as dependent variable and the proximity to the nearest sex work site (distance to any sex work site as well as by type of site, *e.g.*, distance to the nearest city site and distance to the nearest economic growth point site) as independent variables.

We first plotted the untransformed association between travel distance to sex work site, and both HIV prevalence at each sample location, and proportion of men reporting being clients of female sex workers at each sample location. We then tested the univariate association between general population HIV status and proximity to sex work sites using logistic regression using a square root transformed proximity variable as the variable most closely resembled a normal distribution using this transformation. However, we also explored associations with categorical, untransformed continuous, and log-transformed proximity variables (**Supplementary Figure 3**). The associations between HIV status and all demographic and sexual behavioural variables included in this study were also first assessed univariately.

In the multivariate analysis, the association between travel distance to sex work sites and HIV status was adjusted for individual-level and sample location-level demographic and sexual behavioural risk factors related to sex work: age, sex, male circumcision, lifetime sex

partners and being identified as a client of female sex workers, estimated proportion of female sex workers at each sample location, urban or rural classification of each sample location, and population mobility score of each sample location. The DHS sample location was included as a random effect. The final multilevel multivariate model was developed using a backward selection procedure, where all variables that did not significantly improve the model fit (tested using likelihood tests, $p > 0.05$) were excluded. Finally, we separately fitted univariate and multivariate models stratified by sample location mobility score and urban/rural classification to examine potential effect modification. We used R software version 4.0.1 and ArcGIS Pro version 2.3 to perform the analyses.

Ethics approval

Ethics approval was arranged by USAID (https://dhsprogram.com/Methodology/Protecting-the-Privacy-of-DHS-Survey-Respondents.cfm). No separate consent was required to use the anonymised data.

RESULTS

A total of 16,121 individuals from the DHS data were included in our study (**Supplementary Table 1**). The overall HIV prevalence in the study population was 14.7% (11.2% among men; 17.5% among women). Over one in five men (21.6%, N = 1529) reported to have ever visited a female sex worker, and about half of them (11.6%, N = 822) reported to have visited a female sex worker during the past year. HIV prevalence among men who ever visited a female sex worker was 20.5% versus 8.6% for men who never did. Less than half of the study population (41.8%) lived in urban areas, where HIV prevalence was higher as compared to rural areas: 19.9% vs. 11.0%. HIV prevalence was comparable between people with low and high mobility scores (14.5% vs. 15.0%, respectively). HIV prevalence levels for the general population and by subpopulation, that is, men, women and young people (15–24 years), stable partners of clients of female sex workers, clients of female sex workers and female sex workers, are shown in **Supplementary Figure 5**.

The geographical spread of HIV among the general population was highly heterogeneous (**Figure 1A**). Prevalence varied from just below 7% in north Zimbabwe and the eastern and north-western borders, to over 21% and 24% at border crossings with South Africa and Botswana respectively. Prevalence was also high (above 18%) in the Victoria Falls area, north of Harare (mining), and in the surrounding areas of Bulawayo (mining area, transport route).

The geographical locations and primary classification of the 55 sex work sites as registered by CeSHHAR are shown in **Figure 1B**. The nine city sites were located in or close to Harare,

Zimbabwe's capital, and in or close to the other four bigger cities: Bulawayo and Gweru in central Zimbabwe; and Mutare, and Marondera in northeast Zimbabwe. The nine economic growth point sites and 32 seasonal sites were mostly located in the rural areas of the country. Ten international sites were located at border crossings with Botswana (Plumtree), Mozambique (Mokumbura and Nyampanda), South Africa (Beitbridge), and Zambia (Chirundu and Kariba) and around tourist locations (Victoria falls) and the large cities. Twenty-one transport sites were mostly located on the national truck routes throughout the country as well as at the international border crossings.

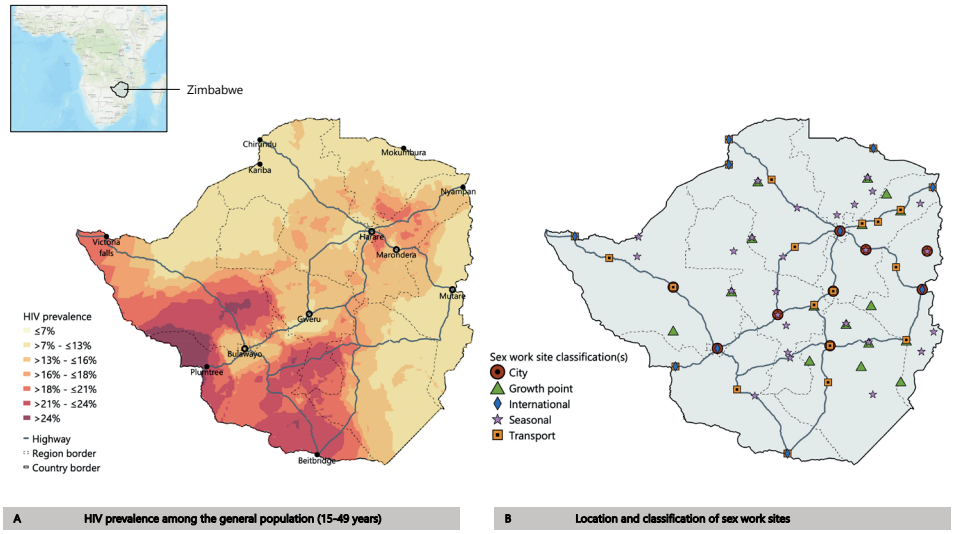

Figure 1. HIV prevalence among the general population in Zimbabwe (panel A) and female sex work (FSW) sites in Zimbabwe by type (panel B). HIV prevalence estimates are acquired using Ordinary Kriging (shown by 5 km^2) and are based on the Zimbabwe 2015 DHS data of males and females (aged 15-49 years). DHS data obtained though https://dhsprogram.com/. Sex work site locations are obtained via CeSHHAR Zimbabwe (http://ceshhar.org/). Twenty-one sites were identified as transport sites, 32 as seasonal sites, 10 as international sites, nine as city sites and nine as economic growth point sites.

Figure 2A shows the association between sample location-level HIV prevalence and untransformed distance to the nearest sex work site. There was a large variation in both general population HIV prevalence per sample location, ranging from 0% to 55%, and proximity to nearest sex work site, ranging from 360 m to 220 km, yet there was no statistically significant association between the two variables (p=0.77). Similarly, **Figure 2B** shows that there was no significant association between the proportion of clients of female sex workers at a sample location, ranging from 0% to 28%, and proximity to nearest sex work site (p=0.92). Scatterplots of the association between HIV prevalence and square root-transformed proximity to the nearest sex work site by type of site are shown in **Supplementary Figure 4**.

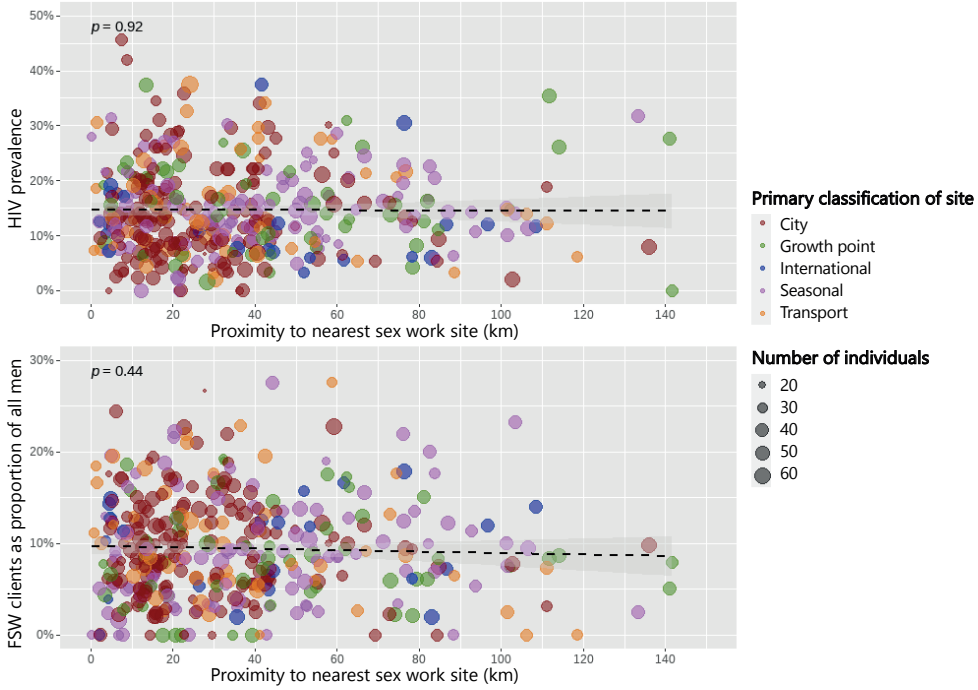

Figure 2. HIV prevalence among the general population (age 15-49 years) (panel A) and the proportion of all men who ever visited a FSW (panel B) in relation to proximity to the nearest sex work site, by DHS sample location. Colours represent the primary classification of the sex work site. Sizes of the bubbles represent the number of individuals in each DHS sample location, numbers shown in legend are approximations. Dashed lines represent smoothed generalized logistic regression fits for the associations, for all types of sex work sites together. Four outliers, with a proximity to the nearest sex work site of over 140 km, were excluded.

Table 1 shows the univariate and multivariate associations between square root transformed proximity to sex work sites and demographic and behavioural covariates, and individual HIV status. Univariately, proximity to the nearest sex work site overall was not associated with HIV prevalence (odds ratio {OR} = 0.995 [95% confidence interval {CI} 0.976–1.013], p=0.563). When stratified by type of sex work site, only distance to economic growth point sites was borderline significantly associated with HIV status (OR = 0.984 [0.968–1.000]; p=0.050), with increasing distance being associated with lower HIV prevalence.

When controlling for demographic and behavioural variables in the multivariate models, proximity to sex work sites remained not significantly associated with HIV seropositivity in the general population for any sex work site type: city site adjusted odds ratio (aOR) = 1.010 [95% CI 0.992–1.028], p=0.290; economic growth point site aOR = 0.982 [95% CI 0.962–1.002], p=0.088; international site aOR = 0.995 [95% CI 0.979–1.012], p=0.564; seasonal site aOR = 0.987 [95% CI 0.968–1.006], p=0.176 and transport site aOR = 1.007 [95% CI 0.987–1.028], p=0.500. In contrast, individual-level covariates indicative of high-risk behaviour and engag-

Table 1. Univariate and multivariate multilevel logistic regression analysis of HIV status among Zimbabwean males and females age 15-49. Both univariate and multivariate models are adjusted for DHS sample location random effects.

			Univariate analysis			Multivariate analysis		
Covariate	***N***	**HIV prevalence**	**OR [95% CI]**	**p-value**		**aOR [95% CI]**	**p-value**	
Proximity to the nearest female sex work site (km, square root transformed)								
All sites	16,121	14.7%	0.995 [0.976–1.013]	0.563		-		
Proximity to the nearest female sex work site (km, square root transformed) by type								
City	6,481[1]	14.5%	0.998 [0.986–1.009]	0.692		1.010 [0.992–1.028]	0.290	
Economic growth point	2,325[1]	15.5%	0.984 [0.968–1.000]	0.050	*	0.982 [0.962–1.003]	0.088	.
International	999[1]	12.2%	1.001 [0.990–1.012]	0.884		0.995 [0.979–1.012]	0.564	
Seasonal	4,124[1]	15.3%	0.988 [0.974–1.003]	0.124		0.987 [0.968–1.006]	0.176	
Transport	2,192[1]	14.5%	1.006 [0.990–1.023]	0.462		1.007 [0.986–1.028]	0.500	
Percentage of clients of female sex workers as proportion of all men in survey at sample location								
<5%	3,493	12.8%	1	-		-		
5%-15%	10,125	15.1%	1.208 [1.022; 1.426]	0.026	*	-		
≥15%	2,503	15.8%	1.259 [1.012; 1.567]	0.039	*	-		
Percentage of female sex workers as proportion of the female population in 50 km radius around sample location								
<5%	7,378	14.0%	1			1		
5%-15%	4,964	16.0%	1.173 [1.008–1.365]	0.039	*	1.155 [0.986–1.353]	0.075	.
≥15%	1,483	14.2%	1.017 [0.804–1.286]	0.889		1.118 [0.874–1.431]	0.375	
Sex								
Male	7,069	11.2%	1			1		
Female	9,052	17.5%	1.684 [1.535–1.849]	<0.001	***	2.540 [2.202–2.930]	<0.001	***
Age								
15-24 years	6,739	5.1%	1			1		
25-34 years	4,922	16.7%	3.848 [3.368–4.397]	<0.001	***	2.454 [2.085–2.890]	<0.001	***
34+ years	4,460	27.0%	7.324 [6.437–8.335]	<0.001	***	5.001 [4.261–5.868]	<0.001	***

Table 1. Univariate and multivariate multilevel logistic regression analysis of HIV status among Zimbabwean males and females age 15-49. Both univariate and multivariate models are adjusted for DHS sample location random effects. (*continued*)

			Univariate analysis			Multivariate analysis		
Covariate	***N***	**HIV prevalence**	**OR [95% CI]**	**p-value**		**aOR [95% CI]**	**p-value**	
Sex work client ever (males only)								
Yes	1,529	20.5%	2.710 [2.312–3.177]	<0.001	***	1.440 [1.188–1.745]	<0.001	***
No	5,540	8.6%	1			1		
Sex work client in the last year (males only)								
Yes	822	19.7%	2.101 [1.728–2.553]	<0.001	***	-		
No	6,247	10.1%	1			-		
Partner of client of female sex worker(s) (females only)								
Yes	787	19.7%	1.147 [0.949–1.386]	0.157		-		
No	8,265	17.3%	1			-		
Lifetime number of sex partners								
None	3,309	3.4%	0.172 [0.141–0.211]	<0.001	***	0.519 [0.407–0.662]	<0.001	***
1-3	9,651	16.0%	1			1		
4-9	2,251	22.8%	1.501 [1.337–1.685]	<0.001	***	1.999 [1.713–2.332]	<0.001	***
9+	910	23.2%	1.538 [1.300–1.818]	<0.001	***	2.072 [1.654–2.596]	<0.001	***
Circumcised (males only)								
Yes	1,150	7.4%	0.558 [0.440–0.708]	<0.001	***	0.654 [0.495–0.865]	0.003	**
No	5,916	11.9%	1			1		
Sample location-level human mobility prevalence								
High	6,334	13.4%	1.088 [0.995–1.190]	0.064	.	-		
Low	9,787	15.6%	1			-		
Type of place of residence								
Urban	6,737	19.9%	1.087 [0.996–1.187]	0.063	.	-		
Rural	9,384	11.0%	1			-		

ing in commercial sex were significantly associated with HIV prevalence. Reported to have ever engaged in transactional sex (men only) showed a 44% increase in the odds of living with HIV (aOR = 1.445 [95% CI 1.188–1.745], p < 0.001). Similarly, reporting nine or more lifetime sexual partners were associated with an over twofold increase in the odds of living with HIV compared to reporting 1–3 lifetime partners (aOR = 2.072 [95% CI 1.654–2.596], p < 0.001). Being circumcised showed a 35% decrease in odds of living with HIV (aOR = 0.654 [95% CI 0.495–0.865], p=0.003).

Multivariate logistic regression models stratified by rural/urban classification or stratified by mobility score of the DHS sample locations showed similar outcomes on the associations between proximity to sex work sites and HIV seropositivity (**Supplementary Tables 2 and 3**). Only for the urban sample, proximity to economic growth points was significantly associated with HIV seropositivity in the multilevel model (aOR 0.953 [95% CI 0.925–0.981], p=0.001).

DISCUSSION

Our analysis of 55 sex work sites and 16,121 individuals from 400 DHS sample locations across Zimbabwe showed no apparent association between proximity to the nearest sex work site and HIV seropositivity among the general population, regardless of which type of sex work site was closest. In contrast, individual-level indicators of engagement in sex work and high-risk behaviour were significantly associated with HIV seropositivity, with ever having been a client of female sex workers being associated with a 1½ times increase in the odds of living with HIV, and having nine or more lifetime partners being associated with a more than two-fold increase in the odds of living with HIV compared to reporting one to three lifetime partners.

Geospatial analyses are increasingly being used to illustrate and explain the heterogeneous spread of HIV [2,8,18]. For example, Palk and Blower showed that the heterogeneous spread of HIV in Malawi is associated with having a high number of lifetime sex partners [18]. Likewise, in a previous study across seven countries in East and Southern Africa, we showed that the large geographic heterogeneity in HIV prevalence among young adults could be linked to areas of high economic activity [2]. In these and other studies, female sex work was univocally hypothesised as an important underlying driver of the geospatial HIV heterogeneity [2,18–20]. However, this hypothesis was never tested empirically due to the lack of suitable data on locations of sex work sites, female sex workers, and clients of female sex workers in areas with nationally representative survey data available. In household surveys such as the DHS, female sex workers are often not identifiable as being a sex worker [21]. Clients are identifiable, although reliant on self-reported behaviour. Using our unique combina-

tion of geolocated individual-level survey data on HIV seropositivity and risk in the general population, and the mapped locations of over 95% of all sex work sites in Zimbabwe, we showed that the hypothesised direct link between proximity to sex work site locations and heterogeneity in HIV prevalence among the general population does not hold for the situation in Zimbabwe.

It is important to note that our results do not refute the well-grounded notion that sex work is a major driver of HIV transmission in Zimbabwe and other settings with generalised epidemics [20,22]. On the contrary, our findings clearly demonstrate that at an individual level, indicators of practising commercial sex as a client are significantly associated with increased risks for HIV. The lack of a geospatial association between sex work sites and HIV prevalence could be explained by a combination of mobility of both female sex workers and clients [14,23], and maturity of the HIV epidemic [22]. Historically, HIV prevalence has been associated with proximity to busy transport routes, truck drivers and migrant mining labour [24–33], which are often locations for sex work sites [34]. However, as epidemics mature, HIV increasingly spreads from transmission hotspots to other areas through bridging populations, diluting the measurable association between HIV prevalence and distance to the hotspots. Furthermore, population mobility is a known key factor among both sex workers and their clients, and the places where they engage in sex are often not equal to places where they live [35]. A previous study on female sex workers in Zimbabwe found that around 20% of female sex workers travelled at least a couple of times a year over smaller distances, and 10% travelled long-distance while staying away from home for weeks or sometimes months [14]. Clients also do not usually visit female sex workers close to where they live, but rather visit female sex workers when they spend some time away from home [22]. This is also supported by our study, where we found a clear association between proximity to sex work sites and the prevalence of clients of female sex workers among the general population.

Our findings show that effective programmatic planning of the HIV response cannot solely depend on the observed geospatial heterogeneity in HIV prevalence, as previously suggested [2,8,18]. While planning testing and treatment services based on geospatial distribution of HIV prevalence within the general population would still suffice, allocating services for key populations requires careful mapping of hotspots and sites independent of general population HIV prevalence levels [7,36]. It is essential to better understand what other factors drive the observed geospatial heterogeneity in HIV prevalence—for example, clustering of cultural, geographical or socioeconomic factors, or heterogeneities in access to and uptake of interventions—so that interventions can be tailored accordingly.

The lack of a spill-over effect of HIV to the general population in areas surrounding sex work sites emphasises that interventions at these areas should primarily be focused on female

sex workers and their clients, preferably through people-centred HIV services specifically for female sex workers and clients at the sex work site where they provide and use the services, with peer-outreach as a central aspect of implementation [37]. Including sex workers in the design of such interventions and hiring them as staff members is recommended to improve the effectiveness and acceptability by ensuring that services are sensitive and acceptable to the target population [37]. Given the often-high mobility levels of these subpopulations, good accessibility of services is crucial, especially since female sex workers and clients might prefer to access HIV clinics at places away from home or utilise several different clinics depending on where they work and engage in commercial sex. Finally, the increased HIV risk among stable partners of clients of female sex workers highlights the need of focused interventions for this specific subpopulation. Reaching partners of clients of female sex workers might be challenging, as the sex worker-visiting partner might be not open to disclose information on engagement in commercial sex to the stable partner. Nevertheless, targeted HIV services for clients of female sex workers could, for example, include their stable partners or include discussing condom use with stable partners.

Our study had some limitations. While the overall number of respondents in the DHS between 15- and 49-years accepting HIV testing was relatively high at 85% [38], the proportion of male respondents was slightly lower; 81% compared to 88% among women. It is often hypothesised that those who decline have higher HIV risk [39]. However, younger people (15–34 years), who are generally at higher risk of acquiring HIV, were somewhat more likely to participate in HIV testing in the 2015 DHS in Zimbabwe. Also in rural areas, with often higher proportions of clients, response rates were generally higher. We therefore do not expect selective non-respondence to have influenced our findings substantially. Furthermore, the sex work sites from the CeSHHAR data were determined based on clinic data collected between 2015 and 2017 as well as locations identified through expert opinion [7], and it is perceivable that some sex work sites in Zimbabwe may not have been captured in our data. Since the DHS are cross-sectional data containing HIV status with no information on lag-time since seropositive status, we cannot make definite claims about causal effects between proximity to sex work sites and HIV risk. Next, there can be underreporting of the amount of sex work visits, or selective non-respondence from the people who visit female sex workers, but it is very unlikely that this potential bias negates the qualitative interference from our study findings, as we did find that reported visiting of female sex workers was associated with increased HIV prevalence. Finally, it is important to note that this work was focused on female sex workers and their clients only, because there were no data available on sex workers who identify as cisgender male, transgender women and transgender men, their clients, and their sex work sites. This does not mean these groups do not exist in Zimbabwe. For example, male sex work in Zimbabwe was described by Tsang *et al.* [40]. It is perceivable that most of these sex workers would work at, or close by, the sex work sites for female sex

workers, and it is therefore unlikely that knowing the locations of non-cisgender female sex workers would alter the qualitative inference of our results.

Conclusions

We found no evidence of an association between the proximity of sex work sites and HIV seroprevalence in Zimbabwe. Programmatic planning of (key population) interventions to curb HIV transmission can therefore not be taken merely based on geospatial heterogeneity of the epidemic, but requires careful mapping and considerations of transmission dynamics related to key populations implicitly. The absence of a geospatial association could be explained by the mobile nature of both female sex workers and their clients, as individual-level indicators of sex work were still significantly associated with HIV. Given that spill-over of HIV into the general population surrounding sex work sites seems limited, prevention and control interventions for HIV at these sites should primarily focus on sex workers and clients, with special emphasis on including and retaining mobile sex workers and their clients into services.

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Author contributors

MK, CAB, SJdeV, and JACH designed the study. FC, EF, and SC were co-responsible for collection and preparation of the CeSHHAR data. MK, CAB, and SC prepared the data and conducted the analyses. MK, CAB, and JACH wrote the initial draft manuscript. All authors have reviewed and provided input to the manuscript.

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Declarations of interest

All authors report no existing conflicts of interest.

Data sharing

The data from the USAID Demographic and Health Surveys is openly available via https://dhsprogram.com/. The data from the Centre for Sexual Health and HIV/AIDS Research (CeSHHAR) is upon request.

REFERENCES

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). Joint United Nations Programme on HIV/AIDS. UNAIDS data 2020. Geneva; 2020. Available: https://www.unAIDS.org/sites/default/files/media_asset/2020_AIDS-data-book_en.pdf
2. Bulstra CA, Hontelez JAC, Giardina F, Steen R, Nagelkerke NJD, Bärnighausen T, *et al.* Mapping and characterising areas with high levels of HIV transmission in sub-Saharan Africa: A geospatial analysis of national survey data. PLOS Med. 2020;17: e1003042. doi:10.1371/journal.pmed.1003042
3. Platt L, Grenfell P, Fletcher A, Sorhaindo A, Jolley E, Rhodes T, *et al.* Systematic review examining differences in HIV, sexually transmitted infections and health-related harms between migrant and non-migrant female sex workers. Sex Transm Infect. 2013;89: 311–319.
4. Shannon K, Strathdee SA, Goldenberg SM, Duff P, Mwangi P, Rusakova M, *et al.* Global epidemiology of HIV among female sex workers: Influence of structural determinants. Lancet. 2015;385: 55–71. doi:10.1016/S0140-6736(14)60931-4
5. ZIMPHIA. Zimbabwe population-based HIV impact assessment. 2020.
6. United Nations Joint Programme on HIV/AIDS (UNAIDS). UNAIDS Data 2019. 2019; 476. Available: https://www.unAIDS.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf_AIDSinfo.unAIDS.org.
7. Fearon E, Chabata ST, Magutshwa S, Ndori-Mharadze T, Musemburi S, Chidawanyika H, *et al.* Estimating the Population Size of Female Sex Workers in Zimbabwe: Comparison of Estimates Obtained Using Different Methods in Twenty Sites and Development of a National-Level Estimate. J Acquir Immune Defic Syndr. 2020;85: 30–38. doi:10.1097/QAI.0000000000002393
8. Cuadros DF, Li J, Branscum AJ, Akullian A, Jia P, Mziray EN, *et al.* Mapping the spatial variability of HIV infection in Sub-Saharan Africa: Effective information for localized HIV prevention and control. Nature. 2017;7: 1–11. doi:10.1038/s41598-017-09464-y
9. Google Maps. https://www.google.com/maps/preview.
10. Buuren S van, Groothuis-Oudshoorn K. MICE: Multivariate imputation by chained equations in R. J Stat Softw. 2010;3: 1–68.
11. Viswasam N, Lyons CE, MacAllister J, Millett G, Sherwood J, Rao A, *et al.* The uptake of population size estimation studies for key populations in guiding HIV responses on the African continent. PLOS ONE. 2020;15: e0228634.
12. WorldPop. Available: http://www.worldpop.org.uk/
13. Agency ZNS. ZimStat. [cited 4 May 2020]. Available: https://www.zimstat.co.zw/
14. Davey C, Dirawo J, Mushati P, Magutshwa S, Hargreaves JR, Cowan FM. Mobility and sex work: why, where, when? A typology of female-sex-worker mobility in Zimbabwe. Soc Sci Med. 2019;220: 322–330. doi:10.1016/j.socscimed.2018.11.027
15. Dobra A, Bärnighausen T, Vandormael A, Tanser F. A method for statistical analysis of repeated residential movements to link human mobility and HIV acquisition. PLOS ONE. 2019;14: e0217284.
16. Miller HJ. Tobler's First Law and Spatial Analysis. Ann Assoc Am Geogr. 2004;94: 284–289. doi:10.1111/j.1467-8306.2004.09402005.x
17. The Humanitarian Data Exchange. Open Street Map Zimbabwe roads. [cited 10 May 2019]. Available: https://data.humdata.org/dataset/hotosm_zwe_roads

18. Palk L, Blower S. Geographic variation in sexual behaviour can explain geospatial heterogeneity in the severity of the HIV epidemic in Malawi. BMC Med. 2018;16: 22. doi:10.1186/s12916-018-1006-x

19. Dzomba A, Govender K, Mashamba-Thompson TP, Tanser F. Mobility and increased risk of HIV acquisition in South Africa: A mixed-method systematic review protocol. Syst Rev. 2018;7: 1–7. doi:10.1186/s13643-018-0703-z

20. Tanser F, de Oliveira T, Maheu-Giroux M, Bärnighausen T. Concentrated HIV sub-epidemics in generalized epidemic settings. Curr Opin HIV AIDS. 2014;9: 115.

21. Edwards JK, Hileman S, Donastorg Y, Zadrozny S, Baral S, Hargreaves JR, *et al.* Estimating sizes of key populations at the national level: considerations for study design and analysis. Epidemiology. 2018;29: 795.

22. Steen R, Hontelez JAC, Mugurungi O, Mpofu A, Matthijsse SM, Vlas SJ De, *et al.* Economy, migrant labour and sex work: interplay of HIV epidemic drivers in Zimbabwe over three decades. AIDS. 2019. doi:10.1097/QAD.0000000000002066

23. Deane KD, Samwell Ngalya P, Boniface L, Bulugu G, Urassa M. Exploring the relationship between population mobility and HIV risk: Evidence from Tanzania. Glob Public Health. 2016; 1–16. doi:10.1080/17441692.2016.1178318

24. Barongo LR, Borgdorff MW, Mosha FF, Nicoll A, Grosskurth H, Senkoro KP, *et al.* The epidemiology of HIV-1 infection in urban areas, roadside settlements and rural villages in Mwanza Region, Tanzania. AIDS. 1992;6: 1521–1528.

25. Boerma JT, Urassa M, Nnko S, Ng'weshemi J, Isingo R, Zaba B, *et al.* Sociodemographic context of the AIDS epidemic in a rural area in Tanzania with a focus on people's mobility and marriage. Sex Transm Infect. 2002;78: i97--i105.

26. Bwayo J, Plummer F, Omari M, Mutere A, Moses S, Ndinya-Achola J, *et al.* Human immunodeficiency virus infection in long-distance truck drivers in east Africa. Arch Intern Med. 1994;154: 1391–1396.

27. Colvin M, Sharp B. Sexually transmitted infections and HIV in a rural community in the Lesotho highlands. Sex Transm Infect. 2000;76: 39–42.

28. Glynn JR, Pönnighaus J, Crampin AC, Sibande F, Sichali L, Nkhosa P, *et al.* The development of the HIV epidemic in Karonga District, Malawi. AIDS. 2001;15: 2025–2029.

29. Mbugua GG, Muthami LN, Mutura CW, Oogo SA, Waiyaki PG, Lindan CP, *et al.* Epidemiology of HIV infection among long distance truck drivers in Kenya. East Afr Med J. 1995;72: 515–518.

30. Parker RG, Easton D, Klein CH. Structural barriers and facilitators in HIV prevention: a review of international research. AIDS. 2000;14: S22--S32.

31. Tanser F, LeSueur D, Solarsh G, Wilkinson D. HIV heterogeneity and proximity of homestead to roads in rural South Africa: An exploration using a geographical information system. Trop Med Int Heal. 2000;5: 40–46. doi:10.1046/j.1365-3156.2000.00513.x

32. Wawer MJ, Serwadda D, Musgrave SD, Konde-Lule JK, Musagara M, Sewankambo NK. Dynamics of spread of HIV-I infection in a rural district of Uganda. Br Med J. 1991;303: 1303–1306.

33. Williams BG, Gouws E. The epidemiology of human immunodeficiency virus in South Africa. Philos Trans R Soc London Ser B Biol Sci. 2001;356: 1077–1086.

34. Wilson D, Halperin DT. "Know your epidemic, know your response": a useful ap-

proach, if we get it right. Lancet. 2008;372: 423–426. doi:https://doi.org/10.1016/S0140-6736(08)60883-1

35. Platt L, Grenfell P, Meiksin R, Elmes J, Sherman SG, Sanders T, *et al.* Associations between sex work laws and sex workers' health: A systematic review and meta-analysis of quantitative and qualitative studies. PLOS Med. 2018;15: e1002680.

36. Davey C, Dirawo J, Mushati P, Magutshwa S, Hargreaves JR, Cowan FM. Mobility and sex work: why, where, when? A typology of female-sex-worker mobility in Zimbabwe. Soc Sci Med. 2019;220: 322–330.

37. World Health Organization (WHO). Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. Bull World Health Organ. 2016. Available: https://www.who.int/publications/i/item/9789241511124

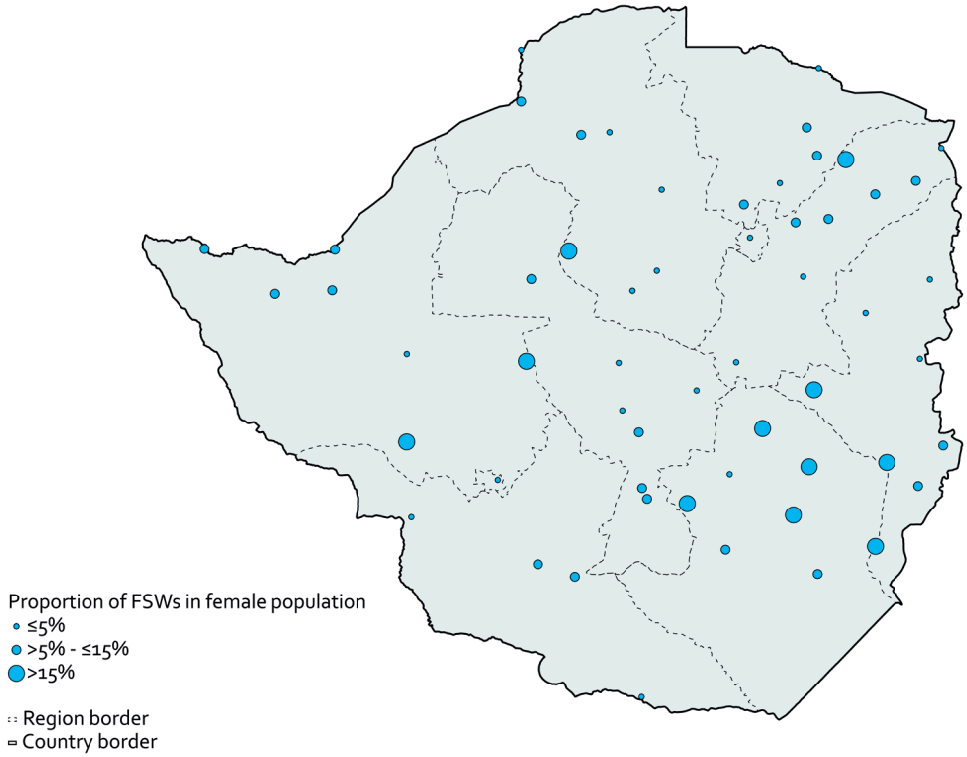
38. USAID. Zimbabwe Demographic and Health Survey 2015. Rockville, Maryland, USA; 2016. doi:10.1017/CBO9781107415324.004

39. United Nations Joint Programme on HIV/AIDS (UNAIDS), World Health Organization. Guidelines for measuring national HIV prevalence in population-based surveys Guidelines for measuring national HIV prevalence in population-based surveys. Geneva, Switzerland; 2006. Available: https://data.unAIDS.org/pub/manual/2005/20050101_gs_guidemeasuringpopulation_en.pdf

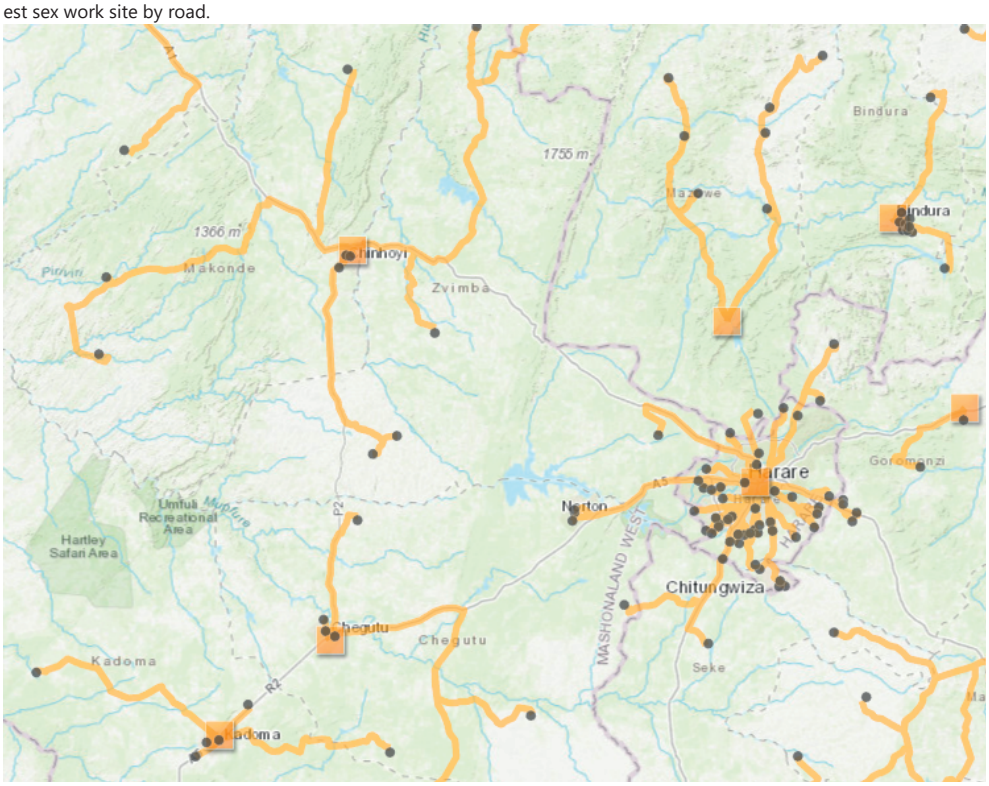
40. Tsang EY, Qiao S, Wilkinson JS, Fung AL, Lipeleke F, Li X. Multilayered stigma and vulnerabilities for HIV infection and transmission: a qualitative study on male sex workers in Zimbabwe. Am J Mens Health. 2019;13: 1557988318823883.

SUPPORTING INFORMATION TO CHAPTER 5

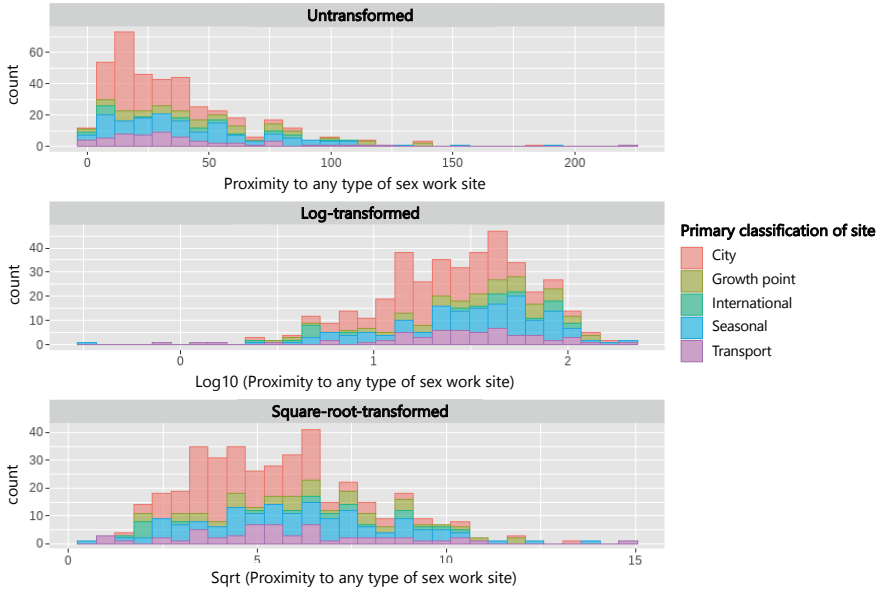
Supplementary Figure 1. Percentage of female sex workers (FSWs) as proportion of the female population per sex work site in Zimbabwe. FSW size estimates come from the CeSHHAR database [12], female population density data are based on population estimates provided by the WorldPop project (https://www.worldpop.org/). Each blue circle represents a sex work site, the size indicated the proportion of FSWs in the underlying female population.



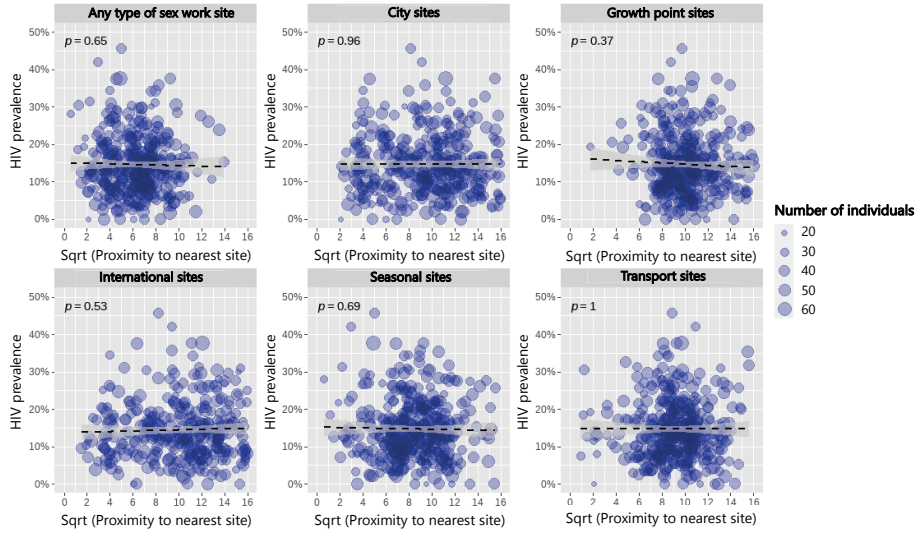
Supplementary Figure 2. Example of the calculation of distance and time from the Zimbabwe 2015 DHS sample location to the nearest sex work site over road. DHS sample locations are represented by black dots and sex work locations by orange squares. Each orange line represents a distance calculation from a DHS sample location to the nearest sex work site by road.



Supplementary Figure 3. Association between proximity to the nearest sex work site and HIV prevalence among the general population (by the DHS sample location in Zimbabwe in 2015), explored as continuous (panel A), logarithmic (panel B), and square root (panel C). The colours represent the primary classification of the sex work site.



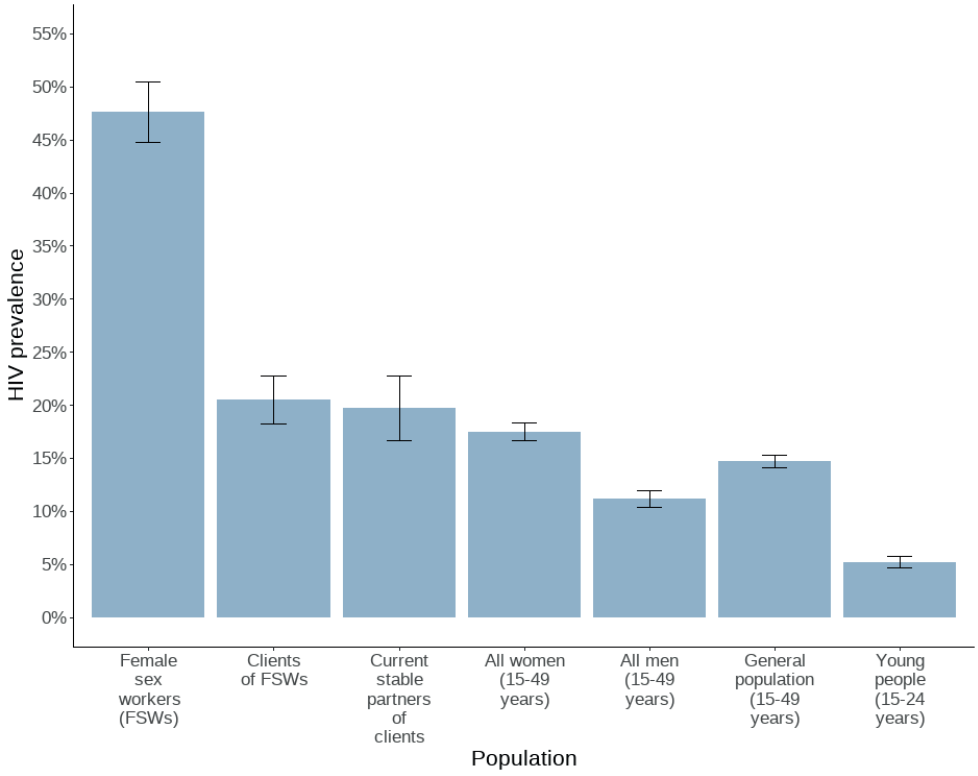
Supplementary Figure 4. Association between proximity to the nearest sex work site and HIV prevalence among the general population (by DHS sample location) for any type (or classification) of sex work site and for all types separately. Sizes of the in total 400 bubbles represent the number of individuals in each DHS sample location. Dashed lines represent generalized linear regression lines. The p-values are given for the association between the HIV prevalence among the general population and square root transformed proximity to the nearest sex work site for each plot. For none of the types of sex work sites the slope was significantly differed from zero.



Supplementary Table 1. Characteristics of the DHS data, Zimbabwe, 2015. Data obtained through https://dhsprogram.com/.

Characteristics	N; %	HIV prevalence
	All individuals N=16,121	***All HIV-positive individuals N=2,373 HIV$^+$ (14.7%)***
Sex		
Male	7,069 (43.8%)	11.2% (791 HIV$^+$)
Female	9,052 (56.2%)	17.5% (1,582 HIV$^+$)
Age		
mean [SD]	*27.2 [9.3]*	*34.2 [8.3]*
15-24 years	6,739 (41.8%)	5.1% (349 HIV$^+$)
25-34 years	4,922 (30.6%)	16.7% (822 HIV$^+$)
35+ years	4,460 (27.7%)	27.0% (1,202 HIV$^+$)
Place of residence		
De Jure (*i.e.,* usual resident)	15,448 (95.8%)	14.5% (2,284 HIV$^+$)
De Facto (*i.e.,* slept at residence last night)	16,121 (100%)	14.7% (2,373 HIV$^+$)
HIV status		
Positive	2,373 (14.7%)	N/A
Negative	13,748 (85.3%)	N/A
Sex work client, ever (males only)		
Yes	1,529 (21.6%)	20.5% (313 HIV$^+$)
No	5,540 (78.4%)	8.6% (478 HIV$^+$)
Sex work client, in the last year (males only)		
Yes	822 (11.6%)	19.7% (162 HIV$^+$)
No	6,247 (88.4%)	10.1% (629 HIV$^+$)
Current partner of sex work client (females only)		
Yes	787 (4.9%)	19.7% (155 HIV$^+$)
No	8,265 (95.1%)	17.3% (1,427 HIV$^+$)
Lifetime number of sex partners		
mean [SD]	*2.7 [6.4]*	*4.6 [9.3]*
None	3,309 (20.5%)	3.4% (106 HIV$^+$)
1-3	9,651 (59.9%)	16.0% (1,543 HIV$^+$)
4-9	2,251 (14.0%)	22.8% (513 HIV$^+$)
9+	910 (5.6%)	23.2% (211 HIV$^+$)
Condom used last sex		
Yes	2,926 (18.2%)	29.9% (875 HIV$^+$)
No	13,195 (81.8%)	11.4% (1,498 HIV$^+$)
Circumcised (males only)		
Yes	1,150 (16.3%)	7.4% (85 HIV$^+$)
No	5,916 (83.7%)	11.9% (706 HIV$^+$)
Type of place of residence		
Urban	6,737 (41.8%)	19.9% (1,340 HIV$^+$)
Rural	9,384 (58.2%)	11.0% (1,033 HIV$^+$)
Human mobility in the last year		
Low	8,505 (52.8%)	14.5% (1,231 HIV$^+$)
High	7,616 (47.2%)	15.0% (1,142 HIV$^+$)

Supplementary Figure 5. HIV prevalence in Zimbabwe among different subpopulation groups. Female sex workers data are obtained from CeSHHAR data, Zimbabwe, July 2018 – June 2020. Other subpopulation data are obtained from the DHS 2015 through https://dhsprogram.com/. HIV prevalence is highest among FSWs (47.6% [44.7%-50.4%]), followed by FSW clients (20.5% [18.2%-22.8%]) and current stable partners of FSW clients (19.7% [16.7%-22.7%]). HIV prevalence among the general population is 14.7% [14.1%-15.3%], among all women 17.7% [16.7%-18.4%], among all men 11.2% [10.4%-12.0%], and among young people (15-24 years) 5.2% [4.7%-5.7%].



Supplementary Table 2. Multivariate multilevel logistic regression analysis of HIV status among Zimbabwean males and females age 15-49 – stratified by urban versus rural classification of DHS sample locations. The models are adjusted for DHS sample location random effects.

	Urban, multivariate analysis			Rural, multivariate analysis		
Covariate	**aOR [95% CI]**	**p-value**		**aOR [95% CI]**	**p-value**	
Proximity to the nearest female sex work site (km, square root transformed)						
All sites	-			-		
Proximity to the nearest female sex work site (km, square root transformed) by type						
City	1.015 [0.991–1.040]	0.223		0.993 [0.971–1.016]	0.536	
Economic growth point	0.953 [0.925–0.981]	0.001	**	1.016 [0.991–1.042]	0.251	
International	0.994 [0.972–1.016]	0.601		1.002 [0.982–1.022]	0.336	
Seasonal	0.984 [0.958–1.010]	0.231		0.993 [0.970–1.016]	0.555	
Transport	1.002 [0.974–1.031]	0.892		1.013 [0.987–1.040]	0.321	
Percentage of clients of female sex workers as proportion of all men in survey at sample location						
<5%	-			-		
5%-15%	-			-		
≥15%	-			-		
Percentage of female sex workers as proportion of the female population in 50 km radius around sample location						
<5%	-			-		
5%-15%	-			-		
≥15%	-			-		
Sex						
Male	1			1		
Female	2.656 [2.157–3.270]	<0.001	***	2.236 [1.902–2.628]	<0.001	***
Age						
15-24 years	1			1		
25-34 years	2.400 [1.905–3.025]	<0.001	***	2.760 [2.262–3.369]	<0.001	***
34+ years	4.670 [3.709–5.879]	<0.001	***	5.325 [4.389–6.461]	<0.001	***

Supplementary Table 2. Multivariate multilevel logistic regression analysis of HIV status among Zimbabwean males and females age 15-49 – stratified by urban versus rural classification of DHS sample locations. The models are adjusted for DHS sample location random effects. (*continued*)

	Urban, multivariate analysis			Rural, multivariate analysis		
Covariate	**aOR [95% CI]**	**p-value**		**aOR [95% CI]**	**p-value**	
Sex work client ever (males only)						
Yes	1.489 [1.137–1.949]	0.004	**	-		
No	1			-		
Sex work client in the last year (males only)						
Yes	-			-		
No	-			-		
Partner of client of female sex worker(s) (females only)						
Yes	-			-		
No	-			-		
Lifetime number of sex partners						
None	0.477 [0.339–0.670]	<0.001	***	0.532 [0.390–0.725]	<0.001	***
1-3	1			1		
4-9	2.061 [1.669–2.545]	<0.001	***	2.143 [1.777–2.583]	<0.001	***
9+	2.498 [1.860–3.355]	<0.001	***	2.075 [1.566–2.751]	<0.001	***
Circumcised (males only)						
Yes	0.672 [0.476–0.948]	0.024	*	0.701 [0.479–1.026]	0.068	**
No	1			1		
Sample location-level human mobility prevalence						
Low[1]	-			-		
High[2]	-			-		

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

[1] DHS sample locations with a prevalence of people with a high human mobility score of less than 50%.

[2] DHS sample locations with a prevalence of people with a high human mobility score of 50% or more.

Supplementary Table 3. Multivariate multilevel logistic regression analysis of HIV status among Zimbabwean males and females age 15-49 – stratified by level of mobility at the sample locations-level. The models are adjusted for DHS sample location random effects.

	Low mobility[1], multivariate analysis			High mobility[2], multivariate analysis		
Covariate	**aOR [95% CI]**	**p-value**		**aOR [95% CI]**	**p-value**	
Proximity to the nearest female sex work site (km, square root transformed)						
All sites	-			-		
Proximity to the nearest female sex work site (km, square root transformed) by type						
City	1.002 [0.977–1.027]	0.264		1.015 [0.990–1.041]	0.244	
Economic growth point	0.981 [0.954–1.008]	0.163		0.978 [0.948–1.008]	0.154	
International	0.997 [0.975–1.019]	0.774		0.992 [0.970–1.015]	0.485	
Seasonal	0.986 [0.961–1.011]	0.264		0.991 [0.963–1.019]	0.525	
Transport	1.009 [0.980–1.038]	0.555		1.002 [0.974–1.031]	0.889	
Percentage of clients of female sex workers as proportion of all men in survey at sample location						
<5%	-			-		
5%-15%	-			-		
≥15%	-			-		
Percentage of female sex workers as proportion of the female population in 50 km radius around sample location						
<5%	1			-		
5%-15%	1.274 [1.024–1.587]	0.030	*	-		
≥15%	1.151 [0.827–1.602]	0.405		-		
Sex						
Male	1			1		
Female	2.678 [2.228–3.220]	<0.001	***	2.235 [1.834–2.723]	<0.001	***
Age						
15-24 years	1			1		
25-34 years	2.547 [2.072–3.131]	<0.001	***	2.559 [1.977–3.313]	<0.001	***
34+ years	5.467 [4.464–6.695]	<0.001	***	4.663 [3.620–6.007]	<0.001	***
Sex work client ever (males only)						

Supplementary Table 3. Multivariate multilevel logistic regression analysis of HIV status among Zimbabwean males and females age 15-49 – stratified by level of mobility at the sample locations-level. The models are adjusted for DHS sample location random effects. (*continued*)

	Low mobility[1], multivariate analysis			High mobility[2], multivariate analysis		
Covariate	**aOR [95% CI]**	**p-value**		**aOR [95% CI]**	**p-value**	
Yes	1.561 [1.218–2.000]	<0.001	***	-		
No	1			-		
Sex work client in the last year (males only)						
Yes	-			-		
No	-			-		
Partner of client of female sex worker(s) (females only)						
Yes	-			-		
No	-			-		
Lifetime number of sex partners						
None	0.533 [0.391–0.726]	<0.001	***	0.537 [0.368–0.783]	0.001	**
1-3	1			1		
4-9	1.834 [1.506–2.233]	<0.001	***	2.282 [1.808–2.880]	<0.001	***
9+	2.180 [1.635–2.907]	<0.001	***	2.241 [1.635–3.073]	<0.001	***
Circumcised (males only)						
Yes	0.603 [0.42–0.865]	0.006	**	-		
No	-			-		
Type of place of residence						
Urban	-			-		
Rural	-			-		

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

[1] DHS sample locations with a prevalence of people with a high human mobility score of less than 50%.

[2] DHS sample locations with a prevalence of people with a high human mobility score of 50% or more.

Chapter 6

Which delivery model innovations can support sustainable HIV treatment?

Caroline A. Bulstra, Jan A.C. Hontelez, Osondu Ogbuoji, Till Bärnighausen

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ABSTRACT

The rapid scale-up of antiretroviral treatment (ART) for HIV since the mid-2000s, mostly through disease-specific or "vertical" programmes, has been a highly successful undertaking, which averted millions of deaths and prevented many new infections. However, the dynamics of the HIV epidemic and changing political and financial commitment to fight the disease will likely require new models for the delivery of ART over the coming decades if the promises of universal treatment are to be met. Delivery model innovations for ART are intended to improve both the effectiveness and efficiency of the HIV treatment cascade, reaching new people who require ART and providing ART to more people without an increase in resources. We describe twelve models for ART delivery, which could be achieved through five categories of delivery innovations: integrating ART ("vertical ART plus", "partially-integrated ART" and "fully-integrated ART"); modifying steps in the ART value chain ("professional task-shifted ART", "people task-shifted ART" and "technology-supported ART"); eliminating steps in the ART value chain ("immediate ART" and "less frequent ART pick-up"); changing ART locations ("private-sector ART", "traditional-sector ART" and "ART outside the health sector"); and keeping the status quo ("vertical ART"). The different delivery model innovations are not mutually exclusive and several could be combined, such as "vertical ART plus" with "task-shifted ART". Suitability of the models will highly depend on local and national contexts, including existing health systems resources, available funding, and type of HIV epidemic. Future implementation research needs to identify which models are the best fit for different contexts.

BACKGROUND

The rapid scale-up of antiretroviral treatment (ART) for HIV since the mid-2000s has been an unprecedented achievement in public health. The rapid expansion of access to treatment – mostly through vertical programmes funded by international donor organisations [1] – has averted millions of deaths and prevented many infections in low- and middle-income countries (LMICs) [2–4]. Despite the success of the current HIV response, there are three important reasons why now is the time to rethink the delivery models for HIV treatment for the coming decades.

First, major global donors are slowly pulling back. The HIV epidemic predominantly affects resource-poor communities, mostly in sub-Saharan Africa. Here, the lack of sufficient health facilities and the push for a rapid scale-up of HIV services resulted in the creation of vertical ART delivery systems. These services are predominantly funded and sustained by international donor organisations, like the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria. Yet, while the number of people on lifelong ART continues to increase [5], the available funding falls short. Although overall health aid is higher than ever before [6], donor HIV spending in LMICs has declined by more than $1 billion annually since 2015 [1,7]. These shortages threaten the sustainability of the international AIDS response.

Second, non-communicable diseases (NCDs), such as diabetes, cardiovascular diseases and cancer, have been recognised as a growing source of morbidity and mortality in LMICs with generalised HIV epidemics [8]. As people with HIV are living longer due to successful ART [9], NCDs have become a leading cause of comorbidity for this population [10–12].

Third, the global health agenda is increasingly pushing for a shift from vertical programmes towards more integrated service delivery within the general health system. The sustainable development goals emphasise targets that call for ending the HIV, tuberculosis, and malaria epidemics; transforming maternal and child health; tackling the growing burden of NCDs; and reaching larger numbers of people for universal-test-and-treat programmes, all of which should be achieved through universal health coverage (UHC) [13,14].

Financial, epidemiological and political sustainability will need to be at the core of every country's future HIV response [15,16], triggering a need for innovative health systems thinking. Sustainable delivery models should allow for tailored country-owned ART delivery models that aim for overall cost reduction while ensuring high quality care, as well as reaching people living with HIV that the current programmes do not reach – these are important but ambitious demands on future ART delivery models.

In this paper, we propose twelve models – based on five delivery model innovations – for ART delivery, which could respond to the current challenges and opportunities. First, we suggest integration of ART with other health services. Integration can be achieved to different degrees – adding health services to vertical ART (model 1), partial integration of ART with other vertical health programmes (model 2), or full integration of ART into primary healthcare (model 3). Second, we propose modifying one or several steps in the healthcare value chain – through task-shifting of ART delivery to lower-level health workers (model 4) or to patients, family members, or community members (model 5), or through ART delivery supported by technology (model 6). Third, we describe models where steps in the healthcare value chain would be eliminated – through immediate ART initiation following a positive HIV test (model 7) or less frequent ART delivery for patients who are stable on treatment (model 8). The fourth innovation is based on using new places for ART delivery, which could be private health facilities (model 9), traditional healers (model 10), or locations outside the healthcare system (model 11). Of course, one important delivery model is the status quo, *i.e.,* vertical ART services provided apart from other health services (model 12). All delivery model innovations need to be benchmarked against the performance of the status quo, which over the past two decades has proven to be highly successful. An overview of the described delivery model innovations and related ART delivery models is presented in **Figure 1**.

INTEGRATING ART

This delivery model innovation comprises models where ART delivery is offered together with other health services. This includes integrating care for other diseases with the care already available for HIV patients in the status quo delivery models (model 1 – 'vertical ART plus'), combining different vertical systems like tuberculosis or maternal health with HIV care (model 2 – 'partially-integrated ART'), or full integration of HIV care within the general primary healthcare system (model 3 – 'fully-integrated ART)'. These models have the potential to lead to efficiency gains for the healthcare system, due to shared use of staff and physical resources. Integrated models can also increase the efficiency of patients' healthcare utilisation: for comorbid HIV patients, care will be available in one clinic visit rather than several visits to different clinics. At the same time, it is plausible that integrated care increases average costs per treatment, because of diseconomies of scope. Vertical care ensures maximal learning and procedural efficiency because patients are very similar. Integrated care implies more dissimilar patients, which reduces learning effects and the potential to optimally prepare and organise the resources for care provision.

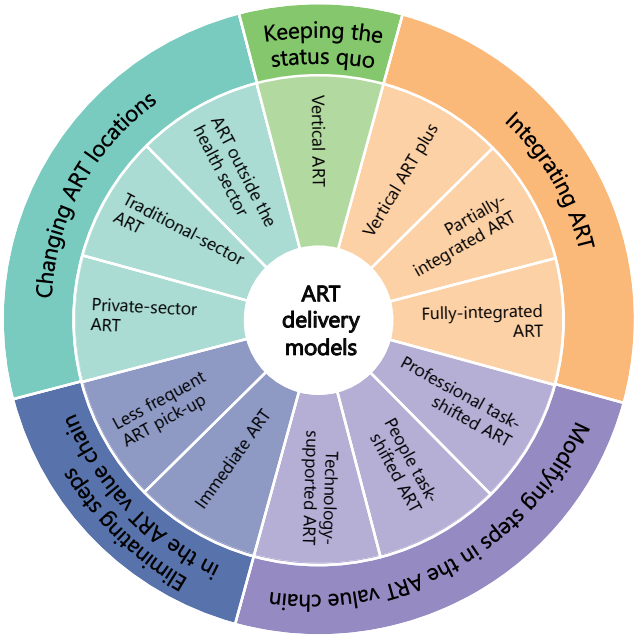

Figure 1. Wheel of ART delivery model innovations.

Model 1 – 'vertical ART plus'

In the vertical ART plus model, ART delivery remains separate from the general health system, but other health services will be offered at the clinic alongside HIV services. Frequent comorbidities of people living with HIV are tuberculosis [17,18], NCDs such as diabetes and hypertension [18], as well as depression and other mental health issues [19]. With completely vertical HIV service provision, these comorbidities are often neglected, and people living with HIV need to visit multiple health facilities to access all the required care. Vertical ART plus services could capitalise on the foundations built with the HIV response to improve the efficiency and coverage of care and treatment of these comorbidities. Furthermore, screening might be offered along with HIV services, which is already done sometimes for cervical cancer in young female HIV patients and for the most common NCDs in older HIV patients [20]. Vertical ART plus may be more cost-effective than purely vertical services as resources are shared, translating to increased technical efficiency (*i.e.* minimalising staff and resources while maximising service delivery) [20]. However, the vertical ART plus model may result in inequalities in access to care, as HIV negative people who require healthcare are not covered here and will need to seek services elsewhere.

Model 2 – 'partially-integrated ART'

This model comprises partial integration of ART delivery with other existing vertical healthcare programmes, of which well-known examples are integration with programmes for tuberculosis [21,22], sexual and reproductive health [23], and NCDs [10,20]. More recently, HIV service integration with mental health programmes has also been explored [24,25]. Generally, this form of integration allows for operational efficiency gains (*i.e.* optimised service delivery due to specialised staff and well-functioning work flows for example) and is most beneficial when target populations of both programmes largely overlap. In contrast to the vertical ART plus model, services are not exclusively available for people living with HIV. Partial integration of ART delivery with other health programmes can be realised at different levels, from complete integration of location, resources and personnel to solely linking both vertical programmes, through strengthened referral. The advantages of this model are highly dependent on the level of integration and context. Similar to the vertical ART plus model, this model has the potential for technical efficiency gains. Depending on the context, also allocative efficiency gains (*i.e.,* optimal allocation of services based on the patients' needs) might be achieved. However, this model does not entail UHC and thus still produces inequalities in access to care.

Model 3 – 'fully-integrated ART'

This integration model can be defined as ART service provision at the same location and with the same (human) resources as primary healthcare [26]. Decentralised ART delivery allows people to access all types of healthcare, regardless of their HIV status, thereby tackling issues of inequality and stigma associated with more vertical systems [27].

Whether efficiency is higher compared to more vertical systems will largely depend on the local context and disease burden. On the one hand, shared resources and shared workload among the staff could enhance technical efficiency and allocative efficiency of the general health system. Furthermore, due to easier referral and access to other health services, uptake of ART will likely increase, at a lower cost [28]. On the other hand, diseconomies of scope may result in less efficient ART delivery, as heath workers and other personnel now need to shift focus between treating a wide variety of patients rather than specialising and optimising care for a specific group of patients. In addition, in high-burden areas, the high numbers of HIV infected people requiring care might overburden the health system and crowd-out other patients. Finally, a fully integrated ART delivery model might be detrimental for care and prevention for specific key populations, such as sex workers, injecting drug users, or men who have sex with men (MSM). In many cases these – often marginalised – populations have poorer access to general healthcare, and benefit greatly from specifically tailored services.

MODIFYING STEPS IN THE ART VALUE CHAIN

This delivery model innovation is aimed at modifying different essential steps of the value chain [29] of ART delivery to increase and improve delivery while ensuring low costs. This can be achieved by shifting the offered HIV services to lower health workers (model 4 – 'professional task-shifted ART'), other people or the patients themselves (model 5 – 'people task-shifted ART'), or technology supported ART delivery (model 6 – 'technology-supported ART'). By bringing services closer to the population, these models may increase ART coverage, and could bolster retention and adherence to ART at relatively low costs. When designed well, this type of innovation might alleviate pressure from the busy clinics providing HIV treatment. The effects on quality of care and patient satisfaction highly depend on the type of model and the specific content and context of modification.

Model 4 – 'professional task-shifted ART'

Health workers have been one – or the – 'binding constraint' even early in the history of the ART scale-up in sub-Saharan Africa [30–32]. Ever since the introduction of nurse-led treatment initiation [33], various task-shifting strategies have been explored to overcome this constraint and to increase the efficiency and sustainability of ART delivery. In the professional task-shifted ART model, HIV testing and ART delivery are partly shifted from nurses to health extension workers or community health workers (CHWs), for example through home-based testing or mobile testing [34,35] and CHW-led ART delivery [36]. Clinics are often busy, and task-shifting and task-sharing can reduce the work load of highly trained health professionals, allowing them to provide other complex and essential care. In addition, costs will remain relatively low compared to fully centralised ART delivery. Community-based testing and service provision increases the number of people reached, that might otherwise not know their status or would not have access to sufficient treatment [37,38]. Professional task-shifting can thus lead to higher ART coverage and operational efficiency gains. Shifting services to CHWs can be realised in both vertical and integrated systems, as CHWs can be associated with either specific HIV clinics or the general health system. In fact, community-based delivery does not need to be unique to HIV, and CHWs may also be able to provide pregnancy and maternal care [39–41], screen for hypertension, and distribute chronic medication to those in need, or provide counselling on where to access other required health services. Nevertheless, specialised HIV doctors and nurses will still be essential when dealing with more complex cases, such as people with poor viral suppression, resistance, or complex comorbidities.

Model 5 – 'people task-shifted ART'

People task-shifted ART delivery involves the local community or even the patients themselves. For instance, HIV positive peers within the community can bolster linkage, retention

and adherence to ART through adherence clubs, community ART distribution points, or non-traditional community-oriented care for patients who are stable on treatment [42,43]. Peer educator-led ART refill groups in South Africa, community ART distribution points in the Democratic Republic of Congo and patient-led community ART groups in Mozambique are other examples of successful 'people task-shifted ART' [35]. These initiatives enable patients to visit clinics less, saving time and travel costs, while peer-groups motivate each other to adhere to their medication. As international donor funding for HIV continues to decline and the number of HIV infected people on ART continues to grow, shifting care to the community or the individual is a logical consideration to improve efficiency and sustainability of the HIV response, while also freeing-up resources for other diseases. However, this model, like other task-shifting initiatives, comes with several disadvantages. Generally, shifting services away from the clinics will challenge quality-control. In addition, bringing care closer to home might affect privacy of patients and therewith discourage patients from seeking care due to HIV-related stigma.

Model 6 – 'technology-supported ART'

Technology-supported ART can include a wide range of technologies, all aimed at reducing work, shifting work away from health workers or supporting patients or CHWs in their routines. Previously explored examples are drone delivery of HIV test kits and other medicines in Malawi [44], and mobile fully-equipped ART clinics in Eswatini [45]. Another example is the strategic placement of electronic pick-up machines, where patients can register with a patient-card to receive a tailored treatment package. Also, smartphone apps are increasingly developed to stimulate adherence and simplify monitoring, for example by providing laboratory test results, treatment schemes and information on side effects. However, active usage of these apps seems challenging, according to a randomised-controlled trial among HIV patients registered at an urban clinic in South Africa [46]. Tablet-based apps for patient registry and monitoring are an example for new technology-support initiatives for CHWs. Although new technologies generally seem promising, in many cases sufficient training is needed to use the technologies adequately. Moreover, the tools are generally costly, risking theft and damage.

ELIMINATING STEPS IN THE ART VALUE CHAIN

Eliminating steps in the ART value chain comprises of either providing immediate ART after diagnosis (model 7 – 'immediate ART') or less frequent ART pick-ups for stable patients (model 8 – 'less frequent ART pick-up'). Both models can be desirable for the patient, while also saving costs for the health system due to less frequent visits. The main challenge of this

innovation lies in sustaining good quality of HIV care over time with less frequent patient-provider interaction.

Model 7 – 'immediate ART'

It is important that people who test positive for HIV must contact care services in a timely manner. However, care-seeking behaviour is highly heterogenous, leading to delay until receiving the first treatment [47]. For instance, if people test positive outside of the central HIV services, for example, through community-based HIV testing, they are often referred to clinics that are busy, not well equipped, and far away. To overcome treatment delays, CHWs could be equipped with ART supply packages to offer to patients directly. Evidence from four trials conducted in African settings suggests that treatment outcomes are similar, compared to outcomes of linkage to care programmes [48]. A potential downside of this strategy is lack of adherence [48], possibly due to insufficient counselling. Also, CHWs would need to have additional training to provide patients with all the information they need, for example on treatment schemes and important side effects. When people are tested in the health clinic, a follow-up appointment often needs to be scheduled to distribute ART. Here, same-day ART delivery could be a solution. A study conducted in an urban setting in Haiti showed that same-day ART delivery leads to an increase in adherence as well as better treatment outcomes [49].

Model 8 – 'less frequent ART pick-up'

Currently, many medical protocols require HIV patients to visit a clinic every one to three months. This is very time consuming and costly both for the patient and the health system. Alternative monitoring and ART pick-up schemes have been proposed, for example in Uganda, where patients are only required to visit their clinic once every six months [50]. Although this model might save costs, the danger lies in the infrequent monitoring of patients. Therefore, this model is only suitable for patients who are stable on treatment.

CHANGING ART LOCATIONS

This delivery model innovation is based on the use of new places for ART delivery, such as private health facilities (model 9 – 'private-sector ART'), traditional healers (model 10 – 'traditional-sector ART') or places outside of the healthcare system (model 11 – 'ART outside the health sector'), including supermarkets, train stations and faith-based organisations. By offering ART at places that are easier to reach, these innovations can increase recruitment, adherence and retention to ART. Suitability of these models highly depends on the context. Primary challenges that should be taken into account when considering these models are ensuring quality of care and privacy of the patients.

Model 9 – 'private-sector ART'

In the context of a well-developed private healthcare sector, the integration of ART delivery into the private sector can be considered. This could be the integration of ART delivery into the general health services provided by big privately-owned hospitals, but also ART distribution via private physicians or pharmacies. Although ART delivery might be improved for patients from higher socioeconomic classes, this distribution method would generally be relatively expensive. Unless treatment costs could be covered using alternative financing strategies, this model likely leads to increased inequality in access to ART, and therefore should not be implemented as a stand-alone solution.

Model 10 – 'traditional-sector ART'

In some high burden countries, traditional medicine plays a central role in society. People infected with HIV might visit their traditional healer first, before seeking professional care. Traditional healers could be used to deliver ART, screen for HIV or do adherence counselling, therewith using their (often) trustworthy image and big network within the community. However, this model needs to be considered with caution. Community healers could have profit motives, and generally it would be challenging to guarantee the quality of the services being offered. In addition, traditional healers follow different believes compared to allopathic medicine: not all of them would be open to supporting allopathic medicine practices, and they provide care that may not be conductive to the clinical success of ART.

Model 11 – 'ART outside the health sector'

Alternatively, ART could be delivered at places outside of the health sectors, at public or frequently visited places. Suitable places would be supermarkets, train stations and faith-based organisations, as well as other places that are easy to access for a vast majority of the population. However, this type of distribution strategy needs to be very well thought out in order to secure the privacy of patients and ensure good quality of care.

KEEPING THE STATUS QUO

Another option is to maintain the status quo, keeping ART delivery models as they currently are (model 12 – 'vertical ART'). In this case, HIV services will continue to be provided apart from the general health systems. There are many good arguments for this choice. Generally, vertical delivery implies high operational efficiency, due to high levels of expertise and standardised work flows. Also, the current delivery models have proven to be successful, and the risk of adapting or changing this model must be considered carefully. Furthermore, the current models have already evolved and are often well-adapted to local contexts. However, solely maintaining this model may not be feasible in resource limited contexts.

Model 12 – 'vertical ART'

In vertical systems, experienced doctors, nurses and other health workers work exclusively with HIV infected people, and therefore likely offer higher quality of care due to specialisation while doing their work more efficiently (*i.e.* economies of scale) in high-burden areas [27,51]. In these contexts, this approach allows for possible cost reduction, as well as enhanced quality of ART delivery. In contrast, a disease-specific service provision model in low-burden areas will likely suffer from diseconomies of scale and scope due to excess capacity. Therefore, although operational efficiency might be high due to specialised personnel, referral chains, and logistics, the technical and allocative efficiency of disease-specific service delivery is highly dependent on the local disease burden. In addition, disease specific models may introduce inequalities in access to care, both in low and high-burden settings, as services for other diseases may remain inadequate [13,52]. HIV patients receiving care at the ART clinic might need to seek care for other conditions, such as hypertension or diabetes, elsewhere.

Table 1. Overview of the definitions and examples of models for ART delivery based on five delivery model innovations.

INNOVATION	DELIVERY MODEL	DEFINITION	EXAMPLES
Integrate with other health services	Vertical-plus ART	Other services are provided within vertical ART services	- Anti-hypertensive care, diabetes prevention and other NCD services provided with ART services in Kenya, Uganda and Nigeria [20] - Depression care offered with ART in the Unites States [53]
	Partially-integrated ART	Integration with other vertical health services	- Integration with tuberculosis services in sub-Saharan Africa, South America and Asia [21,22] - Integration with sexual and reproductive health [23] - Integration with NCD services in sub-Saharan Africa [10,20]
	Fully-integrated ART	Integration of ART services into the general primary healthcare system	- Integration of HIV care with primary healthcare services in rural Kenya [26], and Malawi [28]
Modify steps in the value chain	Professional task-shifted ART	Shifting the delivery of ART from highly to less trained health professionals	- Community health workers delivering ART in Tanzania [38] - Community health workers delivering prevention of mother-to-child transmission services in Tanzania [54] - Expanding testing and linkage to care through community health workers in Uganda [34], Rwanda and Malawi [37]
	People task-shifted ART	Shifting the delivery of ART from healthcare professionals to lay people	- Improving adherence trough peer-support among pregnant women in South Africa [55]. - Peer educator-led ART refill groups in South Africa, community ART distribution points in DRC and patient-led community ART groups in Mozambique are other examples of successful task-shifting models [35]

Table 1. Overview of the definitions and examples of models for ART delivery based on five delivery model innovations. (*continued*)

INNOVATION	DELIVERY MODEL	DEFINITION	EXAMPLES
	Technology-supported ART	ART delivery using technological innovations	- Drone delivery of HIV test kits in rural Malawi [44] - Mobile fully-equipped ART clinics in Eswatini [45].
Eliminate steps in the value chain	Immediate ART	ART services provided immediately following a positive HIV test	- CHWs providing ART packages after HIV testing and counseling, in several African settings [48] - Same-day delivery in urban clinics of Haiti [49]
	Less frequent ART	Decreased frequency of ART provision	- Shift from 1-2 to 6 month clinic visits in Uganda [50]
Use new places	Private-sector ART	ART delivery in private healthcare facilities	- ART delivery at private hospitals, physician practices or pharmacies
	Traditional-sector ART	ART delivery supported by traditional healers	- ART delivery by traditional healers
	ART in places outside the health sectors	ART delivery outside of the healthcare system	- ART delivery at supermarkets, train stations or faith-based organisations
Status quo	Vertical ART	ART delivery remains separate from other health services, in current places, and using current technologies	

Abbreviations: ART = antiretroviral treatment; CHWs = community health workers; NCDs = non-communicable diseases; SSA = sub-Saharan Africa

DISCUSSION

We proposed five categories of 'delivery model innovations' for ART, translated into twelve concrete ART delivery models. None of these proposed models will be a 'silver bullet' for the world. Rather, suitability of the models will highly depend on the epidemic, health systems, political and cultural contexts [56]. For instance, countries with generalised epidemics may continue to benefit from a degree of 'verticality' in the delivery of ART, because in many communities in these countries there are sufficiently large numbers of HIV patients to keep vertical delivery structures fully and constantly occupied. In countries with more concentrated epidemics, among key populations such as sex workers and MSM for example, specific vertical services might be essential to be able to offer specialised care, tackle stigma, and promote easier access to health care for these vulnerable groups. In contrast, HIV care

for the general population may be more efficiently provided as part of general internal medicine and family health services.

Moreover, even within regions or countries with similar epidemics and health systems contexts, multiple innovations might be needed to achieve near-universal ART coverage and optimised ART retention and adherence [57]. Communities living in remote areas would, for example, benefit from implementation of task-shifted and technology supported ART delivery, as this would increase test-and-treat coverage as well as decrease travel time and costs for people already receiving treatment. For patient groups that are mobile, such as truck drivers and seasonal migrants, less frequent ART delivery could be a solution to increase adherence. Other important facets that need to be taken into account while designing the best ART delivery strategies are: the available funding, previous successes in the HIV response (of which trends in HIV incidence and current ART coverage are important markers), burden of other diseases, HIV/AIDS-related stigma and political commitment.

Generally, while it is plausible that delivery model innovations can lead to major improvements in the effectiveness and efficiency of the HIV treatment cascade, we should keep in mind that it is also possible that such innovations fail and the envisioned improvements do not materialise. The status quo should not be hastily abandoned for innovations; careful vetting of novel models through implementation science and causal impact evaluations should come before any large-scale replacement of the current ART delivery programmes.

Optimally tailoring ART delivery to the current financial, epidemiological, and political context will likely not only require innovations in service delivery, but also in the methods used to determine resource allocation. Here science can play an important role. First, delivery models need to be identified and designed with beneficiaries, healthcare providers, and community stakeholders. Based on outcomes of ART delivery model' comparisons and evaluations from various contexts, a framework can be designed to support evidence-based decision making. Complementary models for people-centred services can be developed for each context of the framework. Second, the proposed delivery models need to be tested in prototype and pilot studies – here science can support, by designing studies that allow for causal impact evaluations.

Also, mathematical modelling can be of value for optimising resource allocation for ART. However, these models are also largely disease specific, and generally ignore the general epidemiological and health system context of a specific area. Resource allocation within the UHC era will increasingly require multi-disease mathematical models that can also capture health system dynamics and constraints [12,58].

The proposed delivery model innovations can be utilised similarly to reshape other traditionally vertically delivered health services, *e.g.*, tuberculosis or family planning services.

Conclusions and future perspectives

ART delivery model innovations need to be carefully vetted and evaluated for their potential to increase ART coverage and efficiency. The suitability of the proposed models will depend on local and national contexts. Thus, local design studies are required to determine the most promising delivery model innovations and their precise forms. Prototyping and pilot studies are needed to put these models to the test before large-scale implementation. The promise of ART delivery model innovations is large and implementation science, causal evaluation and mathematical modelling studies can ensure that it is fulfilled.

REFERENCES

1. Dieleman JL, Haakenstad A, Micah A, Moses M, Abbafati C, Acharya P, *et al.* Spending on health and HIV/AIDS: domestic health spending and development assistance in 188 countries, 1995–2015. Lancet. 2018;391: 1799–1829. doi:10.1016/S0140-6736(18)30698-6

2. Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, *et al.* Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. Lancet. 2014;384: 241–248.

3. Murray CJL, Ortblad KF, Guinovart C, Lim SS, Wolock TM, Roberts DA, *et al.* Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990--2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384: 1005–1070.

4. Granich R, Gupta S, Hersh B, Williams B, Montaner J, Young B, *et al.* Trends in AIDS deaths, new infections and ART coverage in the top 30 countries with the highest AIDS mortality burden; 1990--2013. PLOS ONE. 2015;10: e0131353.

5. UNAIDS. UNAIDS report 2017, Joint United Nations Programme on HIV/AIDS (UNAIDS). 2017.

6. Schäferhoff M, Martinez S, Ogbuoji O, Sabin ML, Yamey G. Trends in global health financing. BMJ. 2019;365: 19–20. doi:10.1136/bmj.l2185

7. Kaiser Family Foundation. Donor Government Funding to in Low- Low- and for HIV HIV in and Middle-Income Countries in 2016. 2017.

8. Allen L, Williams J, Townsend N, Mikkelsen B, Roberts N, Foster C, *et al.* Socioeconomic status and non-communicable disease behavioural risk factors in low-income and lower-middle-income countries: a systematic review. Lancet Glob Heal. 2017;5: e277--e289.

9. Hontelez JAC, Vlas SJ de, Baltussen R, Newell M-L, Bakker R, Tanser F, *et al.* The impact of antiretroviral treatment on the age composition of the HIV epidemic in sub-Saharan Africa. AIDS. 2012;23: 1–7. doi:10.1038/jid.2014.371

10. Kemp CG, Weiner BJ, Sherr KH, Kupfer LE, Cherutich PK, Wilson D, *et al.* Implementation science for integration of HIV and non-communicable disease services in sub-Saharan Africa: A systematic review. AIDS. 2018;32: S93–S105. doi:10.1097/QAD.0000000000001897

11. Haacker M, Bärnighausen T, Atun R. HIV and the growing health burden from noncommunicable diseases in Botswana: modelling study. J Glob Health. 2019;9.

12. Osetinsky B, Hontelez JAC, Lurie MN, McGarvey ST, Bloomfield GS, Pastakia SD, *et al.* Epidemiological And Health Systems Implications Of Evolving HIV And Hypertension In South Africa And Kenya. Health Aff. 2019;38: 1173–1181.

13. Bekker LG, Alleyne G, Baral S, Cepeda J, Daskalakis D, Dowdy D, *et al.* Advancing global health and strengthening the HIV response in the era of the Sustainable Development Goals: the International AIDS Society—Lancet Commission. Lancet. 2018;392: 312–358. doi:10.1016/S0140-6736(18)31070-5

14. United Nations. Transforming our world: The 2030 Agenda for Sustainable Development. 2017.

15. Oberth G, Whiteside A. What does sustainability mean in the HIV and AIDS response? African J AIDS Res. 2016;15: 35–43. doi:10.2989/16085906.2016.1138976

16. Phillips A, Shroufi A, Vojnov L, Cohn J, Roberts T, Ellman T, *et al.* Sustainable HIV treatment in Africa through viral

load-informed differentiated care. Nature. 2015;528: S68.

17. Diedrich CR, Flynn JL. HIV-1/mycobacterium tuberculosis coinfection immunology: how does HIV-1 exacerbate tuberculosis? Infect Immun. 2011;79: 1407–1417.

18. Oni T, Youngblood E, Boulle A, McGrath N, Wilkinson RJ, Levitt NS. Patterns of HIV, TB, and non-communicable disease multimorbidity in peri-urban South Africa-a cross sectional study. BMC Infect Dis. 2015;15: 20.

19. Nanni MG, Caruso R, Mitchell AJ, Meggiolaro E, Grassi L. Depression in HIV infected patients: a review. Curr Psychiatry Rep. 2015;17: 530.

20. Duffy M, Ojikutu B, Andrian S, Sohng E, Minior T, Hirschhorn LR. Non-communicable diseases and HIV care and treatment: models of integrated service delivery. Trop Med Int Heal. 2017;22: 926–937. doi:10.1111/tmi.12901

21. Suthar AB, Lawn SD, del Amo J, Getahun H, Dye C, Sculier D, *et al.* Antiretroviral therapy for prevention of tuberculosis in adults with hiv: A systematic review and meta-analysis. PLOS Med. 2012;9. doi:10.1371/journal.pmed.1001270

22. Howard AA, El-Sadr WM. Integration of Tuberculosis and HIV Services in Sub-Saharan Africa: Lessons Learned. Clin Infect Dis. 2010;50: S238–S244. doi:10.1086/651497

23. Warren CE, Hopkins J, Narasimhan M, Collins L, Askew I, Mayhew SH. Health systems and the SDGs: lessons from a joint HIV and sexual and reproductive health and rights response. Health Policy Plan. 2017;32: iv102–iv107. doi:10.1093/heapol/czx052

24. Kaaya S, Eustache E, Lapidos-Salaiz I, Musisi S, Psaros C, Wissow L. Grand Challenges: Improving HIV Treatment Outcomes by Integrating Interventions for Co-Morbid Mental Illness. PLOS Med. 2013;10: e1001447. doi:10.1371/journal.pmed.1001447

25. Freeman MC, Patel V, Collins PY, Bertolote JM. Integrating mental health in global initiatives for HIV/AIDS. Br J Psychiatry. 2005;187: 1–3. doi:10.1192/bjp.187.1.1

26. Odeny TA, Penner J, Lewis-Kulzer J, Leslie HH, Shade SB, Adero W, *et al.* Integration of HIV care with primary health care services: effect on patient satisfaction and stigma in rural Kenya. AIDS Res Treat. 2013;2013.

27. Sweeney S, Obure CD, Maier CB, Greener R, Dehne K, Vassall A. Costs and efficiency of integrating HIV/AIDS services with other health services: A systematic review of evidence and experience. Sex Transm Infect. 2012;88: 85–99. doi:10.1136/sextrans-2011-050199

28. Chan AK, Mateyu G, Jahn A, Schouten E, Arora P, Mlotha W, *et al.* Outcome assessment of decentralization of antiretroviral therapy provision in a rural district of Malawi using an integrated primary care model. Trop Med Int Heal. 2010;15: 90–97. doi:10.1111/j.1365-3156.2010.02503.x

29. Porter ME. The value chain and competitive advantage. Underst Bus Process. 2001; 50–66.

30. Bärnighausen T, Bloom DE, Humair S. Human resources for treating HIV/AIDS: are the preventive effects of antiretroviral treatment a game changer? PLOS ONE. 2016;11: e0163960.

31. Bärnighausen T, Bloom DE, Humair S. Universal antiretroviral treatment: the challenge of human resources. Bull World Health Organ. 2010;88: 951–952.

32. Bärnighausen T, Bloom DE, Humair S. Human resources for treating HIV/AIDS: needs, capacities, and gaps. AIDS Patient Care STDS. 2007;21: 799–812.

33. Samb B, Celletti F, Holloway J, Van Damme W, De Cock KM, Dybul M. Rapid expansion of the health workforce in response to the HIV epidemic. N Engl J Med. 2007;357: 2510–2514. doi:10.1056/NEJMsb071889

34. Asiimwe S, Ross JM, Arinaitwe A, Tumusiime O, Turyamureeba B, Roberts DA, *et al.* Expanding HIV testing and linkage to care in southwestern Uganda with community health extension workers. J Int AIDS Soc. 2017;20: 80–87. doi:10.7448/IAS.20.5.21633

35. Bemelmans M, Baert S, Goemaere E, Wilkinson L, Vandendyck M, van Cutsem G, *et al.* Community-supported models of care for people on HIV treatment in sub-Saharan Africa. Trop Med Int Heal. 2014;19: 968–977. doi:10.1111/tmi.12332

36. Geldsetzer P, Francis JM, Ulenga N, Sando D, Lema IA, Mboggo E, *et al.* The impact of community health worker-led home delivery of antiretroviral therapy on virological suppression: a non-inferiority cluster-randomized health systems trial in Dar es Salaam, Tanzania. BMC Health Serv Res. 2017;17: 160.

37. Zachariah R, Ford N, Philips M, S.Lynch, Massaquoi M, Janssens V, *et al.* Task shifting in HIV/AIDS: opportunities, challenges and proposed actions for sub-Saharan Africa. Trans R Soc Trop Med Hyg. 2009;103: 549–558. doi:10.1016/j.trstmh.2008.09.019

38. Geldsetzer P, Francis JM, Sando D, Asmus G, Lema IA, Mboggo E, *et al.* Community delivery of antiretroviral drugs: A non-inferiority cluster-randomized pragmatic trial in Dar es Salaam, Tanzania. PLOS Med. 2018;15: e1002659.

39. Geldsetzer P, Mboggo E, Larson E, Lema IA, Magesa L, Machumi L, *et al.* Community health workers to improve uptake of maternal healthcare services: A cluster-randomized pragmatic trial in Dar es Salaam, Tanzania. PLOS Med. 2019;16: e1002768.

40. Larson E, Geldsetzer P, Mboggo E, Lema IA, Sando D, Ekström AM, *et al.* The effect of a community health worker intervention on public satisfaction: Evidence from an unregistered outcome in a cluster-randomized controlled trial in Dar es Salaam, Tanzania. Hum Resour Health. 2019;17: 1–8. doi:10.1186/s12960-019-0355-7

41. Lema IA, Sando D, Magesa L, Machumi L, Mungure E, Sando MM, *et al.* Community health workers to improve antenatal care and PMTCT uptake in Dar es Salaam, Tanzania: a quantitative performance evaluation. J Acquir Immune Defic Syndr. 2014;67: S195.

42. Genberg BL, Shangani S, Sabatino K, Rachlis B, Wachira J, Braitstein P, *et al.* Improving Engagement in the HIV Care Cascade: A Systematic Review of Interventions Involving People Living with HIV/AIDS as Peers. AIDS Behav. 2016;20: 2452–2463. doi:10.1007/s10461-016-1307-z

43. Holmes CB, Sanne I. Changing models of care to improve progression through the HIV treatment cascade in different populations. Curr Opin HIV AIDS. 2015;10: 447–450. doi:10.1097/COH.0000000000000194

44. Reuters. Drones could speed up HIV tests in remote areas. 2016.

45. MacKellar D, Williams D, Bhembe B, Dlamini M, Byrd J, Dube L, *et al.* Peer-delivered linkage case management and same-day ART initiation for men and young persons with HIV infection—Eswatini, 2015--2017. Morb Mortal Wkly Rep. 2018;67: 663.

46. Venter W, Coleman J, Chan VL, Shubber Z, Phatsoane M, Gorgens M, *et al.* Improving linkage to HIV care through mobile phone apps: randomized controlled trial. JMIR mHealth uHealth. 2018;6: e155.

47. MacCarthy S, Hoffmann M, Ferguson L, Nunn A, Irvin R, Bangsberg D, *et al.* The HIV care cascade: Models, measures and moving forward. J Int AIDS Soc. 2015;18: 2–6. doi:10.7448/IAS.18.1.19395

48. Kredo T, Adeniyi FB, Bateganya M, Pienaar ED. Task shifting from doctors to non-doctors for initiation and maintenance of antiretroviral therapy. Cochrane Database Syst Rev. 2014.

49. Koenig SP, Dorvil N, Dévieux JG, Hedt-Gauthier BL, Riviere C, Faustin M, *et al.* Same-day HIV testing with initiation of antiretroviral therapy versus standard care for persons living with HIV: A randomized unblinded trial. PLOS Med. 2017;14: e1002357.

50. Nakiwogga-Muwanga A, Katabira E, Kiragga A, Kambugu A, Nakibuuka-Lubwama E, Manabe YC, *et al.* Factors before enrolment are associated with being removed from a Pharmacy-only Refill Programme at a large urban HIV/AIDS clinic, Uganda. Int J STD AIDS. 2014;25: 105–112.

51. Bärnighausen T, Bloom D, Humair S. Going horizontal—shifts in funding of global health interventions. N Engl J Med. 2011;364: 2181–2183.

52. Kim JY, Farmer P, Porter ME. Redefining global health-care delivery. Lancet. 2013;382: 1060–1069.

53. Bengtson AM, Pence BW, Gaynes BN, Quinlivan EB, Heine AD, O'donnell JK, *et al.* Improving depression among HIV-infected adults: transporting the effect of a depression treatment intervention to routine care. J Acquir Immune Defic Syndr. 2016;73: 482.

54. Naburi H, Ekström AM, Mujinja P, Kilewo C, Manji K, Biberfeld G, *et al.* The potential of task-shifting in scaling up services for prevention of mother-to-child transmission of HIV: a time and motion study in Dar es Salaam, Tanzania. Hum Resour Health. 2017;15: 35.

55. Richter L, Rotheram-Borus MJ, Van Heerden A, Stein A, Tomlinson M, Harwood JM, *et al.* Pregnant women living with HIV (WLH) supported at clinics by peer WLH: a cluster randomized controlled trial. AIDS Behav. 2014;18: 706–715.

56. De Neve J-W, Garrison-Desany H, Andrews KG, Sharara N, Boudreaux C, Gill R, *et al.* Harmonization of community health worker programs for HIV: A four-country qualitative study in Southern Africa. PLOS Med. 2017;14: e1002374.

57. Bärnighausen T, Chaiyachati K, Chimbindi N, Peoples A, Haberer J, Newell M-L. Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies. Lancet Infect Dis. 2011;11: 942–951.

58. Bärnighausen T, Hontelez JAC, Hauck K, Bijlmakers L, Jansen MPM, Tromp N, *et al.* Evidence for scaling up HIV treatment in sub-Saharan Africa: A call for incorporating health system constraints. PLOS Med. 2017;14: e1002240. doi:10.1371/journal.pmed.1002240

Chapter 7

Impact of the coronavirus disease 2019-related global recession on the financing of the global HIV response

Caroline A. Bulstra, Che L. Ready, Rifat Atun, Till Bärnighausen, Jan A.C. Hontelez

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BACKGROUND

The global response to the HIV pandemic since the 2000s has been an unprecedented success, with rapid scale-up of HIV prevention and antiretroviral treatment (ART) programmes [1]. Although most low-and-middle-income countries are transitioning towards domestic public funding because of shrinking donor funding, Official Development Assistance (ODA) remains an essential component of HIV financing, especially in sub-Saharan Africa [2].

The coronavirus disease 2019 (COVID-19) pandemic produced an economic crisis characterised as the worst since the Great Depression in the 1930s [3]. The International Monetary Fund (IMF) estimates that reduced economic output and trade because of COVID-19 – and its impactful countermeasures, such as lockdowns and curfews – will shrink the world gross domestic product (GDP) by 4.4% in 2020, and will only gradually recover over the next years [4]. These declines can have devastating effects on donor and domestic healthcare financing for the years to come, including for HIV.

ESTIMATING THE IMPACT

We estimated the potential impact of the global recession on HIV financing in the 10 countries with the largest ART programmes in sub-Saharan Africa – Ethiopia, Malawi, Mozambique, Tanzania, Uganda, Kenya, Nigeria, Zambia, Zimbabwe, and South Africa – over the next 5 years to illustrate potential gaps due to the economic crises, and propose urgent mitigation strategies to ensure continued service delivery. Together, these countries account for roughly 70% of HIV-infected people worldwide [5] and spend an estimated US$7.5 billion on HIV annually, of which almost two-thirds (*i.e.,* about US$ 4.7 billion) comes from ODA [6].

We used IMF economic projections on GDP growth and published estimates of current domestic spending and ODA for HIV in each country [4,5]. We first calculated the share of GDP spend on HIV from domestic sources, and the proportional share of ODA from donor countries. We then developed four scenarios to reflect possible effects of GDP declines and political choices in HIV financing, and calculated the net difference to a no-COVID-19 counterfactual using IMF country-specific economic projections from before the pandemic (**Figure 1**).

Figure 1 shows the projected net difference in country-specific HIV/AIDS budget over the next 5 years for four scenarios, compared with a no-COVID-19 counterfactual, for Ethiopia, Malawi, Mozambique, Tanzania, and Uganda (low-income), Kenya, Nigeria, Zambia, and Zimbabwe (lower-middle-income), and South Africa (upper-middle-income). Estimates were

generated using data on projected country-specific GDP growth from the IMF [4], and latest data on country-specific domestic and donor funding for HIV/AIDS as provided by the Joint United Nations Programme on HIV/AIDS (UNAIDS) [5]. All estimates are reported in 2019 US$. If the share of GDP designated for HIV in both domestic and donor countries remains unchanged, we estimate a gap of about US$1.9 billion over 2020–2024, a decline of about 5% compared with funding over 2015–2019 (Figure 1, scenario 1).

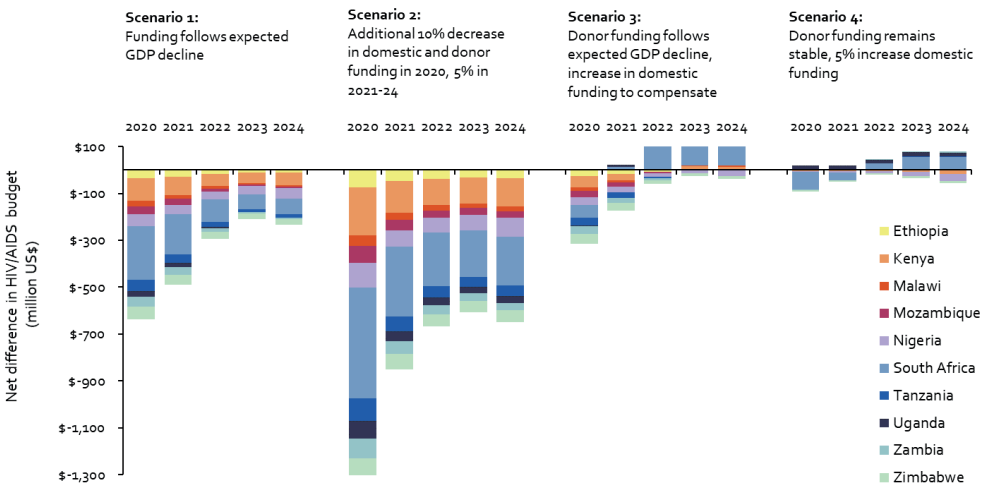

Figure 1. Estimated impact of the coronavirus disease 2019-related global recession on HIV financing in the 10 countries with the largest HIV programs in sub-Saharan Africa. Figure shows the projected net difference in country-specific HIV/AIDS budget over the next five years for four scenarios, compared to a no-COVID-19 counterfactual, for Ethiopia, Malawi, Mozambique, Tanzania, and Uganda (low-income), Kenya, Nigeria, Zambia, and Zimbabwe (lower-middle-income), and South Africa (upper-middle-income). Estimates were generated using data on projected country-specific GDP growth from the IMF [4], and latest data on country-specific domestic and donor funding for HIV/AIDS as provided by UNAIDS [5]. All estimates are reported in 2019 US$.

If the share of GDP designated for HIV falls by an initial 10% in both domestic and external sources in 2020 and 5% in the subsequent years – representing a shift of funding to other sectors, such as COVID-19-related healthcare, economic relief funds, or payment of government debts – we estimate a cumulative gap of US$4.1 billion, amounting to a decline of about 11% in total funding for HIV (Figure 1, scenario 2).

Compensating for gaps in ODA would require substantial increases in domestic HIV funding: by roughly 10% (upper middle-income countries), 15% (lower middle-income countries) or 20% (lower income countries) (Figure 1, scenario 3). Even in an extremely optimistic scenario, in which the absolute amount of donor funding remains unchanged, domestic HIV spending would need to increase by about 5% to maintain current funding levels (Figure 1, scenario

4). Such increases appear unlikely, as most of these countries already struggled to expand domestic HIV funding in the pre-COVID-19 era [6].

Although it is challenging to speculate which of these scenarios will predominate, current events suggest that our most pessimistic scenario, including additional cuts in donor funding on top of the budget declines caused by GDP fluctuations (scenario 2), is at least partly unfolding. The UK government recently announced to consider temporarily cutting foreign aid spending from 0.7% to 0.5% of gross national income [7], a decline of over 25%, and other donor countries may follow suit. For nine out of the 10 countries studied, 77–94% of funding for care and treatment comes from ODA [6]; making these political decisions a direct threat to continuation of ART programs. The only exception is South Africa, where only 18% of the HIV budget stems from ODA and continuation largely depends on local political decisions. However, as South Africa has been severely affected by the pandemic, reprioritisation of domestic resources may well be necessary to finance the COVID-19 response and economic recovery.

If we assume scenario 2 to unfold, we can roughly calculate the detrimental effects on service provision for HIV-infected people. For the 10 countries in our analysis, about US$3 billion [6], enabled 13.6 million people to receive life-saving ART pre-COVID-19 [5]. If relative funding distributions between treatment and prevention are maintained, the most extreme funding shortfalls of $850 million for 2021 (11% compared with 2019) in scenario 2 could, therefore, mean that approximately 1.5 million people enrolled in HIV care could not be served any longer.

Interruption of ART could have direct implications for the health of HIV-infected people: potentially resulting in increased incidence of AIDS-defining illnesses, treatment resistance, and AIDS-related mortality. Moreover, extended lockdowns could lead to decreased ART adherence because of poor access and drug stock-outs, and many outreach programmes for key populations have been reduced or halted. Several mathematical modelers forecast that, of all interventions currently in place for HIV prevention and control, interruption of ART delivery because of COVID-19 will have the biggest impact on relative changes in mortality, and, together with interrupted condom availability, the biggest impact on relative changes in incidence [8]. Whereas shifting funding within limited HIV budgets away from prevention programmes to ensure treatment continuation during the crisis might seem to be an attractive short-term solution, this could have a detrimental impact on the HIV epidemic in the long-run.

COMPLEXITY OF HIV FINANCING

The complex nature of HIV financing makes creating accurate predictions challenging, and our estimates should thus be interpreted as cautionary rather than predictive. In our analyses, we explored the effects of the COVID-19-related recession on HIV financing by making a simplified assumption of a linear relationship between country-specific GDP and HIV financing. Although this seems reasonable, validating our assumption against past observations (*e.g.*, trends in GDP versus trends in HIV financing) is complex, as detailed yearly country-level data is not always available.

Next to the direct GDP-dependent effects of COVID-19 countermeasures, several political decisions and indirect economic disruptions might further adversely affect HIV financing. First, aid distribution for HIV might increasingly be prioritised for low-income countries alone. Although this might mean that the poorest countries in the world are slightly more protected, lower middle-income and upper middle-income countries would need an accelerated process towards country-ownership. Second, several non-governmental financing schemes will be disproportionally affected by the pandemic. For instance, the air tax levy used to finance Unitaid, accounting for approximately 6% of the Global Fund to Fight AIDS, Tuberculosis and Malaria budget [9], will be severely affected by air travel restrictions. Third, financial gaps and shifts in sources indirectly supporting the HIV response, such as international research funding or the announcement by the USA to halt funding to the WHO [10], might adversely affect the HIV response and its financing for years to come. Fourth, domestic funding for HIV may be affected by the severity of the COVID-19 pandemic in the African nations and the political response. The proportion of the population infected with COVID-19, the strength and resilience of the local health system to respond to the COVID-19 pandemic, and the political structure and leadership in a country are all factors that are likely to influence the level of funding appropriated to fight HIV.

THE NEED FOR FINANCING INNOVATIONS

Regardless of how the financial and political complexities unfold and affect prevention and treatment programmes in the individual countries, it is critical to implement mitigation strategies to compensate for the financial gaps. First, continuation of HIV service delivery could be ensured and efficiency improved through accelerated implementation of differentiated care – by enabling less frequent ART pick-ups [11], shifting tasks to community health workers [12], integrating HIV/COVID-19 prevention [13], and focusing on prevention for key populations. Second, resources could be pooled at regional level (facilitated for instance through the Southern African Development Community) to better leverage emergency

funding, sharing of human capital and knowledge, and expertise in health programme management. Third, integration with other health services could improve efficiency, and simultaneously accelerate progress towards universal health coverage [14,15]. Integration will also force a conversation about reprioritisation across all health areas, essential to overcome the broader health system challenges introduced through the COVID-19 pandemic. Most importantly, mitigation strategies should strengthen the HIV response by using existing resources more efficiently, rather than shifting funding from other resources to fill gaps, so that health service provision for other population needs is not endangered.

CONCLUSIONS

The COVID-19 pandemic is putting acute pressure on HIV programmes in high-burden countries. With potential declines in funding of as much as 5% or 11%, the scale-up of HIV prevention and treatment in sub-Saharan Africa could come to halt or even reverse. But, as with any major crisis, the pressure to innovate under challenging circumstances could ultimately result in an HIV response and general health system that is more integrated, efficient and sustainable, improving resilience to future crises, and bolstering efforts to end the HIV pandemic by 2030.

Conflicts of interest

The authors declare that there are no conflicts of interest.

REFERENCES

1. Bor J, Herbst AJ, Newell M-L, Bärnighausen T. Increases in adult life expectancy in rural South Africa: valuing the scale-up of HIV treatment. Science 2013; 339:961–965.
2. Global Burden of Disease Health Financing Collaborator Network. Spending on health and HIV/AIDS: domestic health spending and development assistance in 188 countries, 1995-2015. Lancet 2018; 391:1799–1829.
3. Glied S, Wagner RF, Service P, Levy H, Robert F. The potential effects of coronavirus on national health expenditures. JAMA 2020; 10012:19–20.
4. IMF. World Economic Outlook. 2020.
5. UNAIDS. UNAIDS data 2019. 2019.
6. Haakenstad A, Moses MW, Tao T, Tsakalos G, Zlavog B, Kates J, *et al.* Potential for additional government spending on HIV/AIDS in 137 low-income and middle-income countries: an economic modelling study. Lancet HIV 2019; 6:e382–e395.
7. Kaiser Family Foundation. U.K. Considering temporary reduction in foreign aid spending, from 0.7% to 0.5% of GNI. 2020. Available at: https://www.kff.org/news-summary/u-k-considering-temporary-reduction-in-foreign-aid-spending-from-0-7-to0-5-of-gni/. [Accessed 16 January 2021]
8. Jewell BL, Mudimu E, Stover J, ten Brink D, Phillips AN, Smith JA, *et al.*, HIV Modelling Consortium. Potential effects of disruption to HIV programmes in sub-Saharan Africa caused by COVID-19: results from multiple mathematical models. Lancet HIV 2020; 7:e629–e640.
9. Kaiser Family Foundation, UNAIDS. Donor government funding for HIV in low- and middle-income countries in 2018. 2019.
10. Lovelace B, Higgins-Dunn N. Trump halts US funding for World Health Organization as it conducts coronavirus review. 14 April. 2020. Available at: https://www.cnbc.com/2020/04/14/ trump-calls-for-halt-to-us-funding-for-world-health-organization-amid-coronavirus-outbreak.html. [Accessed 15 June 2020]
11. Bulstra CA, Hontelez JAC, Ogbuoji O, Bärnighausen T. Which delivery model innovations can support sustainable HIV treatment? African J AIDS Res 2019; 18:315–323.
12. Geldsetzer P, Francis JM, Sando D, Asmus G, Lema IA, Mboggo E, *et al.* Community delivery of antiretroviral drugs: a noninferiority cluster-randomized pragmatic trial in Dar es Salaam, Tanzania. PLOS Med 2018; 15:e1002659.
13. U.S. Embassy in Zimbabwe. United States uses $150,000 in PEPFAR funding to help with COVID-19 prevention. 2020. Available at: https://zw.usembassy.gov/united-states-uses150000-in-pepfar-funding-to-help-with-covid-19-prevention/. [Accessed 4 May 2020]
14. Atun R, Silva S, Knaul FM. Innovative financing instruments for global health 2002-15: a systematic analysis. Lancet Glob Heal 2017; 5:e720–e726.
15. Bekker LG, Alleyne G, Baral S, Cepeda J, Daskalakis D, Dowdy D, *et al.* Advancing global health and strengthening the HIV response in the era of the Sustainable Development Goals: the International AIDS Society—Lancet Commission. Lancet 2018; 392:312–358.

Chapter 8

Integrating HIV services and other health services: A systematic review and meta-analysis

Caroline A. Bulstra, Jan A.C. Hontelez, Moritz Otto, Anna Stepanova[1], Erik Lamontagne, Anna Yakusik, Wafaa M. El-Sadr, Tsitsi Apollo, Miriam Rabkin, UNAIDS Expert Group on Integration[#], Rifat Atun, Till Bärnighausen

[#] *UNAIDS Expert Group on Integration participants are listed in the acknowledgements section of this manuscript.*

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ABSTRACT

Background: Integration of HIV services with other health services has been proposed as an important strategy to boost the sustainability of the global HIV response. We conducted a systematic and comprehensive synthesis of the existing scientific evidence on the impact of service integration on the HIV care cascade, health outcomes, and cost-effectiveness.

Methods and findings: We reviewed the global quantitative empirical evidence on integration published between 1 January 2010 and 10 September 2021. We included experimental and observational studies that featured both an integration intervention and a comparator in our review. Of the 7,118 unique peer-reviewed English-language studies that our search algorithm identified, 114 met all of our selection criteria for data extraction. Most of the studies (90) were conducted in sub-Saharan Africa, primarily in East Africa (55) and Southern Africa (24). The most common forms of integration were (i) HIV testing and counselling added to non-HIV services and (ii) non-HIV services added to antiretroviral therapy (ART). The most commonly integrated non-HIV services were maternal and child healthcare, tuberculosis testing and treatment, primary healthcare, family planning, and sexual and reproductive health services. HIV care cascade outcomes tended to be better in integrated services: uptake of HIV testing and counselling (pooled risk ratio (RR) across 37 studies: 1.67 [1.41–1.99], $p<0.001$), ART initiation coverage (pooled RR across 19 studies: 1.42 [1.16–1.75], $p=0.002$), time until ART initiation (pooled RR across 5 studies: 0.45 [0.20–1.00], $p=0.050$), retention in HIV care (pooled RR across 19 studies: 1.68 [1.05–2.69], $p=0.031$), and viral suppression (pooled RR across 9 studies: 1.19 [1.03–1.37], $p=0.025$). Also, treatment success for non-HIV-related diseases and conditions and the uptake of non-HIV services were commonly higher in integrated services. We did not find any significant differences for the following outcomes in our meta-analyses: HIV testing yield, ART adherence, and HIV-free survival among infants, and HIV and non-HIV mortality. We could not conduct meta-analyses for several outcomes (HIV infections averted, costs, and cost-effectiveness), because our systematic review did not identify sufficient poolable studies. Study limitations included possible publication bias of studies with significant or favourable findings and comparatively weak evidence from some world regions and on integration of services for key populations in the HIV response.

Conclusion: Integration of HIV services and other health services tends to improve health and health systems outcomes. Despite some scientific limitations, the global evidence shows that service integration can be a valuable strategy to boost the sustainability of the HIV response and contribute to the goal of "ending AIDS by 2030", while simultaneously supporting progress towards universal health coverage.

AUTHOR SUMMARY

Why was this study done?

- The rapid scale-up of HIV testing and antiretroviral therapy (ART) in many countries and communities over the past two decades has been largely achieved with stand-alone HIV programmes.
- Increasing life expectancy and the side effects of ART are leading to more co-morbidities among people living with HIV, suggesting that ART programmes that also offer other treatments could improve both healthcare effectiveness and patient experience.
- Other reasons for integration include the hope that joint delivery of services will increase coverage and reduce costs.
- The global evidence on integration of HIV services and other health services, to our knowledge, has never been synthesised and it is thus unclear what the empirical effects of integration are.

What did the researchers do and find?

- We conducted a systematic review and meta-analysis to synthesise the results of integrating HIV services and other health services on HIV care cascade outcomes (testing, linkage to care, treatment initiation, treatment adherence, retention, and viral suppression), HIV health outcomes (new infections and mortality), non-HIV health outcomes, and costs and cost-effectiveness.
- In most of the 114 studies that our systematic review identified most outcomes were better in integrated compared to separate services.

What do these findings mean?

- Integration of HIV services and other health services tends to improve health and health systems outcomes.
- The success of integration strategies is highly context-specific and more evidence is needed on integration in specific geographical areas and for the key populations in the HIV response.
- Despite such limitations, our systematic review and meta-analyses support the case for integration as a valuable and viable strategy to boost the sustainability of the HIV response and contribute to the goal of "ending AIDS by 2030", while simultaneously supporting progress towards universal health coverage.

INTRODUCTION

Ambitious goals guide the global HIV response. The 2016 political declaration of the United Nations General Assembly on HIV and AIDS [1] reinforced the commitment of the international community to reach the "getting to zero" targets: zero new HIV infections, zero AIDS-related deaths and zero discrimination by 2030 [2,3]. The so-called fast-track commitments for HIV prevention aim to achieve access to combination prevention for 90% of all key populations in the HIV response (*e.g.*, young women and adolescent girls, men who have sex with men, transgender people, sex workers and their clients, people who inject drugs, and prisoners) by the end of 2020 [2]. The UNAIDS "95-95-95 targets" focus on near-universal and effective coverage with HIV testing and antiretroviral treatment (ART) for people living with HIV (PLHIV) [4]. Despite progress, these ambitious goals remain elusive in many countries [5,6]. Political and financial support for the global HIV response stagnated or even declined in recent years [7,8]. At the same time, the number of PLHIV needing treatment is expected to further rise in the future [9,10]. The economic shock and health financing crisis triggered by the coronavirus disease 2019 (COVID-19) pandemic has further reduced political attention to HIV and will likely further widen the gap between the funding required and available to achieve the global HIV goals [11].

The rapid global scale-up of HIV testing, prevention and treatment services over the past two decades has been largely achieved with stand-alone programmes operating separately from other health system functions [12]. At the same time, increasing life expectancy [13,14] and the side effects of ART have led to more co-morbidities among PLHIV [15], suggesting that more integrated ART programmes could improve the HIV patient's experience and healthcare effectiveness. From the perspective of programmes that currently do not include HIV services, such as testing or treatment, integrating HIV services may lead to powerful benefits for patient, such as HIV status knowledge and needed ART.

In the broadest sense, integration is the joining of two or more health services that were previously separated in some way (for instance, delivered by different health workers or at different locations). The specific integration that was the topic of our systematic review and meta-analyses is the joining of health services for HIV and at least one other disease or condition [16,17].

Integration could improve or worsen aspects of health services. From the perspective of patients and clients, benefits of integration could reduce the time and inconvenience of utilising healthcare for several diseases or conditions, and thus improve the patient experience [17,18]. From the perspective of the providers and funders of care, integration could improve processes and resource allocation [19,20]. For example, integrating the delivery of different

services that one and the same patient needs could increase access [19] and continuity of care [21,22], and improve the clinical coordination of treatments for different diseases and thus health outcomes [23–25]. Integration could also reduce the costs of services because of synergies in joint delivery [19,20]. However, it is also plausible that integration increases costs, because joint delivery of services for multiple diseases reduces specialisation and the efficiency gains that it brings. Another plausible risk of integration includes overburdening healthcare providers [12,26], especially in areas with high HIV prevalence.

We performed a systematic review and meta-analysis of existing empirical quantitative evidence on the integration of HIV services and other health services. We included all empirical quantitative studies that compared outcomes in an intervention and a comparator group, independent of how the intervention and comparator groups were assigned, defined and measured. The reason for the broad scope of study designs that we included in our systematic review is that in our fields of study – health systems, health services and implementation research – experiments are overall rare, while observational study designs are common. We hope that our evidence synthesis will inform policy and implementation strategies aimed at improving the reach, quality, impact and sustainability of HIV and other health services.

METHODS

Search strategy and selection criteria

We followed the PRISMA [27] guidelines for systematic reviews and meta-analyses. We searched Embase, Medline Ovid (database behind PubMed), Web of Science, EconLit (ProQuest), Cochrane CENTRAL Library, and Google Scholar to identify articles published between 1 January 2010 and 28 January 2020, and manually searched the reference lists of identified studies. The search was updated on 10 September 2021 to include studies up to this date. Search strings were constructed in collaboration with a medical librarian (see **Supplementary File 1** for the full search strategy). We used Medical Subject Headings (MeSH) terms and "all fields" terms comprising the themes healthcare integration, HIV/AIDS, utility, health, economic and healthcare quality outcome indicators, and target populations. We included all populations in our systematic review, such as the general population and PLHIV. In addition, we specifically included terms for several key populations in the HIV response in our systematic search algorithm (men who have sex with men, transgender people, sexual and gender minorities, and sex workers) to ensure that we did not miss studies of integration targeting these populations (**Supplementary File 1**) [5]. Database searches were restricted to studies in English.

We included full-text peer-reviewed experimental and observational studies that provided quantitative empirical evidence on integration with both an intervention and a comparator group. We included studies on HIV care cascade outcomes (testing, linkage to care, treatment initiation, treatment adherence, retention, and viral suppression), HIV health outcomes (new infections and mortality), non-HIV health outcomes, and costs and cost-effectiveness. These outcomes align with the five factors of the RE-AIM framework to evaluate public health impact of health systems interventions [28,29]: (i) *reach* – HIV testing and counselling, (ii) *effectiveness* – viral suppression and health outcomes, (iii) *adoption* – cost-effectiveness, (iv) *implementation* – linkage to care, treatment initiation, treatment retention and adherence, and (v) *maintenance* – costs.

Reasons for excluding studies were (i) no integration intervention including an HIV service, (ii) integration of health systems functions other than health services, (iii) no outcome of interest, (iv) no empirical evidence (*e.g.*, editorials, perspectives, reviews, modelling studies), (v) no comparator group, (vi) non-published/non-peer reviewed literature, (vii) study protocols, or (viii) studies whose full text was not available. All included studies reported on integration at the point of care, but integration could also have included "above-patient" and "above-site" levels including healthcare providers, infrastructure, resources, monitoring, evaluation, and supply chain and management [16,30]. Studies concerning all facility types were included; from hospitals to community-level services.

Three independent reviewers (CAB, MO, and AS) screened the titles and abstracts of the primary studies that our search algorithm identified, and for those records that were eligible based on our inclusion and exclusion criteria, we examined full texts to determine eligibility for data extraction. We resolved any disagreements between the independent reviewers by consensus in a discussion with another member of our author team. We did not provide the protocol online; the review was not pre-registered.

Data analysis

Two authors (MO and AS) independently extracted the following study data: (i) general information (title, authors, year of publication, journal), (ii) study characteristics (study objectives and aims, study design, study population, study size, study time and duration), (iii) geographical location and population, (v) intervention (description, rationale for integration, degree of integration, healthcare level of integration), (v) comparator, (vi) outcomes, (vii) results, and (viii) contextual factors. We performed a quality assessment of the primary studies that our systematic search identified using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool [31]. For studies that did not find that integration improves outcomes, we searched the journal articles for reasons for this finding.

We expressed results (i) as risk ratios (RRs) for both HIV and non-HIV care cascade and health outcomes, (ii) as number of infections averted new HIV infections, and (iii) in 2018 US$ for costs and the cost components of incremental cost-effectiveness ratios (ICERs). We did meta-analyses for those outcomes for which pooling of results was meaningful (*i.e.*, for the results in (i)), because the integration interventions studied were the same or functionally similar. We pooled results using inverse-variance weighting. We estimated the proportion of variation across studies that was due to heterogeneity of results rather than chance (I^2 statistic) [32]. We also did meta-analyses for the subset of experimental studies only. All data analyses were done using R version 3.6.3 [33]. Ethical approval was not required for this study because we only used secondary data extracted from published studies.

RESULTS

Our search identified a total of 7,118 unique publications, of which 114 met the inclusion criteria (**Supplementary Figure 1**) [34–147]. Of the 114 included studies, 39 were experimental and 75 were observational. **Figure 1** shows the geographical location and year of publication of the included studies by type of health service. Most of the studies were conducted in East Africa (55 studies) and Southern Africa (24 studies): primarily in Kenya (20 studies), South Africa (18 studies), Zambia (8 studies), Malawi (8 studies), and Uganda (8 studies). The most common services integrated with HIV services were maternal and child health (MCH) (28 studies), tuberculosis (TB) (16 studies), family planning (16 studies), primary healthcare (14 studies), and sexual and reproductive health (SRH) or sexually transmitted infections (STI) services (13 studies). The most common intervention was integration of HIV testing and counselling into non-HIV services (46 studies), followed by integration of additional services into ART (28 studies) and integration of ART into non-HIV programmes (21 studies). Fifty studies focussed on the general population, 40 studies on women or children and 22 studies on at least one of the key populations in the HIV response. Studies duration differed widely (**Supplementary Figure 2**). While the median study duration was 2 years, 28 studies were three years or longer, 8 studies were five years or longer, and the maximum duration among all studies was 8 years. **Supplementary Table 1** shows distributions of study characteristics across all studies; **Supplementary Table 2** shows the study characteristics for each individual study; and **Supplementary Table 3** shows the GRADE assessment. **Table 1** shows a summary of key findings.

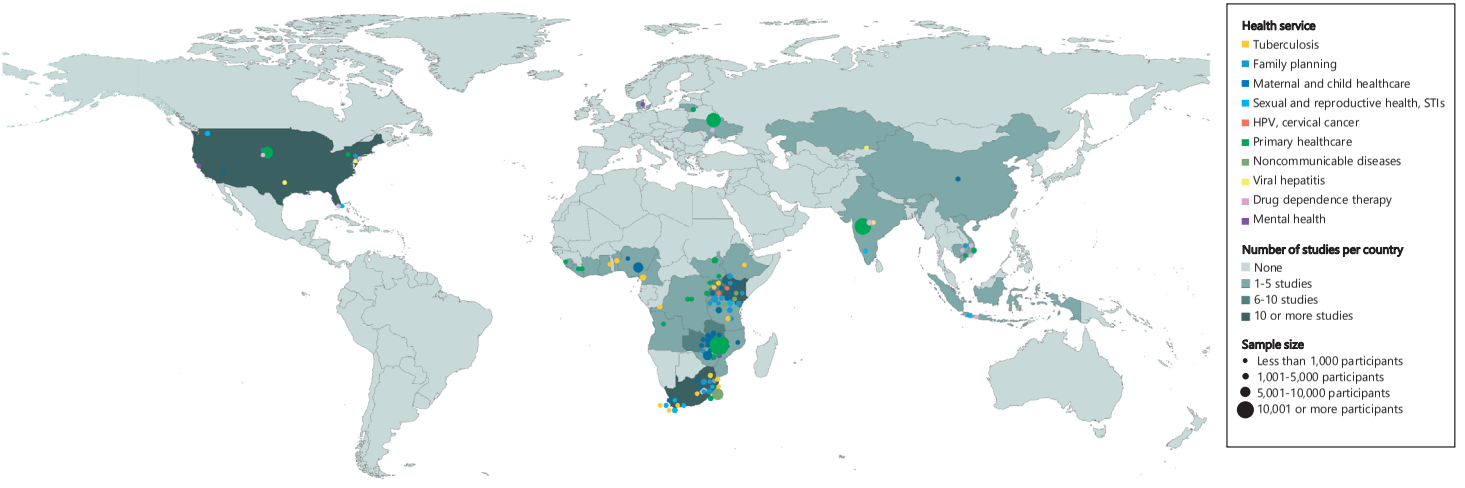

Figure 1. Geographical map of the included empirical studies by type of integration. Bubble colours represent the health service integration area. Bubble sizes represent the study population size. Coordinates are dispersed up to 250 kilometres to prevent overlap of data points from similar or nearby locations. Abbreviations: HPV, human papillomavirus; STI, sexually transmitted infection. Map created using ArcGIS software by ESRI. Base map source: https://www. naturalearthdata.com/downloads/10m-cultural-vectors/10m-admin-0-countries/.

HIV cascade-of-care

HIV testing and counselling uptake was significantly higher across different health services based on all 37 studies (pooled RR 1.67 [95% CI 1.41–1.99], p<0.001, **Figure 2A**), including in all 11 experimental studies (pooled RR 1.42 [95% CI 1.28–1.58], p<0.001). One study – evaluating integration of HIV, hypertension, and diabetes screening in rural South Africa – reported lower uptake of HIV testing, which the authors attributed to a lack of human resources and inadequate staff training [56]. Integration yielded a higher percentage of HIV-positive people in 4 out of 10 studies and a lower percentage in the remaining studies (**Figure 2B**).

ART initiation was significantly higher based on all 19 studies (pooled RR 1.42 [95% CI 1.16–1.75], p=0.002, **Figure 3A**), but non-significantly higher based on the 6 experimental studies only (pooled RR 1.50 [95% CI 0.97–2.33], p=0.064). Two studies that examined integration of HIV testing and counselling with MCH reported lower initiation rates of ART and prevention of mother-to-child-transmission, which the authors attributed to poor linkage to HIV services beyond testing and counselling [34,98]. People initiated ART significantly faster in integrated programmes, measured in 5 studies, all of which reported on integration with TB or MCH services (pooled RR 0.45 [95% CI 0.20–1.00], p=0.050, **Figure 3B**).

Retention in care was significantly higher in integrated programmes based on all 19 studies (pooled RR 1.68 [95% CI 1.05–2.69], p=0.031; **Figure 4A**), but non-significantly higher in integrated programmes based on the 7 experimental studies only (pooled RR 1.46 [95% CI 0.67–3.17], p=0.282). ART adherence was non-significantly higher based on all 7 studies (pooled RR 1.13 [95% CI 0.95–1.34], p=0.146; **Figure 4B**) and based on the 3 experimental studies only (pooled RR 1.06 [95% CI 0.91–1.23], p=0.245). One study reported lower retention and adherence in integrated antenatal care and HIV services, which the researchers attributed to non-retention when women who initiated ART in antenatal care eventually had to switch from ART in antenatal care to ART in stand-alone HIV services [82]. Viral suppression was significantly higher in integrated programmes based on all 9 studies (pooled RR 1.19 [95% CI 1.03–1.37], p=0.025; **Figure 4C**), and borderline significantly higher based on the 6 experimental studies only (pooled RR 1.23 [95% CI 1.00–1.51], p=0.054). One study reported no significant difference in viral suppression between integrated and separate services, which the researchers attributed to the scarcity of staff to provide HIV services and insufficient adherence support in the integrated programmes [37].

New HIV infections, HIV-related mortality, and stigma

HIV-free survival among infants was only modestly and non-significantly higher in integrated programmes based on all 5 studies (pooled RR 1.04 [95% CI 0.98–1.11], p=0.135; **Figure 5A**), but it was significantly higher based on the 2 experimental studies only (pooled RR 1.11

[95% CI 1.03–1.20], p=0.033). Reported explanations for the moderate improvements in HIV-free survival outcomes were a low overall prevalence of mother-to-child transmission of HIV [97,105], as well as national scale-up of ART for prevention of mother-to-child-transmission [126] and other events promoting HIV testing and treatment initiation during the intervention period [105]. The number of HIV infections averted in integrated compared to separate services was similar in 2 studies and higher in 2 other studies (**Figure 5B**). AIDS-related mortality, measured in 8 studies, was non-significantly lower in integrated programmes (pooled RR 0.72 [95% CI 0.47–1.11], p=0.118; **Figure 5C**). The increased mortality in integrated services in one study was attributed to weak implementation of integration and lack of coordination of integrated service delivery, affecting overall quality of care [78]. One study provided quantitative comparative outcomes related to the third UNAIDS "getting to zero" target of "zero discrimination" [3]. In this study, the integrated delivery of clinical HIV services and psychosocial interventions for adolescents in Zambia was significantly associated with reduced stigma (adjusted prevalence rate ratio 0.49 [95% CI 0.28–0.88]) and reduced negative community attitudes towards HIV (adjusted prevalence rate ratio 0.77 [95% CI 0.62–0.96]) [145].

Non-HIV-related outcomes

Uptake of other health services, measured in 32 studies, was significantly higher in integrated programmes (pooled RR 2.42 [95% CI 1.59–3.66], p<0.001; **Figure 6**). In two studies, uptake of non-HIV services was significantly lower in integrated services, which the authors attributed to high HIV client loads, insufficient staff training to provide broader service packages, and insufficient human resource capacity to provide additional services [45,108]. Treatment success for other diseases or conditions than HIV, measured in 21 studies, was significantly higher in integrated programmes (pooled RR 1.56 [95% CI 1.11–2.20], p=0.014; **Figure 7A**). Mortality from other causes than HIV (either TB or viral hepatitis), measured in 6 studies, was non-significantly lower in integrated programmes (pooled RR 0.43 [95% CI 0.16–1.17], p=0.083; **Figure 7B**).

Costs and cost-effectiveness

We found that costs of basic HIV and non-HIV services, measured in 10 studies, tended to be lower in integrated programmes (**Figure 8**). The ICERs of integrated services were universally positive, showing a wide range from approximately 2018 US$ 10 to over US$ 3000 per DALY averted or QALY gained (**Figure 8E**).

Table 1. Summary of key findings. Colours indicate the outcome groups: UNAIDS 95-95-95 targets (purple); UNAIDS "getting to zero" targets (blue); non-HIV-related outcomes (green); and costs and cost-effectiveness (orange).

Outcome	Relationship to global policy goals	Total number of studies (number of experimental studies)	Total study population size	Number of studies with:			I^2 (meta-analysis)	Pooled RR [95% CI] or mean outcome [range] based on all studies	Pooled RR [95% CI] based on experimental studies only
				Unfavourable outcomes	No difference	Favourable outcomes			
Uptake of HIV services	1st 95 of the 95-95-95 targets	37 (11)	637,148	1 (0)	1 (0)	34 (11)	99.0%	1.67 [1.41–1.99], p<0.001	1.42 [1.28–1.58], p<0.001
HIV testing yield	1st 95 of the 95-95-95 targets	10 (1)	461,486	3 (0)	2 (1)	5 (0)	97.7%	0.68 [0.38–1.24], p=0.185	0.91 [0.61–1.36], p=0.652
ART initiation	2nd 95 of the 95-95-95 targets	19 (6)	271,689	2 (1)	1 (0)	16 (5)	99.8%	1.42 [1.16–1.75], p=0.002	1.50 [0.97–2.33], p=0.064
Time until ART initiation	2nd 95 of the 95-95-95 targets	5 (1)	3,052	0 (0)	0 (0)	5 (1)	93.1%	0.45 [0.20–1.00], p=0.050	0.13 [0.05–0.29], p<0.001
Retention in care	3rd 95 of the 95-95-95 targets	19 (7)	66,151	3 (1)	4 (2)	11 (4)	93.4%	1.68 [1.05–2.69], p=0.031	1.46 [0.67–3.17], p=0.282
ART adherence	3rd 95 of the 95-95-95 targets	7 (3)	52,140	1 (0)	2 (2)	4 (1)	98.8%	1.13 [0.95–1.34], p=0.146	1.06 [0.91–1.23], p=0.245
Viral suppression	3rd 95 of the 95-95-95 targets	9 (6)	24,615	0 (0)	2 (1)	6 (5)	46.1%	1.19 [1.03–1.37], p=0.025	1.23 [1.00–1.51], p=0.054
HIV-free survival infants	"Zero new infections" of the "getting to zero" strategy	5 (2)	242,196	0 (0)	3 (1)	2 (1)	99.5%	1.04 [0.98–1.11], p=0.135	1.11 [1.03–1.20], p=0.033
HIV infections averted	"Zero new infections" of the "getting to zero" strategy	4 (3)	2,181	0 (0)	1 (1)	3 (3)	N/A[1]	1.16 infections averted per 100-person-years [range 0.0–3.6]	N/A
AIDS-related mortality	"Zero AIDS-related deaths" of the "getting to zero" strategy	8 (4)	39,630	2 (1)	3 (1)	3 (2)	97.8%	0.72 [0.47–1.11], p=0.118	0.99 [0.66–1.51], p=0.985

Table 1. Summary of key findings. Colours indicate the outcome groups: UNAIDS 95-95-95 targets (purple); UNAIDS "getting to zero" targets (blue); non-HIV-related outcomes (green); and costs and cost-effectiveness (orange). (*continued*)

Outcome	Relationship to global policy goals	Total number of studies (number of experimental studies)	Total study population size	Number of studies with:			I^2 (meta-analysis)	Pooled RR [95% CI] or mean outcome [range] based on all studies	Pooled RR [95% CI] based on experimental studies only
				Unfavourable outcomes	No difference	Favourable outcomes			
Uptake of other health services	Non-HIV-related outcomes	32 (11)	278,042	2 (0)	4 (2)	24 (8)	98.4%	2.42 [1.59–3.66], p<0.001	2.03 [1.31–3.15], p=0.005
Treatment success for other diseases/conditions	Non-HIV-related outcomes	21 (5)	40,452	0 (0)	8 (3)	11 (2)	81.1%	1.56 [1.11–2.20], p=0.014	1.64 [0.75–3.58], p=0.156
Non-AIDS-related mortality	Non-HIV-related outcomes	6 (2)	25,879	1 (1)	1 (1)	4 (0)	94.7%	0.43 [0.16–1.17], p=0.083	1.00 [0.01–1.62], p=0.997
HIV-only costs	Costs and cost-effectiveness	6 (1)	119,830	2 (0)	0 (0)	4 (1)	N/A[1]	1.06 [range 0.59–1.92][1]	N/A
Non-HIV-only costs	Costs and cost-effectiveness	2 (0)	202	0 (0)	0 (0)	2 (0)	N/A[1]	0.62 [range 0.50–0.73][1]	N/A
HIV and non-HIV costs	Costs and cost-effectiveness	2 (1)	8,027	0 (0)	0 (0)	2 (1)	N/A[1]	0.83 [range 0.69–0.97][1]	N/A
Costs of integrated services *vs.* HIV-only costs	Costs and cost-effectiveness	7 (1)	132,306	N/A[2]	N/A[2]	N/A[2]	N/A[1]	2.31 [range 1.20–6.12][1]	N/A
Cost-effectiveness	Costs and cost-effectiveness	6 (2)	142,881	0 (0)	1 (0)	5 (2)	N/A[1]	N/A	N/A

Colours indicate the outcome groups: UNAIDS 95-95-95 targets, purple; UNAIDS 'getting to zero' targets, blue; non-HIV-related outcomes, green; and costs and cost-effectiveness, orange.

[1] Meta-analysis not possible because of insufficient poolable data.

[2] Costs of both HIV and non-HIV services as compared to HIV services only; it was thus impossible to judge whether integration increased or reduced costs.

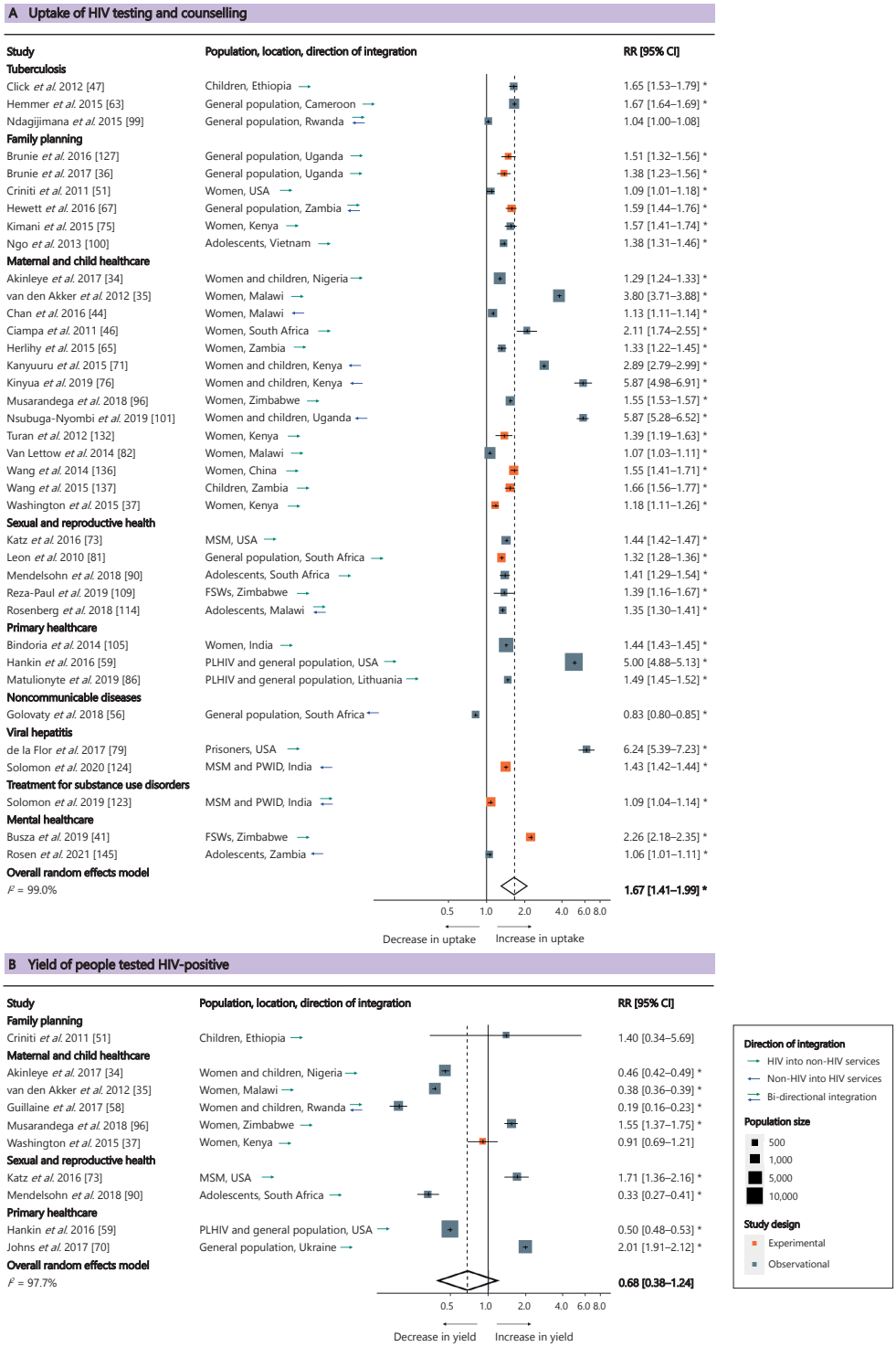

Figure 2. Results of integration of HIV services: (A) uptake of HIV testing and counselling and (B) yield of people tested HIV-positive. Outcomes are related to the "first 95" of the 95-95-95 targets for the HIV cascade-of-care. Each estimate indicates the size of the relationship between integration exposure and outcome. We measure these relationships as risk ratios; asterisks indicate statistically significant results. The diamond at the bottom of each panel shows the overall random-effects meta-analytical estimate. Abbreviations: CI = confidence interval; FSWs = female sex workers; MSM = men who have sex with men; PLHIV = people living with HIV; PWID = people who inject drugs; RR = risk ratio; USA = United States of America.

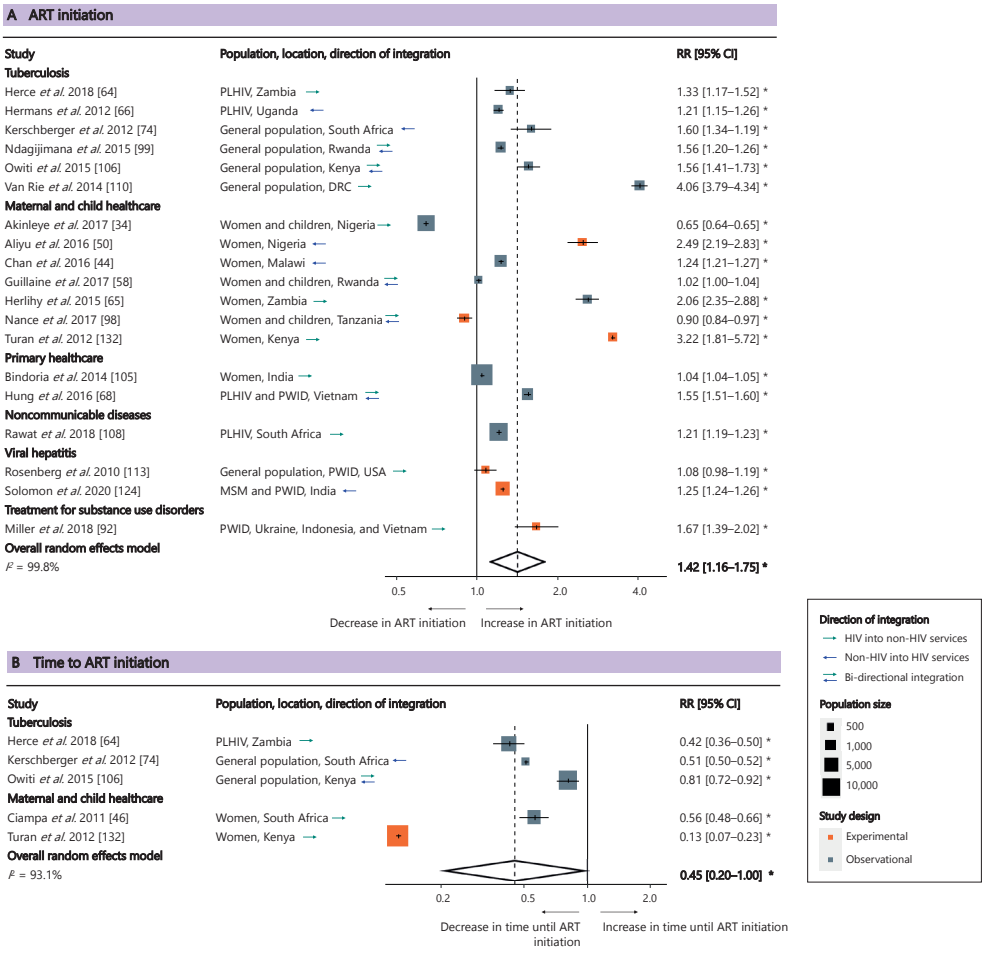

Figure 3. Results of integration of HIV services: (A) antiretroviral therapy (ART) initiation and (B) time until ART initiation. Outcomes are related to the "second 95" of the 95-95-95 HIV cascade-of-care. Each estimate indicates the size of the relationship between integration exposure and outcome. We measure these relationships as risk ratios; asterisks indicate statistically significant results. The diamond at the bottom of each panel shows the overall random-effects meta-analytical estimate. Abbreviations: ART = antiretroviral therapy; CI = confidence interval; DRC = Democratic Republic of the Congo; MSM = men who have sex with men; PLHIV = people living with HIV; PWID = people who inject drugs; RR = risk ratio; USA = United States of America.

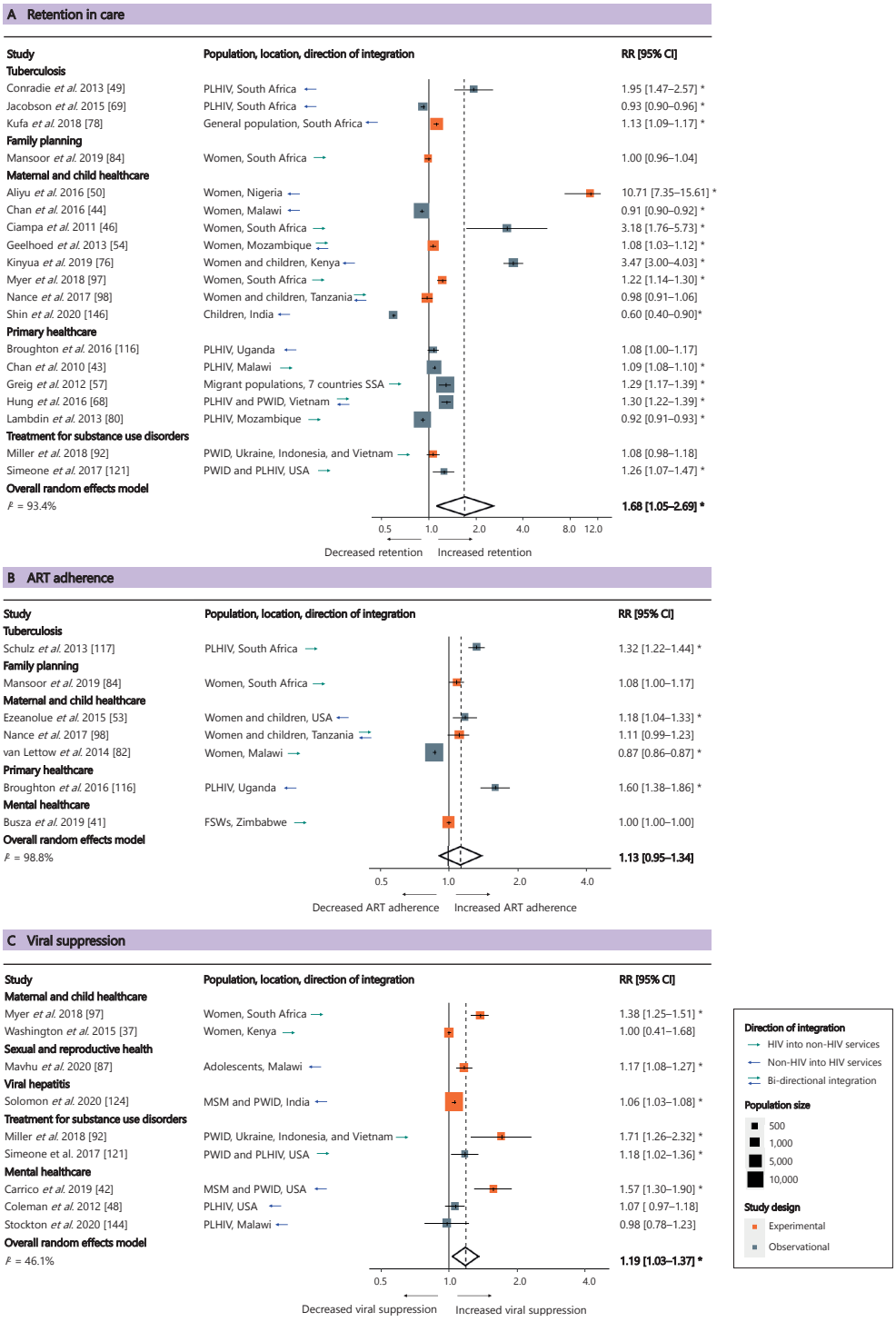

Figure 4. Results of integration of HIV services for people living with HIV (PLHIV): (A) retention in care, (B) antiretroviral therapy (ART) adherence, and (C) viral suppression of those on ART. Outcomes are related to the "third 95" of the 95-95-95 HIV cascade-of-care. Each estimate indicates the size of the relationship between integration exposure and outcome. We measure these relationships as risk ratios; asterisks indicate statistically significant results. The diamond at the bottom of each panel shows the overall random-effects meta-analytical estimate. Abbreviations: ART = antiretroviral therapy; CI = confidence interval; FSWs = female sex workers; MSM = men who have sex with men; PLHIV = people living with HIV; PWID = people who inject drugs; RR = risk ratio; SSA = sub-Saharan Africa; USA = United States of America.

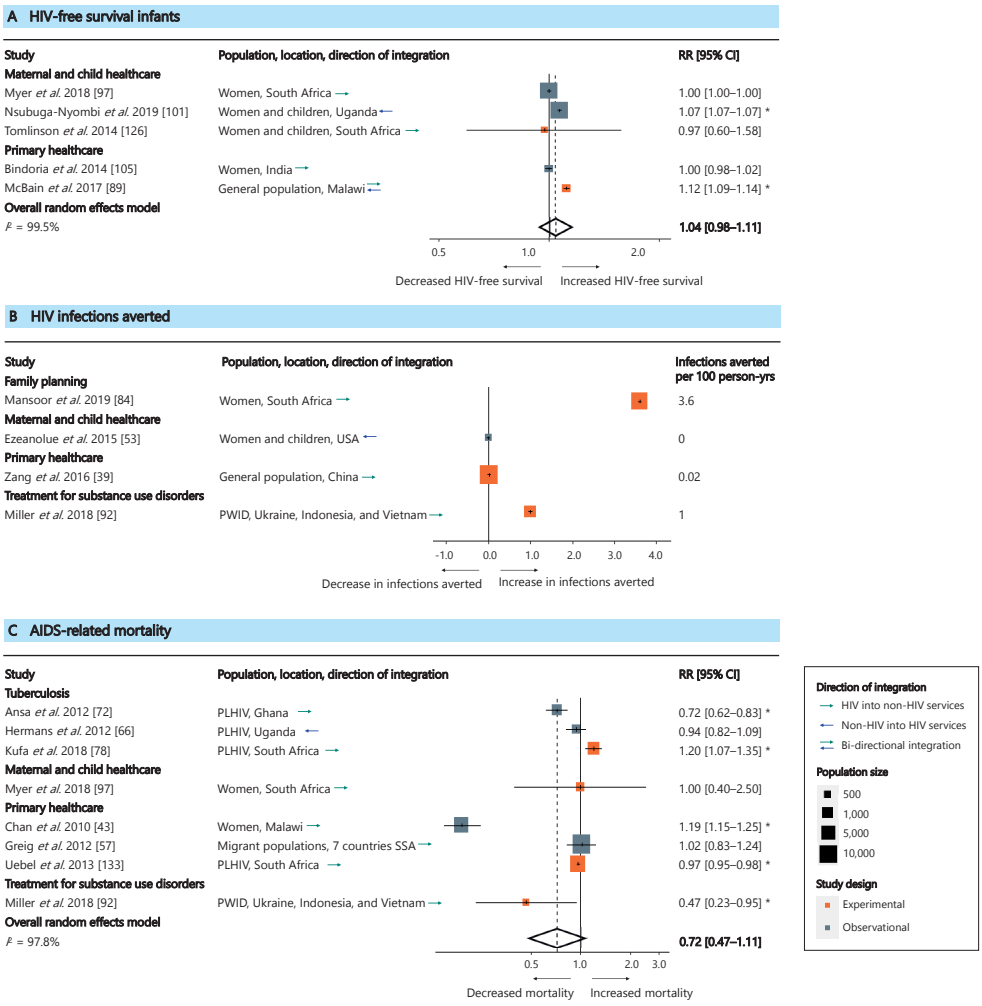

Figure 5. Results of HIV services integration: (A) HIV-free survival, (B) HIV infections averted, and (C) AIDS-related mortality. Outcomes are related to the "getting to zero" targets for HIV/AIDS. Each estimate in panel A and C indicates the effect size as derived from a single study, either directly, or by recalculating reported outcomes. Each estimate indicates the size of the relationship between integration exposure and outcome. We measure these relationships as risk ratios; asterisks indicate statistically significant results. The diamond at the bottom of each panel shows the overall random-effects meta-analytical estimate. Infections averted (panel B) are displayed by 100-person years. Abbreviations: CI = confidence interval; PLHIV = people living with HIV; PWID = people who inject drugs; RR = risk ratio; SSA = sub-Saharan Africa; USA = United States of America.

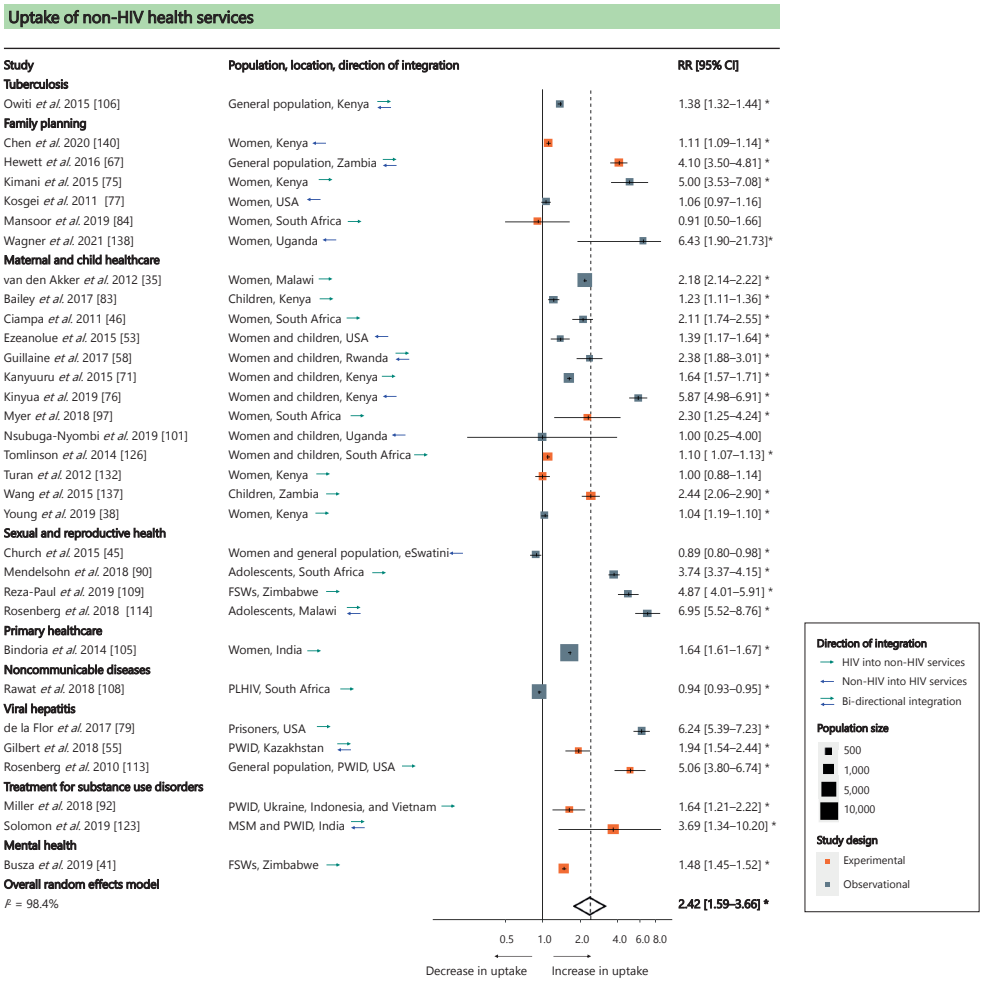

Figure 6. Results of HIV services integration: uptake of non-HIV health services. Each estimate indicates the effect size as derived from a single study, either directly, or through recalculating reported outcomes, and represents the relative risk ratio. Each estimate indicates the size of the relationship between integration exposure and outcome. We measure these relationships as risk ratios; asterisks indicate statistically significant results. The diamond at the bottom of each panel shows the overall random-effects meta-analytical estimate. Abbreviations: CI = confidence interval; DRC = Democratic Republic of the Congo; FSWs = female sex workers; PLHIV = people living with HIV; PWID = people who inject drugs; RR = risk ratio; SRH = sexual and reproductive healthcare; SSA = sub-Saharan Africa; USA = United States of America.

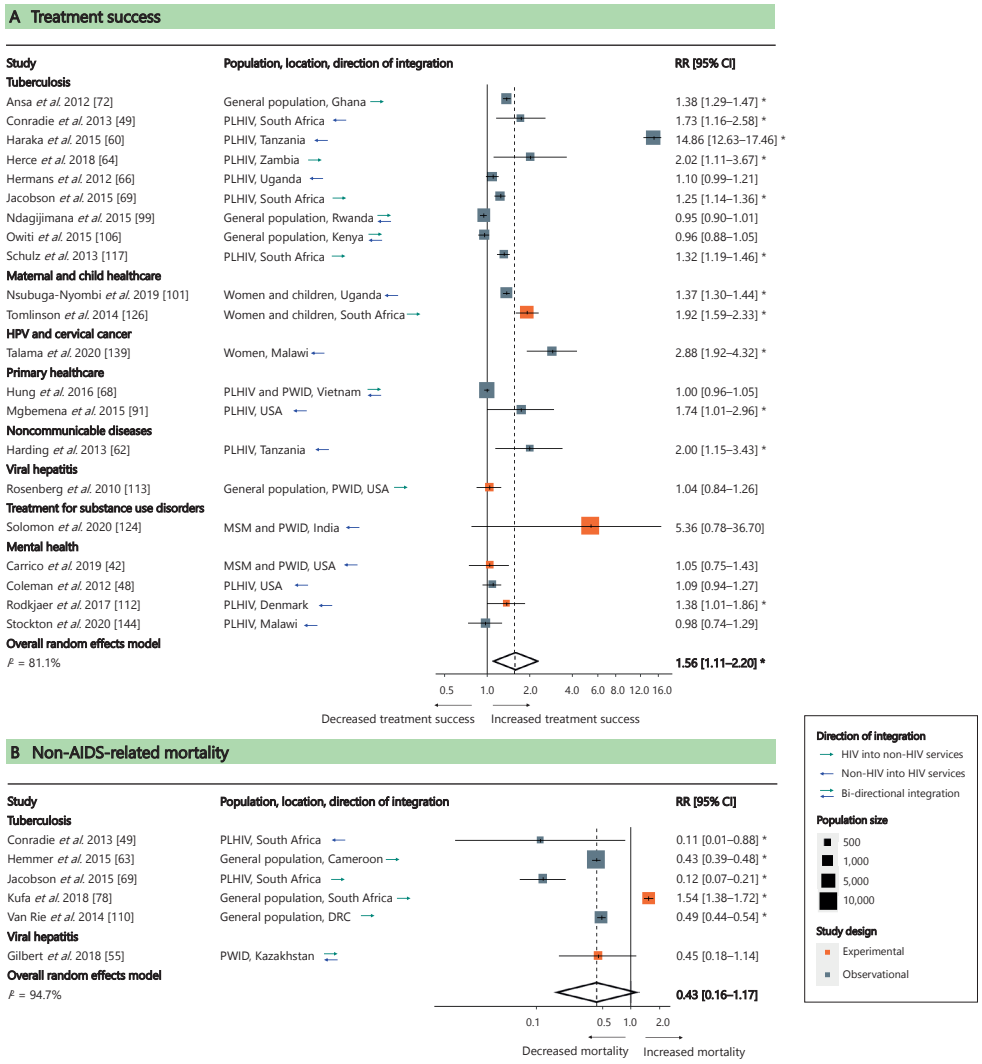

Figure 7. Results of HIV services integration: (A) treatment success for non-HIV related diseases and/or conditions and (B) non-AIDS-related mortality. Each estimate indicates the size of the relationship between integration exposure and outcome. We measure these relationships as risk ratios; asterisks indicate statistically significant results. The diamond at the bottom of each panel shows the overall random-effects meta-analytical estimate. Abbreviations: CI = confidence interval; DRC = Democratic Republic of the Congo; FSWs = female sex workers; PLHIV = people living with HIV; PWID = people who inject drugs; RR = risk ratio; SRH = sexual and reproductive healthcare; SSA = sub-Saharan Africa; USA = United States of America.

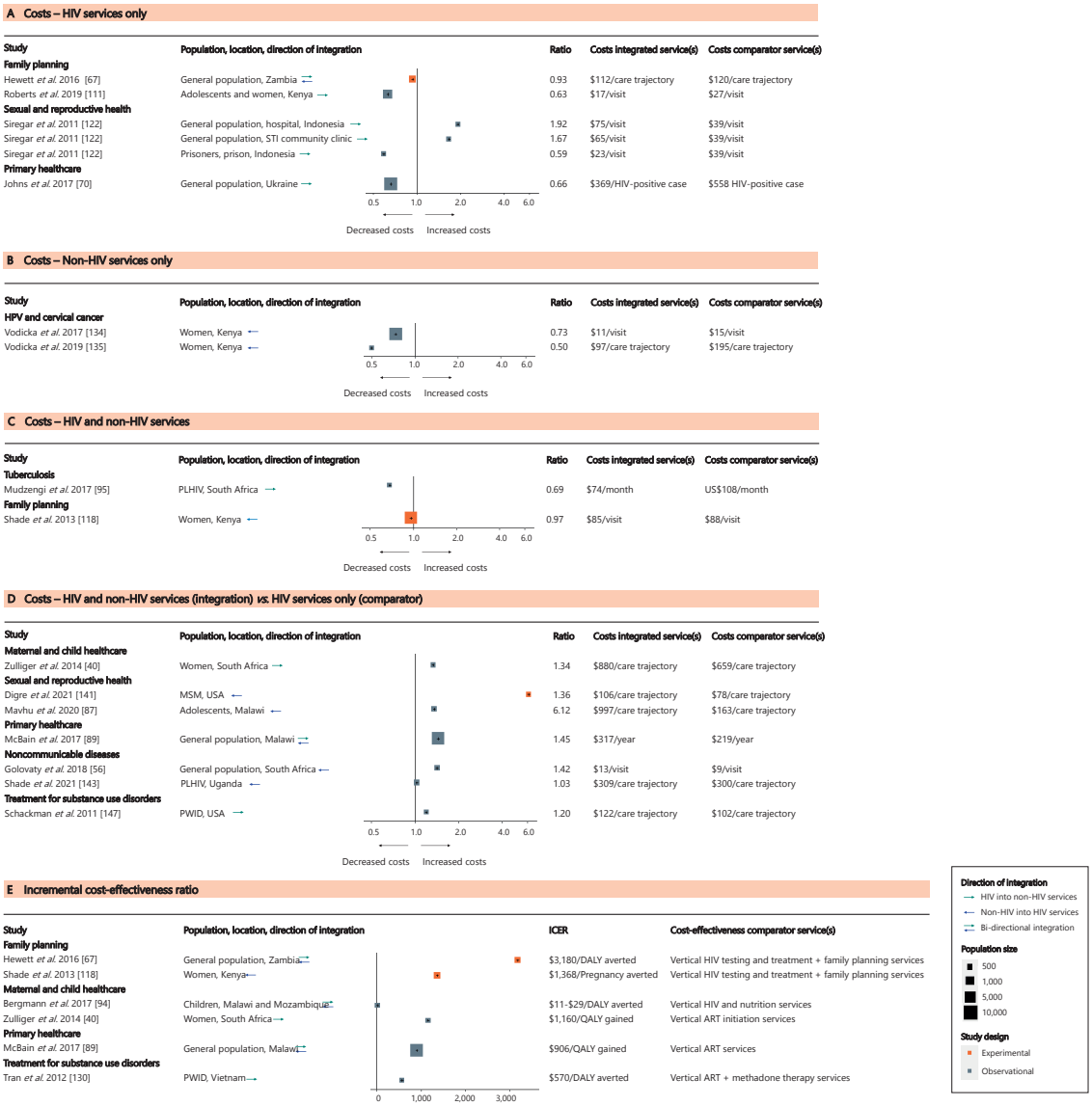

Figure 8. Results of integration of HIV services and economic outcomes: Costs of (A) HIV services only, (B) non-HIV services only, (C) HIV and non-HIV services combined, and (D) integrated non-HIV with HIV services as compared to HIV services only. (E) Cost-effectiveness as incremental cost-effectiveness ratios (ICERs). Each cost estimate indicates the effect size as derived from a single study, either directly, or through recalculating reported outcomes. The estimates represent the costs of services in integrated compared to separate services. The ICERs measure the cost-effectiveness of integration, compared to the cost-effectiveness of stand-alone HIV service delivery as reported in the studies. Abbreviations: ART = antiretroviral therapy; ICER = incremental cost-effectiveness ratio; PWID = people who inject drugs; USA = United States of America.

DISCUSSION

Our systematic review of integration of HIV services and other health services identified 114 relevant empirical peer-reviewed studies. Generally, outcomes were better in integrated compared to separate services: the meta-analytical averages for HIV testing and counselling, ART initiation, retention in HIV care, and viral suppression rates were all higher in integrated services. Similarly, uptake of non-HIV health services and non-HIV health outcomes were on average better in integrated services.

To our knowledge, this is the first systematic review and meta-analysis that quantifies the global evidence on integration of HIV services and other health services on a broad scope of health systems and health outcomes. Our systematic review was comprehensive in four important aspects. First, we included both directions of integration: HIV services integrated into services for other diseases or conditions and services for diseases other than HIV – such as depression or hypertension screening and treatment – integrated into HIV services [26,30]. Second, we designed our search algorithm such that it identified all primary studies on the integration of HIV services with any other types of services. Third, we included a broad scope of outcomes in our review: HIV care cascade outcomes (testing, linkage to care, treatment initiation, treatment adherence, retention, and viral suppression), HIV health outcomes (new infections and mortality), non-HIV health outcomes, and costs and cost-effectiveness. Fourth, we included all study types as long as the study included a comparator of some sort for effect or impact estimation, *i.e.*, we included experimental and observational quasi- and non-experimental studies in our review. Our results are broadly in line with earlier findings from systematic and scoping reviews on integration of services with narrower scopes of integration interventions or outcomes. Previous reviews on integration of HIV and TB [148,149], MCH [22,150], family planning [151–153], SRH [154], primary healthcare [155], non-communicable disease treatments [23,151], and mental health services [156] generally found that integration led to improved service uptake and better health outcomes, but that high-quality evidence was limited [148,151–153,157–159]. Our synthesis also broadly concurs with the previous literature that integration evidence is particularly scarce for key populations [154], cost-effectiveness outcomes [156], and long-term impacts of integration [19,20,151,156,160–162].

Our results should be useful for policy makers, practitioners and researchers concerned with health systems structures and processes supporting HIV services over the coming decades. Whether or not to integrate services and how to design integrated delivery models will likely depend on a wide range of factors, including the existing health system, resources, and the HIV and other disease burdens. Although integration was generally successful, several specific integration interventions failed to improve outcomes. We identified several reasons

why integration interventions were not successful. Integration failed to improve outcomes when it resulted in increased flows of more diverse patients in already overburdened health systems [45,108]. When integration remained limited to individual stages in care cascades (for instance, when integration focused only on adding HIV testing or ART initiation) health outcomes did not improve in some studies, because of losses in other stages of the care cascades (such as retention and adherence) [34,82,98]. Other major reasons for integration failures were (i) imperfect fidelity of integration implementation (*e.g.,* because of limited availability, training, or coordination of health workers) and (ii) low quality of care [45,56,78,82,108]. Overall, the studies identified in our review rarely reported on implementation fidelity, and if they did, fidelity was typically not quantified [45,78,82,98,108]. Future research should aim to capture both the fidelity of integration interventions, as well as meaningful and necessary local adaptations.

Quality of care is a is a critical element of studies of health services integration – it is plausible that integration either increases quality of care (because integration ensures that individual patients receive services that are well-coordinated across multiple healthcare needs) or decreases quality of care (because integration decreases the specialisation of service delivery structures and processes, leading to lower average quality of care of individual services). A key indicator of clinical quality of HIV care, viral suppression [163–165], consistently improved across different integration interventions covered in our systematic review, but with widely varying effect sizes. Data on other important aspects of quality of care were not available in the studies we identified in your systematic review. In particular, the studies covered did not provide estimates of the relationships between integration interventions and subjective perceptions of quality of care, the patient experience, and patient satisfaction. Such measures of peoples' and patients' subjective evaluations of health services are important – fundamentally, because they operationalise the health systems outcomes of "patient satisfaction" [166] and "responsiveness" [167], and instrumentally, because subjective evaluations influence health services uptake, retention and adherence [168]. Future studies of integration of HIV services and other health services should include subjective measures and more detailed objective measures of quality of care. One promising approach for this purpose are patient reported outcome and experience measures (PROMs and PREMs) [169] and in particular PROM and PREM elicitation via digital devices.

Another important objective on the global HIV agenda is "zero discrimination" [3], we explicitly searched for outcomes of integration interventions related to discriminations and stigma, but found only one article that provided quantitative evidence [145]. However, emerging evidence suggests that interventions explicitly aimed at achieving 'zero discrimination' may produce greater population health benefits in jurisdictions with inequities in access to care [170,171]. Such evidence will be important because integration could plausibly reduce

discrimination by "normalising" HIV services [172], but it may also cause discrimination, *e.g.*, by reducing privacy of vulnerable people [173,174]. Only 22 out of the 114 studies reported outcomes for key populations, demonstrating important knowledge gaps [159,175–181].

The current empirical evidence-base on the impact of integration on costs and cost-effectiveness of integration does not provide insights into whether integration could indeed result in the hypothesised mitigation of the impact of declining resources for HIV. Our review showed that empirical evidence on costs and cost-effectiveness of integration is limited and highly heterogeneous in terms of measured outcomes. For instance, some studies only reported HIV-related costs pre- and post-integration, while others reported only non-HIV costs. Furthermore, the complex trade-off between per-patient efficiency gains versus overall programmatic costs requires careful attention when implementing integration strategies, yet are rarely combined. The existing empirical cost-effectiveness analyses [40,67,94] and modelling studies [182–191], show that, even if per-patient costs of service delivery go down, the increase in patient volume due to integration increases overall programme costs and resource needs. Finally, none of the studies assessed the overall healthcare quality impact of integration alongside changes in costs, yet especially if resources are more stretched due to integration, per-patient costs may be lower, but so be quality of care. Advancing our understanding of the economic impacts of integration will require more experimental or quasi-experimental studies that combine top-down macro-costing and bottom-up micro-costing approaches, with quality and impact estimates of service delivery, *e.g.,* through measuring health outcomes and satisfaction surveys among patients and providers [192,193].

Our study had several limitations. First, as with any systematic review, the outcomes of our review are prone to publication bias, because studies reporting clearly positive findings may be more likely to be published than studies reporting null or negative findings. Second, the exclusion of case reports and "grey" literature (*e.g.,* project reports, conference abstracts) may have limited the range of evidence, especially for novel integration models. For example, our review excluded descriptions of HIV services integration into primary healthcare in Latin America [194], provision of hormone therapy alongside HIV services for transgender people [173], and HPV vaccination programmes integrated into HIV prevention and testing at secondary schools. Third, the experimental and observational primary studies that we synthesise in our meta-analysis may be biased. Findings from experimental studies provide the highest quality comparison, but may not be generalisable outside research settings. Evidence from quasi-experimental studies could remedy this situation by providing evidence with both high internal and high external validity [195,196]. Although some studies had relatively long study durations (4 years or more), none of them specifically reported on sustainment of the effects of integration. Despite these limitations, for many outcomes

our synthesis is encouraging, because the magnitudes of effects were large and consistent across the different study types.

In conclusion, our results support the integration of HIV services with other health services. The evidence indicates that integration of HIV testing and counselling services into non-HIV health programmes for people at risk of acquiring HIV and integration of non-HIV services into ART programmes for PLHIV, tends to lead to improved services uptake and health benefits for HIV and other diseases or conditions. However, the effects of integrating HIV services into broader health systems and the economic impacts of integration are less clear and require further study. In addition, integration success will depend on a wide range of determinants and path dependencies, such as local epidemics and health systems structures and processes. Despite the need for more studies on specific integration opportunities and key populations, it seems likely that integration of HIV and other health services can contribute to reaching the UNAIDS target of ending AIDS by 2030, while simultaneously meeting other UHC targets.

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Contributions

All authors were involved in aspects of study design and the analysis and interpretation of data used in the manuscript. CAB, AS, and MO performed the literature searches, study selections, and data extraction. CAB, JACH, and TB wrote the first draft of the manuscript. All authors contributed to subsequent drafts of the manuscript and reviewed the final version prior to submission.

REFERENCES

1. United Nations. Political Declaration on HIV and AIDS: On the Fast-Track to Accelerate the Fight against HIV and to End the AIDS Epidemic by 2030. New York; 2016. doi:10.1093/oxfordhb/9780199560103.003.0005

2. Joint United Nations Programme on HIV/AIDS (UNAIDS). Fast-Track - Ending the AIDS epidemic by 2030. Geneva; 2014. Available: https://www.unAIDS.org/sites/default/files/media_asset/JC2686_WAD-2014report_en.pdf

3. Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS 2011-2015 Strategy: Getting to Zero. Geneva; 2013. Available: https://www.unAIDS.org/sites/default/files/media_asset/JC2034_UNAIDS_Strategy_en_1.pdf

4. Joint United Nations Programme on HIV/AIDS (UNAIDS). 90-90-90: An ambitious treatment target to help end the AIDS epidemic. Geneva; 2014. Available: https://www.unAIDS.org/sites/default/files/media_asset/90-90-90_en.pdf

5. Joint United Nations Programme on HIV/AIDS (UNAIDS). Seizing the moment: Tackling entrenched inequalities to end epidemics - Global AIDS update 2020. Geneva; 2020. Available: https://www.unAIDS.org/sites/default/files/media_asset/2020_global-AIDS-report_en.pdf

6. Joint United Nations Programme on HIV/AIDS (UNAIDS). Joint United Nations Programme on HIV/AIDS. UNAIDS data 2020. Geneva; 2020. Available: https://www.unAIDS.org/sites/default/files/media_asset/2020_AIDS-data-book_en.pdf

7. Kaiser Family Foundation. U.K. Considering Temporary Reduction In Foreign Aid Spending, From 0.7% To 0.5% Of GNI. 2020 [cited 16 Jan 2021]. Available: https://www.kff.org/news-summary/u-k-considering-temporary-reduction-in-foreign-aid-spending-from-0-7-to-0-5-of-gni/

8. U.S. Department of State, Office of the U.S. Global AIDS Coordinator and Health Diplomacy. The United States President's Emergency Plan for AIDS Relief: 2019 Annual Report to Congress. Washington; 2019. Available: https://www.state.gov/wp-content/uploads/2019/09/PEPFAR-2019ARC.pdf

9. Atun R, Chang AY, Ogbuoji O, Silva S, Resch S, Hontelez JAC, *et al.* Long-term financing needs for HIV control in sub-Saharan Africa in 2015–2050: a modelling study. BMJ Open. 2016; 1–9. doi:10.1136/bmjopen-2015-009656

10. Hontelez JAC, Chang AY, Ogbuoji O, De Vlas SJ, Bärnighausen T, Atun R. Changing HIV treatment eligibility under health system constraints in sub-Saharan Africa: Investment needs, population health gains, and cost-effectiveness. AIDS. 2016;30: 2341–2350. doi:10.1097/QAD.0000000000001190

11. Bulstra CA, Reddy CL, Atun R, Bärnighausen T, Hontelez JAC. Impact of the COVID-19-related global recession on the financing of the global HIV response. AIDS. 2021. doi:10.1097/QAD.0000000000002872

12. Bekker LG, Alleyne G, Baral S, Cepeda J, Daskalakis D, Dowdy D, *et al.* Advancing global health and strengthening the HIV response in the era of the Sustainable Development Goals: the International AIDS Society—Lancet Commission. Lancet. 2018;392: 312–358. doi:10.1016/S0140-6736(18)31070-5

13. Bor J, Herbst AJ, Newell ML, Bärnighausen T. Increases in adult life expectancy in rural South Africa: valuing the scale-up of HIV treatment. Science (80-). 2013;339: 961–965. doi:10.1126/science.1230413

14. Hontelez JAC, Vlas SJ de, Baltussen R, Newell M-L, Bakker R, Tanser F, *et al.* The impact of antiretroviral treatment on the age composition of the HIV epidemic in sub-Saharan Africa. AIDS. 2012;23: 1–7. doi:10.1038/jid.2014.371

15. Narayan KMV, Miotti PG, Anand NP, Kline LM, Harmston C, Gulakowski III R, *et al.* HIV and noncommunicable disease comorbidities in the era of antiretroviral therapy: a vital agenda for research in low-and middle-income country settings. JAIDS J Acquir Immune Defic Syndr. 2014;67: S2--S7. doi:10.1097/QAI.0000000000000267

16. World Health Organization (WHO). Integrated Health Services - What and Why? Making health systems work series. Geneva; 2008. Available: https://www.who.int/healthsystems/technical_brief_final.pdf

17. Atun R, De Jongh T, Secci F, Ohiri K, Adeyi O. Integration of targeted health interventions into health systems: A conceptual framework for analysis. Health Policy Plan. 2010;25: 104–111. doi:10.1093/heapol/czp055

18. Atun R, de Jongh TE, Secci F V, Ohiri K, Adeyi O, Car J. Integration of priority population, health and nutrition interventions into health systems: systematic review. BMC Public Health. 2011;11: 780. doi:10.1186/1471-2458-11-780

19. Sweeney S, Obure CD, Maier CB, Greener R, Dehne K, Vassall A. Costs and efficiency of integrating HIV/AIDS services with other health services: A systematic review of evidence and experience. Sex Transm Infect. 2012;88: 85–99. doi:10.1136/sextrans-2011-050199

20. Siapka M, Remme M, Obure CD, Maier CB, Dehne KL, Vassall A. Is there scope for cost savings and efficiency gains in HIV services? A systematic review of the evidence from low- and middle-income countries. Bull World Health Organ. 2014;92: 499-511AD. doi:10.2471/BLT.13.127639

21. Hope R, Kendall T, Langer A, Bärnighausen T. Health systems integration of sexual and reproductive health and HIV services in Sub-Saharan Africa: A scoping study. J Acquir Immune Defic Syndr. 2014;67: S259–S270. doi:10.1097/qai.0000000000000381

22. Vrazo AC, Firth J, Amzel A, Sedillo R, Ryan J, Phelps BR. Interventions to significantly improve service uptake and retention of HIV-positive pregnant women and HIV-exposed infants along the prevention of mother-to-child transmission continuum of care: systematic review. Trop Med Int Heal. 2018;23: 136–148. doi:10.1111/tmi.13014

23. Duffy M, Ojikutu B, Andrian S, Sohng E, Minior T, Hirschhorn LR. Non-communicable diseases and HIV care and treatment: models of integrated service delivery. Trop Med Int Heal. 2017;22: 926–937. doi:10.1111/tmi.12901

24. Haldane V, Legido-Quigley H, Chuah FLH, Sigfrid L, Murphy G, Ong SE, *et al.* Integrating cardiovascular diseases, hypertension, and diabetes with HIV services: a systematic review. AIDS Care Psychol Socio-Med Asp AIDS HIV. 2018;30: 103–115. doi:10.1080/09540121.2017.1344350

25. Suthar AB, Rutherford GW, Horvath T, Doherty MC, Negussie EK. Improving antiretroviral therapy scale-up and effectiveness through service integration and decentralization. AIDS. 2014;28: S175–S185. doi:10.1097/qad.0000000000000259

26. Atun RA, Bennett S, Duran A, World Health Organization (WHO). When do vertical

(stand-alone) programmes have a place in health systems? Geneva; 2008. Available: https://www.who.int/management/district/services/WhenDoVerticalProgrammesPlaceHealthSystems.pdf

27. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLOS Med. 2009;6: e1000100. doi:10.1371/journal.pmed.1000100

28. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Am J Public Health. 1999;89: 1322–1327. doi:10.2105/ajph.89.9.1322

29. Glasgow RE, Klesges LM, Dzewaltowski DA, Estabrooks PA, Vogt TM. Evaluating the impact of health promotion programs: using the RE-AIM framework to form summary measures for decision making involving complex issues. Health Educ Res. 2006;21: 688–694. doi:10.1093/her/cyl081

30. Atun R, Jongh T De, Secci F, Ohiri K, Adeyi O. A systematic review of the evidence on integration of targeted health interventions into health systems. Health Policy Plan. 2010; 1–14. doi:10.1093/heapol/czp053

31. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, *et al.* GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64: 383–394. doi:10.1016/j.jclinepi.2010.04.026

32. Van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med. 2002;21: 589–624. doi:10.1002/sim.1040

33. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria; 2017. Available: https://www.r-project.org/

34. Akinleye O, Dura G, de Wagt A, Davies A, Chamla D. Integration of HIV testing into maternal, newborn, and child health weeks for improved case finding and linkage to prevention of mother-to-child transmission services in Benue State, Nigeria. Front public Heal. 2017;5: 71. doi:10.3389/fpubh.2017.00071

35. Van Den Akker T, Bemelmans M, Ford N, Jemu M, Diggle E, Scheffer S, *et al.* HIV care need not hamper maternity care: A descriptive analysis of integration of services in rural Malawi. BJOG Int J Obs Gynaecol. 2012;119: 431–438. doi:10.1111/j.1471-0528.2011.03229.x

36. Brunie A, Mucheri PNW, Akol A, Chen M, Mercer SJ, Petruney T. Integrating Family Planning and HIV Services at the Community Level: Formative Assessment with Village Health Teams in Uganda. Afr J Reprod Heal. 2017;21: 73–80. doi:10.29063/ajrh2017/v21i2.9

37. Washington S, Owuor K, Turan JM, Steinfeld RL, Onono M, Shade SB, *et al.* Implementation and operational research: effect of integration of HIV care and treatment into antenatal care clinics on mother-to-child HIV transmission and maternal outcomes in Nyanza, Kenya: results from the SHAIP cluster randomized controlled trial. JAIDS J Acquir Immune Defic Syndr. 2015;69: e164--e171. doi:10.1097/QAI.0000000000000656

38. Young N, Taetgmeyer M, Zulaika G, Aol G, Desai M, Ter Kuile F, *et al.* Integrating HIV, syphilis, malaria and anaemia point-of-care testing (POCT) for antenatal care at dispensaries in western Kenya: discrete-event simulation modelling of operational

impact. BMC Public Health. 2019;19: 1629. doi:10.1186/s12889-019-7739-4

39. Zang X, Tang H, Min JE, Gu D, Montaner JSG, Wu Z, *et al.* Cost-Effectiveness of the "One4All" HIV Linkage intervention in guangxi zhuang autonomous region, China. PLOS ONE. 2016;11. doi:10.1371/journal.pone.0167308

40. Zulliger R, Black S, Holtgrave DR, Ciaranello AL, Bekker L-G, Myer L. Cost-effectiveness of a package of interventions for expedited antiretroviral therapy initiation during pregnancy in Cape Town, South Africa. AIDS Behav. 2014;18: 697–705. doi:10.1007/s10461-013-0641-7

41. Busza J, Chiyaka T, Musemburi S, Fearon E, Davey C, Chabata S, *et al.* Enhancing national prevention and treatment services for sex workers in Zimbabwe: a process evaluation of the SAPPH-IRe trial. Heal Policy Plan. 2019;34: 337–345. doi:10.1093/heapol/czz037

42. Carrico AW, Neilands TB, Dilworth SE, Evans JL, Gómez W, Jain JP, *et al.* Randomized controlled trial of a positive affect intervention to reduce HIV viral load among sexual minority men who use methamphetamine. J Int AIDS Soc. 2019;22. doi:10.1002/jia2.25436

43. Chan AK, Mateyu G, Jahn A, Schouten E, Arora P, Mlotha W, *et al.* Outcome assessment of decentralization of antiretroviral therapy provision in a rural district of Malawi using an integrated primary care model. Trop Med Int Heal. 2010;15: 90–97. doi:10.1111/j.1365-3156.2010.02503.x

44. Chan AK, Kanike E, Bedell R, Mayuni I, Manyera R, Mlotha W, *et al.* Same day HIV diagnosis and antiretroviral therapy initiation affects retention in Option B+ prevention of mother-to-child transmission services at antenatal care in Zomba District, Malawi. J Int AIDS Soc. 2016;19. doi:10.7448/ias.19.1.20672

45. Church K, Wringe A, Lewin S, Ploubidis GB, Fakudze P, Initiative I, *et al.* Exploring the feasibility of service integration in a low-income setting: A mixed methods investigation into different models of reproductive health and HIV care in Swaziland. PLOS ONE. 2015;10. doi:10.1371/journal.pone.0126144

46. Ciampa PJ, Burlison JR, Blevins M, Sidat M, Moon TD, Rothman RL, *et al.* Improving retention in the early infant diagnosis of HIV program in rural Mozambique by better service integration. JAIDS J Acquir Immune Defic Syndr. 2011;58: 115–119. doi:10.1097/QAI.0b013e31822149bf

47. Click ES, Feleke B, Pevzner E, Fantu R, Gadisa T, Assefa D, *et al.* Evaluation of integrated registers for tuberculosis and HIV surveillance in children, Ethiopia, 2007-2009. Int J Tuberc Lung Dis. 2012;16: 625–627. doi:10.5588/ijtld.11.0655

48. Coleman SM, Blashill AJ, Gandhi RT, Safren SA, Freudenreich O. Impact of Integrated and Measurement-Based Depression Care: Clinical Experience in an HIV Clinic. Psychosomatics. 2012;53: 51–57. doi:10.1016/j.psym.2011.07.004

49. Conradie H, Khati P, Pharoah H, Adams S. Integrating tuberculosis/HIV treatment: An evaluation of the tuberculosis outcomes of patients co-infected with tuberculosis and HIV in the Breede Valley subdistrict. S Afr Fam Pr. 2013;55: 478–479. doi:10.1080/20786204.2013.10874399

50. Aliyu MH, Blevins M, Audet CM, Kalish M, Gebi UI, Onwujekwe O, *et al.* Integrated prevention of mother-to-child HIV transmission services, antiretroviral therapy initiation, and maternal and infant retention in care in rural north-central Nigeria: A cluster-randomised controlled trial. Lancet

HIV. 2016;3: e202–e211. doi:10.1016/s2352-3018(16)00018-7

51. Criniti SM, Aaron E, Hilley A, Wolf S. Integration of routine rapid HIV screening in an urban family planning clinic. J Midwifery Womens Health. 2011;56: 395–399. doi:10.1111/j.1542-2011.2011.00031.x

52. Deo S, Topp S, Garcia A, Soldner M, Yagci Sokat K, Chipukuma J, *et al.* Modeling the impact of integrating HIV and outpatient health services on patient waiting times in an urban health clinic in Zambia. PLOS ONE. 2012;7. doi:10.1371/journal.pone.0035479

53. Ezeanolue EE, Pharr JR, Hunt A, Patel D, Jackson D. Why are Children Still Being Infected with HIV? Impact of an Integrated Public Health and Clinical Practice Intervention on Mother-to-Child HIV Transmission in Las Vegas, Nevada, 2007-2012. Ann Med Health Sci Res. 2015;5: 253–259. doi:10.4103/2141-9248.160189

54. Geelhoed D, Lafort Y, Chissale E, Candrinho B, Degomme O. Integrated maternal and child health services in Mozambique: structural health system limitations overshadow its effect on follow-up of HIV-exposed infants. BMC Heal Serv Res. 2013;13: 207. doi:10.1186/1472-6963-13-207

55. Gilbert L, Hunt T, Primbetova S, Terlikbayeva A, Chang M, Wu E, *et al.* Reducing opioid overdose in Kazakhstan: A randomized controlled trial of a couple-based integrated HIV/HCV and overdose prevention intervention "Renaissance." Int J Drug Policy. 2018;54: 105–113. doi:10.1016/j.drugpo.2018.01.004

56. Golovaty I, Sharma M, Van Heerden A, Van Rooyen H, Baeten JM, Celum C, *et al.* Cost of integrating noncommunicable disease screening into home-based HIV testing and counseling in South Africa. J Acquir Immune Defic Syndr. 2018;78: 522–526. doi:10.1097/qai.0000000000001713

57. Greig J, O'Brien DP, Ford N, Spelman T, Sabapathy K, Shanks L. Similar mortality and reduced loss to follow-up in integrated compared with vertical programs providing antiretroviral treatment in Sub-Saharan Africa. J Acquir Immune Defic Syndr. 2012;59: e92–e98. doi:10.1097/QAI.0b013e31824206c7

58. Guillaine N, Mwizerwa W, Odhiambo J, Hedt-Gauthier BL, Hirschhorn LR, Mugwaneza P, *et al.* A novel combined mother-infant clinic to optimize postpartum maternal retention, service utilization, and linkage to services in HIV care in rural Rwanda. Int J MCH AIDS. 2017;6: 36. doi:10.21106/ijma.186

59. Hankin A, Freiman H, Copeland B, Travis N, Shah B. A comparison of parallel and integrated models for implementation of routine HIV screening in a large, urban emergency department. Public Health Rep. 2016;131: 90–95. doi:10.1177/00333549161310s111

60. Haraka F, Glass TR, Sikalengo G, Gamell A, Ntamatungiro A, Hatz C, *et al.* A Bundle of Services Increased Ascertainment of Tuberculosis among HIV-Infected Individuals Enrolled in a HIV Cohort in Rural Sub-Saharan Africa. PLOS ONE. 2015;10. doi:10.1371/journal.pone.0123275

61. Ameh S, Klipstein-Grobusch K, Musenge E, Kahn K, Tollman S, Gómez-olivé FX. Effectiveness of an Integrated Approach to HIV and Hypertension Care in Rural South Africa: Controlled Interrupted Time-Series Analysis. AIDS. 2017;75: 472–479. doi:10.1097/QAI.0000000000001437

62. Harding R, Simms V, Alexander C, Collins K, Combo E, Memiah P, *et al.* Can palliative care integrated within HIV outpatient settings improve pain and symptom control in a low-income country? A prospective, longitudinal, controlled intervention

evaluation. AIDS Care. 2013;25: 795–804. doi:10.1080/09540121.2012.736608

63. Hemmer CJ, Pohl JC, Noeske J, Kuaban C, Reisinger EC. Integration of HIV services into the National Tuberculosis Program of Cameroon: The experience of the Littoral Province. Asian Pac J Trop Dis. 2015;5: 525–528. doi:10.1016/s2222-1808(15)60829-5

64. Herce ME, Morse J, Luhanga D, Harris J, Smith HJ, Besa S, *et al.* Integrating HIV care and treatment into tuberculosis clinics in Lusaka, Zambia: Results from a before-after quasi-experimental study. BMC Infect Dis. 2018;18. doi:10.1186/s12879-018-3392-2

65. Herlihy JM, Hamomba L, Bonawitz R, Goggin CE, Sambambi K, Mwale J, *et al.* Implementation and operational research: Integration of PMTCT and antenatal services improves combination antiretroviral therapy uptake for HIV-positive pregnant women in southern Zambia: A prototype for Option B+? JAIDS J Acquir Immune Defic Syndr. 2015;70: e123–e129. doi:10.1097/QAI.0000000000000760

66. Hermans SM, Castelnuovo B, Katabira C, Mbidde P, Lange JM, Hoepelman AI, *et al.* Integration of HIV and TB services results in improved TB treatment outcomes and earlier prioritized ART initiation in a large urban HIV clinic in Uganda. J Acquir Immune Defic Syndr. 2012/03/08. 2012;60: e29-35. doi:10.1097/QAI.0b013e318251aeb4

67. Hewett PC, Nalubamba M, Bozzani F, Digitale J, Vu L, Yam E, *et al.* Randomized evaluation and cost-effectiveness of HIV and sexual and reproductive health service referral and linkage models in Zambia. BMC Public Health. 2016;16: 785. doi:10.1186/s12889-016-3450-x

68. Hung V, Nguyen ST, Tieu VTT, Nguyen TTT, Duong TH, Lyss S, *et al.* Evaluation of the integrated clinic model for HIV/AIDS services in Ho Chi Minh City, Viet Nam, 2013–2014. Public Heal Action. 2016;6: 255–260. doi:10.5588/pha.16.0065

69. Jacobson KB, Moll AP, Friedland GH, Shenoi S V. Successful tuberculosis treatment outcomes among HIV/TB coinfected patients down-referred from a district hospital to primary health clinics in rural South Africa. PLOS ONE. 2015;10. doi:10.1371/journal.pone.0127024

70. Johns B, Doroshenko O, Tarantino L, Cowley P. The Cost-Effectiveness of Integrating HIV Counseling and Testing into Primary Health Care in the Ukraine. AIDS Behav. 2017;21: 655–664. doi:10.1007/s10461-016-1554-z

71. Kanyuuru L, Kabue M, Ashengo TA, Ruparelia C, Mokaya E, Malonza I. RED for PMTCT: an adaptation of immunization's Reaching Every District approach increases coverage, access, and utilization of PMTCT care in Bondo District, Kenya. Int J Gynecol Obstet. 2015;130: S68--S73. doi:10.1016/j.ijgo.2015.04.002

72. Ansa GA, Walley JD, Siddiqi K, Wei X. Assessing the impact of TB/HIV services integration on TB treatment outcomes and their relevance in TB/HIV monitoring in Ghana. Infect Dis Pover. 2012;1. doi:10.1186/2049-9957-1-13

73. Katz DA, Dombrowski JC, Kerani RP, Aubin MR, Kern DA, Heal DD, *et al.* Integrating HIV Testing as an Outcome of STD Partner Services for Men Who Have Sex with Men. AIDS Patient Care STDs. 2016;30: 208–214. doi:10.1089/apc.2016.0027

74. Kerschberger B, Hilderbrand K, Boulle AM, Coetzee D, Goemaere E, de Azevedo V, *et al.* The Effect of Complete Integration of HIV and TB Services on Time to Initiation of Antiretroviral Therapy: A Before-After Study. PLOS ONE. 2012;7. doi:10.1371/journal.pone.0046988

75. Kimani J, Warren CE, Abuya T, Ndwiga C, Mayhew S, Vassall A, *et al.* Use of HIV counseling and testing and family planning services among postpartum women in Kenya: a multicentre, non-randomised trial. BMC Womens Health. 2015;15: 104. doi:10.1186/s12905-015-0262-6

76. Kinyua K, Muange P, Makenzi B, Kimani C, Amoah AO. Applying Quality Improvement Strategies to Health Services for HIV-Affected Mother-Baby Pairs in Rural Kenya. J Int Assoc Provid AIDS Care. 2019;18: 1–23. doi:10.1177/2325958219857977

77. Kosgei RJ, Lubano KM, Shen C, Wools-Kaloustian KK, Musick BS, Siika AM, *et al.* Impact of integrated family planning and HIV care services on contraceptive use and pregnancy outcomes: a retrospective cohort study. J Acquir Immune Defic Syndr. 2011;58: e121. doi:10.1097/QAI.0b013e318237ca80

78. Kufa T, Fielding KL, Hippner P, Kielmann K, Vassall A, Churchyard GJ, *et al.* An intervention to optimise the delivery of integrated tuberculosis and HIV services at primary care clinics: results of the MERGE cluster randomised trial. Contemp Clin Trials. 2018;72: 43–52. doi:10.1016/j.cct.2018.07.013

79. De La Flor C, Porsa E, Nijhawan AE. Opt-out HIV and hepatitis C testing at the dallas county Jail: Uptake, prevalence, and demographic characteristics of testers. Public Heal Action. 2017;132: 617–621. doi:10.1177/0033354917732755

80. Lambdin BH, Micek MA, Sherr K, Gimbel S, Karagianis M, Lara J, *et al.* Integration of HIV care and treatment in primary health care centers and patient retention in central Mozambique: a retrospective cohort study. J Acquir Immune Defic Syndr. 2013;62: e146. doi:10.1097/QAI.0b013e3182840d4e

81. Leon N, Naidoo P, Mathews C, Lewin S, Lombard C. The impact of provider-initiated (opt-out) HIV testing and counseling of patients with sexually transmitted infection in Cape Town, South Africa: a controlled trial. Implement Sci. 2010;5: 8. doi:10.1186/1748-5908-5-8

82. Van Lettow M, Bedell R, Mayuni I, Mateyu G, Landes M, Chan AK, *et al.* Towards elimination of mother-to-child transmission of HIV: performance of different models of care for initiating lifelong antiretroviral therapy for pregnant women in Malawi (Option B+). J Int AIDS Soc. 2014;17: 18994. doi:10.7448/IAS.17.1.18994

83. Bailey RC, Adera F, Mackesy-Amiti ME, Adipo T, Nordstrom SK, Mehta SD, *et al.* Prospective comparison of two models of integrating early infant male circumcision with maternal child health services in Kenya: The Mtoto Msafi Mbili Study. PLOS ONE. 2017;12. doi:10.1371/journal.pone.0184170

84. Mansoor LE, Yende-Zuma N, Baxter C, Mngadi KT, Dawood H, Gengiah TN, *et al.* Integrated provision of topical pre-exposure prophylaxis in routine family planning services in South Africa: a non-inferiority randomized controlled trial. J Int AIDS Soc. 2019;22. doi:10.1002/jia2.25381

85. Mantell JE, Cooper D, Exner TM, Moodley J, Hoffman S, Myer L, *et al.* Emtonjeni-A Structural Intervention to Integrate Sexual and Reproductive Health into Public Sector HIV Care in Cape Town, South Africa: Results of a Phase II Study. AIDS Behav. 2017;21: 905–922. doi:10.1007/s10461-016-1562-z

86. Matulionyte R, Žagminas K, Balčiunaite E, Matulyte E, Paulauskiene R, Bajoriūniene A, *et al.* Routine HIV testing program in the University Infectious Diseases Centre in Lithuania: A four-year analysis 11 Medical and Health Sciences 1117 Public Health

and Health Services 11 Medical and Health Sciences 1103 Clinical Sciences. BMC Infect Dis. 2019;19. doi:10.1186/s12879-018-3661-0

87. Mavhu W, Willis N, Mufuka J, Bernays S, Tshuma M, Mangenah C, *et al.* Effect of a differentiated service delivery model on virological failure in adolescents with HIV in Zimbabwe (Zvandiri): a cluster-randomised controlled trial. Lancet Glob Heal. 2020;8: e264–e275. doi:10.1016/S2214-109X(19)30526-1

88. Mayhew SH, Sweeney S, Warren CE, Collumbien M, Ndwiga C, Mutemwa R, *et al.* Numbers, systems, people: how interactions influence integration. Insights from case studies of HIV and reproductive health services delivery in Kenya. Heal Policy Plan. 2017;32: iv67–iv81. doi:10.1093/heapol/czx097

89. McBain RK, Petersen E, Tophof N, Dunbar EL, Kalanga N, Nazimera L, *et al.* Impact and economic evaluation of a novel HIV service delivery model in rural Malawi. AIDS. 2017;31: 99–106. doi:10.1097/qad.0000000000001578

90. Mendelsohn AS, Gill K, Marcus R, Robbertze D, Van de Venter C, Mendel E, *et al.* Sexual reproductive healthcare utilisation and HIV testing in an integrated adolescent youth centre clinic in Cape Town, South Africa. South Afr J HIV Med. 2018;19: 1–7. doi:10.4102/sajhivmed.v19i1.826

91. Mgbemena O, Westfall AO, Ritchie CS, Hicks J, Raper JL, Overton ET, *et al.* Preliminary outcomes of a pilot physical therapy program for HIV-infected patients with chronic pain. AIDS Care Psychol Socio-Med Asp AIDS HIV. 2015;27: 244–247. doi:10.1080/09540121.2014.940272

92. Miller WC, Hoffman IF, Hanscom BS, Ha T V, Dumchev K, Djoerban Z, *et al.* A scalable, integrated intervention to engage people who inject drugs in HIV care and medication-assisted treatment (HPTN 074): a randomised, controlled phase 3 feasibility and efficacy study. Lancet. 2018;392: 747–759. doi:10.1016/s0140-6736(18)31487-9

93. Momplaisir F, Mounzer K, Long JA. Preventive cancer screening practices in HIV-positive patients. AIDS Care Psychol Socio-Med Asp AIDS HIV. 2014;26: 87–94. doi:10.1080/09540121.2013.802276

94. Bergmann JN, Legins K, Sint TT, Snidal S, Amor YB, McCord GC. Outcomes and Cost-Effectiveness of Integrating HIV and Nutrition Service Delivery: Pilots in Malawi and Mozambique. AIDS Behav. 2017;21: 703–711. doi:10.1007/s10461-016-1400-3

95. Mudzengi D, Sweeney S, Hippner P, Kufa T, Fielding K, Grant AD, *et al.* The patient costs of care for those with TB and HIV: a cross-sectional study from South Africa. Health Policy Plan. 2017;32: 48–56. doi:10.1093/heapol/czw183

96. Musarandega R, Mutede B, Mahomva A, Nyamayaro W, Mushavi A, Lindan C, *et al.* Scaling up Pediatric HIV Testing by Incorporating Provider-Initiated HIV Testing Into all Child Health Services in Hurungwe District, Zimbabwe. J Acquir Immune Defic Syndr. 2018;77: 78–85. doi:10.1097/qai.0000000000001564

97. Myer L, Phillips TK, Zerbe A, Brittain K, Lesosky M, Hsiao N-Y, *et al.* Integration of postpartum healthcare services for HIV-infected women and their infants in South Africa: A randomised controlled trial. PLOS Med. 2018;15. doi:10.1371/journal.pmed.1002547

98. Nance N, Pendo P, Masanja J, Ngilangwa DP, Webb K, Noronha R, *et al.* Short-term effectiveness of a community health worker intervention for HIV-infected pregnant women in Tanzania to improve treatment adherence and retention in care: a cluster-

randomized trial. PLOS ONE. 2017;12. doi:10.1371/journal.pone.0181919

99. Ndagijimana A, Rugigana E, Uwizeye CB, Ntaganira J. One-stop TB-HIV services evaluation in Rwanda: comparison of the 2001-2005 and 2006-2010 cohorts. Public Heal Action. 2015;5: 209–213. doi:10.5588/pha.15.0093

100. Ngo AD, Ha TH, Rule J, Dang C V. Peer-based education and the integration of HIV and sexual and reproductive health services for young people in Vietnam: Evidence from a project evaluation. PLOS ONE. 2013;8. doi:10.1371/journal.pone.0080951

101. Nsubuga-Nyombi T, Karamagi E, Nabitaka L, Namukose S, Calnan J, Nyakwezi S, *et al.* Increasing HIV-Free Survival of Infants: Reorganizing Care Using Quality Improvement for the Optimal Health and Nutrition of HIV-Positive Women and Their Exposed Infants in Uganda. J Int Assoc Provid AIDS Care. 2019;18. doi:10.1177/2325958219857724

102. Obure CD, Sweeney S, Darsamo V, Michaels-Igbokwe C, Guinness L, Terris-Prestholt F, *et al.* The costs of delivering integrated HIV and sexual reproductive health services in limited resource settings. PLOS ONE. 2015;10. doi:10.1371/journal.pone.0124476

103. Obure CD, Jacobs R, Guinness L, Mayhew S, Vassall A. Does integration of HIV and sexual and reproductive health services improve technical efficiency in Kenya and Swaziland? An application of a two-stage semi parametric approach incorporating quality measures. Soc Sci Med. 2016;151: 147–156. doi:10.1016/j.socscimed.2016.01.013

104. Obure CD, Guinness L, Sweeney S, Initiative I, Vassall A. Does integration of HIV and SRH services achieve economies of scale and scope in practice? A cost function analysis of the Integra Initiative. Sex Transm Infect. 2016;92: 130–134. doi:10.1136/sextrans-2015-052039

105. Bindoria S V, Devkar R, Gupta I, Ranebennur V, Saggurti N, Ramesh S, *et al.* Development and pilot testing of HIV screening program integration within public/primary health centers providing antenatal care services in Maharashtra, India. BMC Res Notes. 2014;7: 177. doi:10.1186/1756-0500-7-177

106. Owiti P, Zachariah R, Bissell K, Kumar AM, Diero L, Carter EJ, *et al.* Integrating tuberculosis and HIV services in rural Kenya: Uptake and outcomes. Public Heal Action. 2015;5: 36–44. doi:10.5588/pha.14.0092

107. Palma AM, Rabkin M, Simelane S, Gachuhi AB, McNairy ML, Nuwagaba-Biribonwoha H, *et al.* A time-motion study of cardiovascular disease risk factor screening integrated into HIV clinic visits in Swaziland. J Int AIDS Soc. 2018;21: e25099. doi:10.1002/jia2.25099

108. Rawat A, Uebel K, Moore D, Yassi A. Integrated HIV-Care into Primary Health Care Clinics and the Influence on Diabetes and Hypertension Care: An Interrupted Time Series Analysis in Free State, South Africa over 4 Years. J Acquir Immune Defic Syndr. 2018;77: 476–483. doi:10.1097/qai.0000000000001633

109. Reza-Paul S, Lazarus L, Maiya R, Venukumar KT, Lakshmi B, Roy A, *et al.* Delivering community-led integrated HIV and sexual and reproductive health services for sex workers: A mixed methods evaluation of the DIFFER study in Mysore, South India. PLOS ONE. 2019;14. doi:10.1371/journal.pone.0218654

110. Van Rie A, Patel MR, Nana M, Vanden Driessche K, Tabala M, Yotebieng M, *et al.* Integration and task shifting for TB/HIV care

and treatment in highly resource-scarce settings: One size may not fit all. J Acquir Immune Defic Syndr. 2014;65: e110–e117. doi:10.1097/01.qai.0000434954.65620.f3

111. Roberts DA, Barnabas R V, Abuna F, Lagat H, Kinuthia J, Pintye J, *et al.* The role of costing in the introduction and scale-up of HIV pre-exposure prophylaxis: evidence from integrating PrEP into routine maternal and child health and family planning clinics in western Kenya. J Int AIDS Soc. 2019;22. doi:10.1002/jia2.25296

112. Rodkjaer LO, Laursen T, Seeberg K, Drouin M, Johansen H, Dyrehave C, *et al.* The Effect of a Mind-Body Intervention on Mental Health and Coping Self-Efficacy in HIV-Infected Individuals: A Feasibility Study. J Altern Complement Med. 2017;23: 326–330. doi:10.1089/acm.2016.0251

113. Rosenberg SD, Goldberg RW, Dixon LB, Wolford GL, Slade EP, Himelhoch S, *et al.* Assessing the STIRR model of best practices for blood-borne infections of clients with severe mental illness. Psychiatr Serv. 2010;61: 885–891. doi:10.1176/appi.ps.61.9.885

114. Rosenberg NE, Bhushan NL, Vansia D, Phanga T, Maseko B, Nthani T, *et al.* Comparing youth-friendly health services to the standard of care through "girl Power-Malawi": A quasi-experimental cohort study. J Acquir Immune Defic Syndr. 2018;79: 458–466. doi:10.1097/qai.0000000000001830

115. Rutaremwa G, Kabagenyi A. Utilization of integrated HIV and sexual and reproductive health services among women in Uganda. BMC Health Serv Res. 2016;16: 494. doi:10.1186/s12913-016-1761-3

116. Broughton EI, Muhire M, Karamagi E, Kisamba H. Cost-effectiveness of implementing the chronic care model for HIV care in Uganda. Int J Qual Heal Care. 2016;28: 802–807. doi:10.1093/intqhc/mzw116

117. Schulz SA, Draper HR, Naidoo P. A comparative study of tuberculosis patients initiated on ART and receiving different models of TB-HIV care. Int J Tuberc Lung Dis. 2013;17: 1558–1563. doi:10.5588/ijtld.13.0247

118. Shade SB, Kevany S, Onono M, Ochieng G, Steinfeld RL, Grossman D, *et al.* Cost, cost-efficiency and cost-effectiveness of integrated family planning and HIV services. AIDS. 2013;27: S87–S92. doi:10.1097/qad.0000000000000038

119. Shenoi S V, Moll AP, Brooks RP, Kyriakides T, Andrews L, Kompala T, *et al.* Integrated tuberculosis/human immunodeficiency virus community-based case finding in rural South Africa: Implications for tuberculosis control efforts. Open Forum Infect Dis. 2017;4: 1–7. doi:10.1093/ofid/ofx092

120. Siapka M, Obure CD, Mayhew SH, Sweeney S, Fenty J, Vassall A. Impact of integration of sexual and reproductive health services on consultation duration times: results from the Integra Initiative. Health Policy Plan. 2017;32: 82–90. doi:10.1093/heapol/czx141

121. Simeone C, Shapiro B, Lum PJ. Integrated HIV care is associated with improved engagement in treatment in an urban methadone clinic. Addict Sci Clin Pr. 2017;12: 1–19. doi:10.1186/s13722-017-0084-y

122. Siregar AYM, Komarudin D, Wisaksana R, Van Crevel R, Baltussen R. Costs and outcomes of VCT delivery models in the context of scaling up services in Indonesia. Trop Med Int Heal. 2011;16: 193–199. doi:10.1111/j.1365-3156.2010.02675.x

123. Solomon SS, Solomon S, McFall AM, Srikrishnan AK, Anand S, Verma V, *et al.* Integrated HIV testing, prevention, and treatment intervention for key populations

in India: a cluster-randomised trial. Lancet HIV. 2019;6: 283–296. doi:10.1016/S2352-3018(19)30034-7

124. Solomon SS, Quinn TC, Solomon S, McFall AM, Srikrishnan AK, Verma V, *et al.* Integrating HCV testing with HIV programs improves hepatitis C outcomes in people who inject drugs: A cluster-randomized trial. J Hepatol. 2020;72: 67–74.

125. Sweeney S, Obure CD, Terris-Prestholt F, Darsamo V, Michaels-Igbokwe C, Muketo E, *et al.* The impact of HIV/SRH service integration on workload: analysis from the Integra Initiative in two African settings. Hum Resour Heal. 2014;12: 1–42. doi:10.1186/1478-4491-12-42

126. Tomlinson M, Doherty T, Ijumba P, Jackson D, Lawn J, Persson LA, *et al.* Goodstart: A cluster randomised effectiveness trial of an integrated, community-based package for maternal and newborn care, with prevention of mother-to-child transmission of HIV in a South African township. Trop Med Int Heal. 2014;19: 256–266. doi:10.1111/tmi.12257

127. Brunie A, Wamala-Mucheri P, Akol A, Mercer S, Chen M. Expanding HIV testing and counselling into communities: Feasibility, acceptability, and effects of an integrated family planning/HTC service delivery model by Village Health Teams in Uganda. Heal Policy Plan. 2016;31: 1050–1057. doi:10.1093/heapol/czw035

128. Topp SM, Chipukuma JM, Giganti M, Mwango LK, Chiko LM, Tambatamba-Chapula B, *et al.* Strengthening health systems at facility-level: Feasibility of integrating antiretroviral therapy into primary health care services in Lusaka, Zambia. PLOS ONE. 2010;5. doi:10.1371/journal.pone.0011522

129. Topp SM, Chipukuma JM, Chiko MM, Matongo E, Bolton-Moore C, Reid SE. Integrating HIV Treatment with Primary Care Outpatient Services: Opportunities and Challenges from a Scaled-Up Model in Zambia. Health Policy Plan. 2013;28: 347–357.

130. Tran BX, Ohinmaa A, Duong AT, Nguyen LT, Vu PX, Mills S, *et al.* Cost-effectiveness of integrating methadone maintenance and antiretroviral treatment for HIV-positive drug users in Vietnam's injection-driven HIV epidemics. Drug Alcohol Depend. 2012;125: 260–266. doi:10.1016/j.drugalcdep.2012.02.021

131. Tran BX, Ohinmaa A, Duong AT, Do NT, Nguyen LT, Nguyen QC, *et al.* Changes in drug use are associated with health-related quality of life improvements among methadone maintenance patients with HIV/AIDS. Qual Life Res. 2012;21: 613–623. doi:10.1007/s11136-011-9963-y

132. Turan JM, Steinfeld RL, Onono M, Bukusi EA, Woods M, Shade SB, *et al.* The Study of HIV and Antenatal Care Integration in Pregnancy in Kenya: Design, Methods, and Baseline Results of a Cluster-Randomized Controlled Trial. PLOS ONE. 2012;7. doi:10.1371/journal.pone.0044181

133. Uebel KE, Lombard C, Joubert G, Fairall LR, Bachmann MO, Mollentze WF, *et al.* Integration of HIV care into primary care in South Africa: effect on survival of patients needing antiretroviral treatment. JAIDS J Acquir Immune Defic Syndr. 2013;63: 94–100. doi:10.1097/QAI.0b013e318291cd08

134. Vodicka EL, Babigumira JB, Mann MR, Kosgei RJ, Lee F, Mugo NR, *et al.* Costs of integrating cervical cancer screening at an HIV clinic in Kenya. Int J Gynaecol Obs. 2017;136: 220–228. doi:10.1002/ijgo.12025

135. Vodicka EL, Chung MH, Zimmermann MR, Kosgei RJ, Lee F, Mugo NR, *et al.* Estimating the costs of HIV clinic integrated versus non-integrated treatment of pre-

cancerous cervical lesions and costs of cervical cancer treatment in Kenya. PLOS ONE. 2019;14: e0217331. doi:10.1371/journal.pone.0217331

136. Wang AL, Qiao YP, Wang LH, Fang LW, Wang F, Jin X, *et al.* Integrated prevention of mother-to-child transmission for human immunodeficiency virus, syphilis and hepatitis B virus in China. Bull WHO. 2014;93: 52–56. doi:10.2471/blt.14.139626

137. Wang PC, Mwango A, Moberley S, Brockman BJ, Connor AL, Kalesha-Masumbu P, *et al.* A cluster randomised trial on the impact of integrating early infant HIV diagnosis with the expanded programme on immunization on immunization and HIV testing rates in rural health facilities in southern Zambia. PLOS ONE. 2015;10. doi:10.1371/journal.pone.0141455

138. Wagner GJ, Wanyenze RK, Beyeza-Kashesya J, Gwokyalya V, Hurley E, Mindry D, *et al.* "Our Choice" improves use of safer conception methods among HIV serodiscordant couples in Uganda: a cluster randomized controlled trial evaluating two implementation approaches. Implement Sci. 2021;16: 1–13. doi:10.1186/s13012-021-01109-z

139. Talama GC, Shaw M, Maloya J, Chihana T, Nazimera L, Wroe EB, *et al.* Improving uptake of cervical cancer screening services for women living with HIV and attending chronic care services in rural Malawi. BMJ open Qual. 2020;9. doi:10.1136/bmjoq-2019-000892

140. Chen Y, Begnel E, Muthigani W, Achwoka D, Mcgrath CJ, Singa B, *et al.* Higher contraceptive uptake in HIV treatment centers offering integrated family planning services: A national survey in Kenya. Contraception. 2020;102: 39–45. doi:10.1016/j.contraception.2020.04.003

141. Digre P, Avoundjian T, Johnson K, Peyton D, Lewis C, Barnabas R V., *et al.* Barriers, Facilitators, and Cost of Integrating HIV-Related Activities Into Sexually Transmitted Disease Partner Services in Jackson, Mississippi. Sex Transm Dis. 2021;48: 145–151. doi:10.1097/OLQ.0000000000001296

142. Dovel K, Shaba F, Offorjebe OA, Balakasi K, Nyirenda M, Phiri K, *et al.* Effect of facility-based HIV self-testing on uptake of testing among outpatients in Malawi: a cluster-randomised trial. Lancet Glob Heal. 2020;8: e276–e287. doi:10.1016/S2214-109X(19)30534-0

143. Shade SB, Osmand T, Kwarisiima D, Brown LB, Luo A, Mwebaza B, *et al.* Costs of integrating hypertension care into HIV care in rural East African clinics. AIDS. 2021;35: 911–919. doi:10.1097/QAD.0000000000002834

144. Stockton MA, Udedi M, Kulisewa K, Hosseinipour MC, Gaynes BN, Mphonda SM, *et al.* The impact of an integrated depression and HIV treatment program on mental health and HIV care outcomes among people newly initiating antiretroviral therapy in Malawi. PLOS ONE. 2020;15: 1–20. doi:10.1371/journal.pone.0231872

145. Rosen JG, Phiri L, Chibuye M, Namukonda ES, Mbizvo MT, Kayeyi N. Integrated psychosocial, economic strengthening, and clinical service-delivery to improve health and resilience of adolescents living with HIV and their caregivers: Findings from a prospective cohort study in Zambia. PLOS ONE. 2021;16: 1–19. doi:10.1371/journal.pone.0243822

146. Shin SS, Satyanarayana VA, Ekstrand ML, Carpenter CL, Wang Q, Yadav K, *et al.* The effect of community-based nutritional interventions on children of women living with human immunodeficiency virus in rural India: A 2 × 2 factorial intervention

trial. Clin Infect Dis. 2020;71: 1539–1546. doi:10.1093/cid/ciz1009

147. Schackman BR, Leff JA, Botsko M, Fiellin DA, Altice FL, Korthuis PT, *et al.* The cost of integrated HIV care and buprenorphine/naloxone treatment: Results of a cross-site evaluation. J Acquir Immune Defic Syndr. 2011;56: S76–S82. doi:10.1097/QAI.0b013e31820a9a66

148. Uyei J, Coetzee D, Macinko J, Guttmacher S. Integrated delivery of HIV and tuberculosis services in sub-Saharan Africa: A systematic review. Lancet Infect Dis. 2011;11: 855–867. doi:10.1016/s1473-3099(11)70145-1

149. Hudson M, Rutherford GW, Weiser S, Fair E. Linking private, for-profit providers to public sector services for HIV and tuberculosis co-infected patients: A systematic review. PLOS ONE. 2018;13. doi:10.1371/journal.pone.0194960

150. Car LT, Brusamento S, Elmoniry H, van Velthoven MHMMT, Pape UJ, Welch V, *et al.* The Uptake of Integrated Perinatal Prevention of Mother-to-Child HIV Transmission Programs in Low- and Middle-Income Countries: A Systematic Review. PLOS ONE. 2013;8. doi:10.1371/journal.pone.0056550

151. Hyle EP, Naidoo K, Su AE, El-Sadr WM, Freedberg KA. HIV, tuberculosis, and noncommunicable diseases: What is known about the costs, effects, and cost-effectiveness of integrated care? J Acquir Immune Defic Syndr. 2014;67: S87–S95. doi:10.1097/qai.0000000000000254

152. Narasimhan M, Yeh PT, Haberlen S, Warren CE, Kennedy CE. Integration of HIV testing services into family planning services: A systematic review. Reprod Heal. 2019;16. doi:10.1186/s12978-019-0714-9

153. Wilcher R, Hoke T, Adamchak SE, Cates Jr W. Integration of family planning into HIV services: A synthesis of recent evidence. AIDS. 2013;27: 65–75. doi:10.1097/qad.0000000000000051

154. Rinaldi G, Kiadaliri AA, Haghparast-Bidgoli H. Cost effectiveness of HIV and sexual reproductive health interventions targeting sex workers: A systematic review. Cost Eff Resour Alloc. 2018;16. doi:10.1186/s12962-018-0165-0

155. Dudley L, Garner P. Strategies for integrating primary health services in low- and middle-income countries at the point of delivery. Cochrane Database Syst Rev. 2011;6: CD003318. doi:10.1002/14651858.CD003318.pub3

156. Chuah FLH, Haldane VE, Cervero-Liceras F, Ong SE, Sigfrid LA, Murphy G, *et al.* Interventions and approaches to integrating HIV and mental health services: a systematic review. Heal Policy Plan. 2017;32: 27–47. doi:10.1093/heapol/czw169

157. Haberlen SA, Narasimhan M, Beres LK, Kennedy CE. Integration of Family Planning Services into HIV Care and Treatment Services: A Systematic Review. Stud Fam Plann. 2017;48: 153–177. doi:10.1111/sifp.12018

158. De Jongh T, Gurol-Urganci I, Allen E, Zhu NJ, Atun R. Integration of antenatal care services with health programmes: systematic review. Int J Gynaecol Obstet. 2015;6: 363-364. doi:10.7189/jogh.06.010403

159. Viviano M, De Beaudrap P, Tebeu PM, Fouogue JT, Vassilakos P, Petignat P. A review of screening strategies for cervical cancer in human immunodeficiency virus-positive women in sub-Saharan Africa. Int J Womens Heal. 2017;9: 69–79. doi:10.2147/ijwh.S103868

160. Haldane V, Cervero-Liceras F. Integrating HIV and substance use services: a systematic review. J Int AIDS Soc. 2017;20. doi:10.7448/IAS.20.1.21585

161. Juma K, Reid M, Roy M, Vorkoper S, Temu TM, Levitt NS, *et al.* From HIV prevention to non-communicable disease health promotion efforts in sub-Saharan Africa: A Narrative Review. AIDS. 2018;32: 63–73. doi:10.1097/qad.0000000000001879

162. Joseph Davey D, Myer L, Bukusi E, Ramogola-Masire D, Kilembe W, Klausner JD. Integrating Human Immunodeficiency Virus and Reproductive, Maternal and Child, and Tuberculosis Health Services Within National Health Systems. Curr HIV/AIDS Rep. 2016;13: 170–176. doi:10.1007/s11904-016-0316-x

163. Catumbela E, Certal V, Freitas A, Costa C, Sarmento A, da Costa Pereira A. Definition of a core set of quality indicators for the assessment of HIV/AIDS clinical care: a systematic review. BMC Health Serv Res. 2013;13: 1–11. doi:10.1186/1472-6963-13-236

164. Yapa HM, De Neve J-W, Chetty T, Herbst C, Post FA, Jiamsakul A, *et al.* The impact of continuous quality improvement on coverage of antenatal HIV care tests in rural South Africa: Results of a stepped-wedge cluster-randomised controlled implementation trial. PLOS Med. 2020;17: 31–50. doi:10.1371/journal.pmed.1003150

165. Bor J, Gage A, Onoya D, Maskew M, Tripodis Y, Fox MP, *et al.* Variation in HIV care and treatment outcomes by facility in South Africa, 2011--2015: A cohort study. PLOS Med. 2021;18: e1003479. doi:10.1371/journal.pmed.1003479

166. Roberts M, Hsiao W, Berman P, Reich M. Getting health reform right: a guide to improving performance and equity. New York: Oxford University Press; 2003.

167. World Health Organization (WHO). Everybody business: strengthening health systems to improve health outcomes. WHO's framework for action. Geneva; 2007. Available: https://www.who.int/healthsystems/strategy/everybodys_business.pdf

168. Chimbindi N, Bärnighausen T, Newell M-L. Patient satisfaction with HIV and TB treatment in a public programme in rural KwaZulu-Natal: evidence from patient-exit interviews. BMC Health Serv Res. 2014;14: 1–13. doi:10.1186/1472-6963-14-32

169. Kingsley C, Patel S. Patient-reported outcome measures and patient-reported experience measures. Bja Educ. 2017;17: 137–144. doi:10.1093/bjaed/mkw060

170. Joint United Nations Programme on HIV/AIDS (UNAIDS). Evidence for elimination HIV-related stigma and discrimination. Geneva; 2020. Available: https://www.unAIDS.org/sites/default/files/media_asset/eliminating-discrimination-guidance_en.pdf

171. Nosyk B, Krebs E, Zang X, Piske M, Enns B, Min JE, *et al.* "Ending the Epidemic" Will Not Happen Without Addressing Racial/Ethnic Disparities in the United States Human Immunodeficiency Virus Epidemic. Clin Infect Dis. 2020;71: 2968–2971. doi:10.1093/cid/ciaa566

172. Viljoen L, Bond VA, Reynolds LJ, Mubekapi-Musadaidzwa C, Baloyi D, Ndubani R, *et al.* Universal HIV testing and treatment and HIV stigma reduction: a comparative thematic analysis of qualitative data from the HPTN 071 (PopART) trial in South Africa and Zambia. Sociol Health Illn. 2020;43: 167–185. doi:10.1111/1467-9566.13208

173. Reisner SL, Radix A, Deutsch MB. Integrated and Gender-Affirming Transgender Clinical Care and Research. J Acquir Immune Defic Syndr. 2016;72: S235–S242. doi:10.1097/QAI.0000000000001088

174. Decker MR, Crago AL, Chu SKH, Sherman SG, Seshu MS, Buthelezi K, *et al.* Human rights violations against sex workers: Burden and effect on HIV. Lancet.

2015;385: 186–199. doi:10.1016/S0140-6736(14)60800-X

175. Jere E, Mafiala F, Jim G, Banda H, Nyasulu HM, Dambula I, *et al.* Growing Together: Multisectoral Investments in Malawi's Youth. Lilongwe; 2019. Available: https://www.prb.org/wp-content/uploads/2019/08/malawi-engage-presentation-guide.pdf

176. Grimsrud AT, Pike C, Bekker LG. The power of peers and community in the continuum of HIV care. Lancet Glob Heal. 2020;8: e167–e168. doi:10.1016/S2214-109X(19)30544-3

177. Saul J, Bachman G, Allen S, Toiv NF, Cooney C, Beamon T. The DREAMS core package of interventions: a comprehensive approach to preventing HIV among adolescent girls and young women. PLOS ONE. 2018;13. doi:10.1371/journal.pone.0208167

178. Mayer KH, Bekker LG, Stall R, Grulich AE, Colfax G, Lama JR. Comprehensive clinical care for men who have sex with men: An integrated approach. Lancet. 2012;380: 378–387. doi:10.1016/S0140-6736(12)60835-6

179. United Nations Office on Drugs and Crime (UNODC). Implementing Comprehensive HIV and HCV Programmes with People Who Inject Drugs. Geneva; 2012. Available: https://www.unAIDS.org/sites/default/files/media_asset/2017_HIV-HCV-programmes-people-who-inject-drugs_en.pdf

180. Burr CK, Storm DS, Hoyt MJ, Dutton L, Berezny L, Allread V, *et al.* Integrating health and prevention services in syringe access programs: a strategy to address unmet needs in a high-risk population. Public Health Rep. 2014;129: 26–32. doi:10.1177/00333549141291S105

181. Roberts A, Mathers B, Degenhardt L, others. Women who inject drugs: A review of their risks, experiences and needs. A Rep Prep behalf Ref Gr to United Nations HIV Inject Drug Use Aust Sydney Natl Drug Alcohol Res Cent (NDARC), Univ New South Wales. 2010. Available: https://www.unodc.org/documents/hiv-AIDS/Women_who_inject_drugs.pdf

182. Zhang L, Tao Y, Woodring J, Rattana K, Sovannarith S, Rathavy T, *et al.* Integrated approach for triple elimination of mother-to-child transmission of HIV, hepatitis B and syphilis is highly effective and cost-effective: An economic evaluation. Int J Epidemiol. 2019;48: 1327–1339. doi:10.1093/ije/dyz037

183. Irungu EM, Sharma M, Maronga C, Mugo N, Ngure K, Celum C, *et al.* The Incremental Cost of Delivering PrEP as a Bridge to ART for HIV Serodiscordant Couples in Public HIV Care Clinics in Kenya. AIDS Res Treat. 2019;2019. doi:10.1155/2019/4170615

184. Barocas JA, Morgan JR, Fiellin DA, Schackman BR, Eftekhari Yazdi G, Stein MD, *et al.* Cost-effectiveness of integrating buprenorphine-naloxone treatment for opioid use disorder into clinical care for persons with HIV/hepatitis C co-infection who inject opioids. Int J Drug Policy. 2019;72: 160–168. doi:10.1016/j.drugpo.2019.05.010

185. Owusu-Edusei K, Tao G, Gift TL, Wang A, Wang L, Tun Y, *et al.* Cost-effectiveness of integrated routine offering of prenatal HIV and syphilis screening in China. Sex Transm Dis. 2014;41: 103–110. doi:10.1097/olq.0000000000000085

186. Mbah MLN, Kjetland EF, Atkins KE, Poolman EM, Orenstein EW, Meyers LA, *et al.* Cost-effectiveness of a community-based intervention for reducing the transmission of Schistosoma haematobium and HIV in Africa. Proc Natl Acad Sci U S A. 2013;110: 7952–7957. doi:10.1073/pnas.1221396110

187. Kahn JG, Harris B, Mermin JH, Clasen T, Lugada E, Grabowksy M, *et al.* Cost of community integrated prevention campaign for malaria, HIV, and diarrhea in rural Kenya. BMC Heal Serv Res. 2011;11: 346. doi:10.1186/1472-6963-11-346

188. Dugdale CM, Phillips TK, Myer L, Hyle EP, Brittain K, Freedberg KA, *et al.* Cost-effectiveness of integrating postpartum antiretroviral therapy and infant care into maternal & child health services in South Africa. PLOS ONE. 2019;14: 1–16. doi:10.1371/journal.pone.0225104

189. Hu QH, Meyers K, Xu JJ, Chu ZX, Zhang J, Ding HB, *et al.* Efficacy and cost-effectiveness of early antiretroviral therapy and partners' pre-exposure prophylaxis among men who have sex with men in Shenyang, China: A prospective cohort and costing study. BMC Infect Dis. 2019;19. doi:10.1186/s12879-019-4275-x

190. Ying R, Sharma M, Heffron R, Celum CL, Baeten JM, Katabira E, *et al.* Cost-effectiveness of pre-exposure prophylaxis targeted to high-risk serodiscordant couples as a bridge to sustained ART use in Kampala, Uganda. J Int AIDS Soc. 2015;18: 2–13. doi:10.7448/IAS.18.4.20013

191. Vickerman P, Devine A, Foss AM, Delany-Moretlwe S, Mayaud P, Meyer-Rath G. The cost-effectiveness of herpes simplex virus-2 suppressive therapy with daily aciclovir for delaying HIV disease progression among HIV-1-infected women in South Africa. Sex Transm Dis. 2011;38: 401–409. doi:10.1097/OLQ.0b013e31820b8bc8

192. Bilinski A, Neumann P, Cohen J, Thorat T, McDaniel K, Salomon JA. When cost-effective interventions are unaffordable: Integrating cost-effectiveness and budget impact in priority setting for global health programs. PLOS Med. 2017;14: e1002397. doi:10.1371/journal.pmed.1002397

193. Bärnighausen T, Hontelez JAC, Hauck K, Bijlmakers L, Jansen MPM, Tromp N, *et al.* Evidence for scaling up HIV treatment in sub-Saharan Africa: A call for incorporating health system constraints. PLOS Med. 2017;14: e1002240. doi:10.1371/journal.pmed.1002240

194. Luz PM, Veloso VG, Grinsztejn B. The HIV epidemic in Latin America: accomplishments and challenges on treatment and prevention. Curr Opin HIV AIDS. 2019;14: 1–366. doi:10.1097/COH.0000000000000564

195. Bärnighausen T, Tugwell P, Røttingen J-A, Shemilt I, Rockers P, Geldsetzer P, *et al.* Quasi-experimental study designs series—paper 4: uses and value. J Clin Epidemiol. 2017;89: 21–29. doi:10.1016/j.jclinepi.2017.03.012

196. Rockers PC, Tugwell P, Grimshaw J, Oliver S, Atun R, Røttingen J-A, *et al.* Quasi-experimental study designs series—paper 12: strengthening global capacity for evidence synthesis of quasi-experimental health systems research. J Clin Epidemiol. 2017;89: 98–105. doi:10.1016/j.jclinepi.2016.03.034

SUPPORTING INFORMATION TO CHAPTER 8

Supplementary File 1. Search strategy.

Searches performed 28 January 2020, updated searches performed 10 September 2021; search terms were adapted to fit requirements by each database.

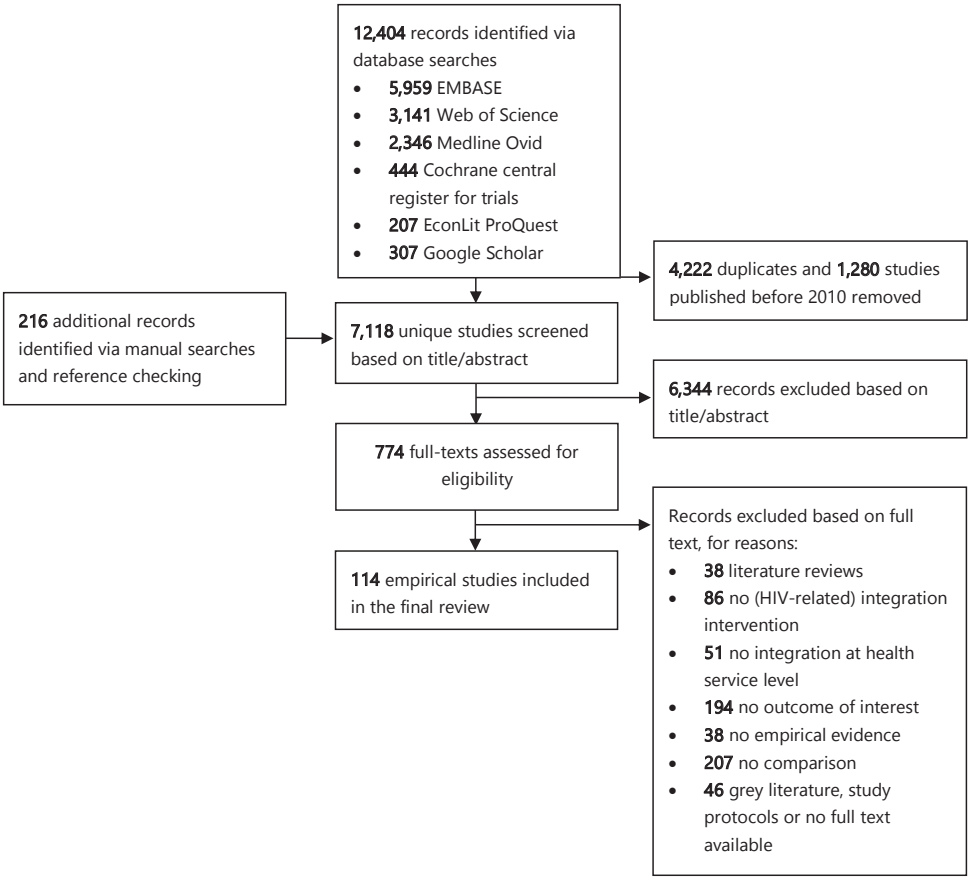
1. ('integrated health care system'/de OR ((integrat* OR coordinat* OR interdisciplin* OR inter-disciplin*) NEAR/8 (service* OR care OR healthcare OR deliver* OR hospital* OR public-health OR program* OR health-system* OR routine* OR intervention* OR centre* OR center*)):ab,ti OR (deliver* NEAR/3 model*):ti)

2. AND ('Human immunodeficiency virus infection'/exp OR 'Human immunodeficiency virus'/exp OR 'acquired immune deficiency syndrome'/exp OR 'highly active antiretroviral therapy'/exp OR (hiv OR AIDS OR haart OR (Human NEAR/3 (immunodeficien* OR immuno-deficien* OR immune-deficien*) NEAR/3 virus*) OR (acquir* NEAR/3 (immunodeficien* OR immuno-deficien* OR immune-deficien*) NEAR/3 syndrome*) OR antiretroviral-therap* OR anti-retroviral-therap*):ab,ti)
3. AND ('economic aspect'/exp OR economics/de OR 'health economics'/exp OR 'cost'/de OR 'health care cost'/exp OR 'disability-adjusted life year'/de OR 'quality adjusted life year'/de OR 'health care utilization'/exp OR 'facilities and services utilization'/de OR 'health care quality'/de OR 'clinical effectiveness'/de OR 'health equity'/de OR 'clinical indicator'/de OR benchmarking/de OR 'personnel management'/de OR 'quality improvement study'/de OR 'total quality management'/de OR 'feasibility study'/de OR (economic* OR cost OR costs OR financ* OR ((disabilit* OR qualit*) NEAR/3 adjust* NEAR/3 (life-year* OR lifeyear*)) OR daly* OR qaly* OR ((service* OR healthcare OR care OR equipment* OR supplies* OR procedure* OR technique*) NEAR/3 (utili* OR uptake*)) OR ((clinical* OR care OR healthcare OR service*) NEAR/3 (effectiv* OR efficien* OR indicator*)) OR ((qualit* OR performance*) NEAR/3 (indicator* OR measure* OR improve* OR management*)) OR equity OR benchmark* OR ((personnel OR staff) NEAR/3 (management* OR utili*)) OR utilization* OR utilization* OR feasib* OR sustainab*):Ab,ti OR quality:ti) NOT ([Conference Abstract]/lim)

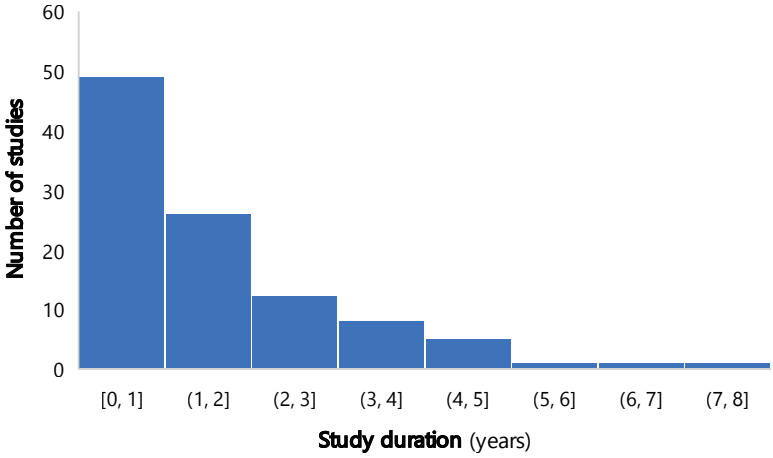
4. AND ('Human immunodeficiency virus infection'/exp OR 'Human immunodeficiency virus'/exp OR 'acquired immune deficiency syndrome'/exp OR 'highly active antiretroviral therapy'/exp OR 'transgender'/exp OR 'sex worker'/exp OR 'prostitution'/exp OR 'men who have sex with men'/de OR 'sexual and gender minority'/exp OR (hiv OR AIDS OR haart OR (Human NEAR/3 (immunodeficien* OR immuno-deficien* OR immune-deficien*) NEAR/3 virus*) OR (acquir* NEAR/3 (immunodeficien* OR immuno-deficien* OR immune-deficien*) NEAR/3 syndrome*) OR antiretroviral-therap* OR anti-retroviral-therap* OR transgender* OR trans-gender* OR trans-people* OR sex-work* OR sex-traffick* OR prostitut* OR ((men-who OR men-having OR men-reporting) NEAR/3 sex-with-men) OR lgbtq):ab,ti)

5. AND [English]/

Supplementary Figure 1. Flow chart of study selection.



Supplementary Figure 2. Study durations of the included primary studies. Figure shows the duration of studies on the X-axis (by bins, each indicating minimum up to and including the maximum duration) and the number of studies per bin on the Y-axis.



Supplementary Table 1. Characteristics of included primary studies.

	Total number of studies[1]	HIV testing and/or counselling (and/or secondary prevention)	Antiretroviral treatment (ART)
All included studies	**114**	**60**	**54**
Study design			
Experimental studies: randomised-controlled trials	13	6	7
Experimental studies: cluster-randomised-controlled trials	17	10	7
Experimental studies: non-randomised trials	9	7	2
Quasi-experimental studies: pre-post intervention studies, time series analyses	26	16	11
Observational comparison studies: prospective or retrospective cohort studies	36	15	21
Observational comparison studies: cross-sectional studies	11	6	6
Geographical region			
Eastern and Southern Africa	79	42	7
Western and Central Europe and North America	13	7	7
Southeast Asia and the Pacific	11	6	6
West and Central Africa	5	3	2
Eastern Europe and Central Asia	4	2	2
Health service area			
Maternal and child healthcare	28	16	13
Tuberculosis	16	6	10
Primary healthcare	14	5	9
Family planning	16	14	2
Sexual and reproductive health and STIs	13	10	3
Substance use therapy	9	4	6
Non-communicable diseases	5	2	3
Mental health	5	0	5
Viral hepatitis	3	2	1
HPV/cervical cancer	3	1	2
Target population			
General population or PLHIV within the general population (*e.g.,* HIV/TB co-infected people)	50	26	24
Women and/or children	40	22	19
Adolescents	6	4	2
Men who have sex with men (MSM)	4	3	1
Transgender people	0	0	0

Supplementary Table 1. Characteristics of included primary studies. (*continued*)

	Total number of studies[1]	HIV testing and/or counselling (and/or secondary prevention)	Antiretroviral treatment (ART)
Sex workers	2	0	2
People who inject drugs (PWID)	8	4	5
Prisoners and incarcerated people	1	1	0
Migrants and displaced people	1	0	1
Direction of integration			
HIV services into non-HIV programmes (including broader primary healthcare programmes)	67	46	21
Non-HIV services into HIV programmes	36	9	29
Bi-directional integration (or newly set-up services)	9	5	4
Healthcare setting			
Hospital(s), outpatient clinic(s), emergency clinic(s)	22	12	10
Local public health clinic(s)	51	22	30
Community-level	20	10	11
Multiple settings, other type(s) of setting(s)	19	16	3
Urban/rural			
Urban	38	21	18
Semi-urban	7	3	4
Rural	25	13	13
Mixed	29	20	9
Unknown	13	3	10

Supplementary Table 2. Characteristics of studies that evaluated outcomes of HIV services integration with other health services.

Author(s) and year of publication	HIV services integration area	Target population	Location	Study period	Study design
Akinleye *et al.* (2017) [34]	Maternal and child healthcare	Pregnant women and children below five years	Nigeria (Benue State)	2014	Cross-sectional study
Akker *et al.* (2012) [35]	Maternal and child healthcare, family planning, SRH and STIs	Women attending reproductive health services	Malawi (Thyolo)	2005-10	Pre-post study
Aliyu *et al.* (2016) [50]	Maternal and child healthcare	HIV-positive pregnant women presenting for antenatal care	Nigeria (Niger State)	2013-14	Randomized controlled trial
Ameh *et al.* (2017) [61]	NCDs	PLHIV accessing HIV care	South Africa (Bushbuckridge)	2011-13	Pre-post study (controlled interrupted time-series)
Ansa *et al.* (2012) [72]	Tuberculosis	TB-positive people already accessing TB services	Ghana (Eastern region)	2006-08	Pre-post study
Bailey *et al.* (2017) [83]	Maternal and child healthcare	Parents and male infants	Kenya (Homa Bay County)	2014-16	Non-randomised trial
Bergmann *et al.* (2017) [94]	Maternal and child healthcare; nutrition	HIV-exposed infants under five years of age	Malawi, Mozambique	2011-13	Pre-post intervention study
Bindoria *et al.* (2014) [105]	Primary healthcare	Pregnant women	India (Maharashtra)	2010-12	Pre-post study
Broughton *et al.* (2016) [116]	Primary healthcare; non-communicable diseases	PLHIV	Uganda (Mityana and Nakaseke)	2013-14	Pre-post intervention study (difference-in-difference)

Intervention(s), comparison(s)	Healthcare setting	Sample size	Outcome measures
Integration of HIV testing and PMTCT services into MCH weeks (mainly ANC provision)	Community-level (rural)	50,253 (at multiple sites)	(1) New HIV cases identified (2) Linkage to PMTCT (3) Service uptake
Integration of PMTCT into MCH, family planning and SRH services	Local public health clinic(s) (unknown)	53,330 (at multiple sites)	(1) Uptake of SRH, antenatal services (2) HIV incidence among infants (3) Utilisation of PMTCT services
Integration of HIV testing and counselling, CD4 testing, PMTCT, infant feeding, home-based primary care and early infant HIV testing at primary and secondary level healthcare facilities	Local public health clinic(s) (rural)	369 (at 12 sites)	(1) ART adherence (2) Retention in care
Integration of chronic disease management into ART programmes at primary healthcare clinics	Local public health clinic(s) (rural)	870 (at 21 sites)	(1) Control of CD4 counts (2) Control of hypertension
Integration of collaborative HIV/TB activities into existing TB services through one-stop-shop, partially integrated site or referral site	Hospital(s) (urban, rural)	1,330 (at 3 sites)	(1) TB health outcomes (2) Retention in care
Integration of HIV screening and community-level early infant male circumcision (EIMC) promotion and provision into MCH services	Community-level (urban, rural)	2,117 (at 16 sites)	(1) EIMC acceptability (2) EIMC uptake
Integration of HIV testing, PMTCT and nutrition service delivery into one-stop-shops with additional innovative healthcare components (*e.g.,* male motivators, SMS services)	Multiple settings (unknown)	N/A (at multiple sites)	(1) Numbers of lives saved, (2) Infections averted (3) Undernutrition cases cured (4) Cost-effectiveness (5) Enrolment in ART programmes
Integration of HIV screening into primary healthcare clinics providing antenatal services and linkage to ART delivery programmes	Local public health clinic(s) (rural)	105,650 (at 36 sites)	(1) Feasibility (2) Relative benefits (3) Incremental cost-effectiveness ratio
Integration of a chronic disease care model into ART programmes	Local public health clinic(s) (rural)	102 (at 3 sites	(1) ART adherence (2) CD4 counts (3) Incremental cost-effectiveness ratio

Supplementary Table 2. Characteristics of studies that evaluated outcomes of HIV services integration with other health services. (*continued*)

Author(s) and year of publication	HIV services integration area	Target population	Location	Study period	Study design
Brunie *et al.* (2016) [127]	Family planning	General population accessing family planning services	Uganda	2012-13	Cluster-randomised-controlled study
Brunie *et al.* (2017) [36]	Family planning	General population accessing family planning services	Uganda	2012-13	Cluster-randomised-controlled study
Busza *et al.* (2019) [41]	Mental health; SRH and STIs; PrEP	Female sex workers	Zimbabwe	2014-16	Randomised-controlled trial
Carrico *et al.* (2019) [42]	Mental health	PLHIV who fall under MSM and/or PWID	USA (San Francisco)	2013-17	Randomised-controlled trial
Chan *et al.* (2010) [43]	Primary healthcare	PLHIV registered for ART services	Malawi (Zomba District)	2008	Retrospective cohort study
Chan *et al.* (2016) [44]	Maternal and child healthcare; PMTCT	Pregnant women seeking ANC at primary health facilities	Malawi (Zomba District)	2011-12	Cohort study
Chen *et al.* (2020) [140]	Family planning	Women visiting routine HIV care and treatment	Kenya	2016	Cross-sectional study
Church *et al.* (2015) [45]	SRH and STIs; family planning	Female (of reproductive age) and male (all ages) HIV service clients	Eswatini (Manzini)	2009	Non-randomised trial

Intervention(s), comparison(s)	Healthcare setting	Sample size	Outcome measures
Integration of HIV testing and counselling into existing family planning services	Community-level (rural)	137 (at 1 site)	(1) Feasibility (2) Acceptability (3) Quality of care
Integration of HIV testing and counselling into existing family planning services	Community-level (rural)	256 (at 1 site)	(1) Feasibility (2) Acceptability (3) Uptake of HIV and FP services (4) Time spent on healthcare provision
Integration of HIV testing, ART, adherence counselling, PrEP, psychosocial support, into existing SRH services (SAPPH-IRe trial, Sisters with a Voice)	Community-level (semi-urban)	8,231 (at 28 sites)	(1) HIV-tests performed (2) Number of new HIV-cases diagnosed (3) Programme implementation fidelity
Integration of positive affect intervention or attention-control programmes into ART adherence programmes, financial incentives for abstinence	Community-level (urban)	110 (at 1 site)	(1) HIV viral load at 6, 12 and 15 months (2) Risk of unsuppressed HIV RNA (>200 copies/mL) over 15 months (3) Positive affect, self-reported frequency of stimulant use at 6 and 12 months
Integration of ART services into broader basic primary care clinics – decentralised model	Local public health clinic(s) (rural)	8,093 (at 24 sites)	(1) (Equity in) access to HIV services (2) ART adherence (3) AIDS-related mortality
Integration of multi-disease testing, ANC into HIV pogrammes (HIV testing and counselling, ART provision)	Local public health clinic(s) (rural)	10,528 (at 23 sites)	(1) ART uptake rates (2) Retention rates
Integration of family planning services into HIV clinics	Local public health clinic(s) (mixed)	(at 108 sites)	(1) Volume of integrated family planning services into HIV services (2) Uptake of contraceptives
Integration of different SRH and family planning delivery models into HIV care	Local public health clinic(s) (semi-urban)	602 (at 4 clinics)	(1) Unmet family planning service needs

Supplementary Table 2. Characteristics of studies that evaluated outcomes of HIV services integration with other health services. (*continued*)

Author(s) and year of publication	HIV services integration area	Target population	Location	Study period	Study design
Ciampa *et al.* (2011) [46]	Maternal and child healthcare	HIV-positive pregnant women and/or women with young infants presenting at MCH services	Mozambique (Zambezia Province)	2009-10	Cohort Study
Click *et al.* (2012) [47]	Tuberculosis	Children registered at TB clinics	Ethiopia	2007-09	Pre-post study
Coleman *et al.* (2012) [48]	Mental health	PLHIV: HIV patients suffering from depression	USA (Boston)	2004-10	Pre-post intervention study
Conradie *et al.* (2013) [49]	Tuberculosis	HIV/TB co-infected patients presenting at ART clinics	South Africa (Breede Valley)	2009-10	Retrospective cohort study
Criniti *et al.* (2011) [51]	Family planning	Women visiting urban family planning and adult HIV care clinic in the same university system	USA (Philadelphia, Pennsylvania)	2007-09	Cohort study
Deo *et al.* (2012) [52]	Primary healthcare	Outpatient department patients	Zambia (Lusaka)	2008-09	Prospective cohort study
De la Flor *et al.* (2017) [79]	Viral hepatitis	Prisoners and incarcerated people: inmates entering jail	USA (Dallas, Texas)	2015-16	Pre-post study
Digre *et al.* (2021) [141]	SRH and STIs; PrEP	STI clinics	USA (Mississippi)	2016-18	Pre-post study
Dovel *et al.* (2020) [142]	Outpatient services	Outpatient clinics	Malawi (Central and Southern areas)	2017-18	Cluster-randomised-controlled trial

Intervention(s), comparison(s)	Healthcare setting	Sample size	Outcome measures
Integration of HIV testing of exposed infants into MCH locations	Hospital(s) (rural)	395 (at 2 sites)	(1) Retention in care of infants (2) Infant testing timing
Integration of HIV testing into TB services	Multiple settings (mixed)	496 (at 8 sites)	(1) Documented HIV rapid test results among children
Integration of depression care into ART programmes	Hospital(s) (unknown)	124 (at 1 site)	(1) Depression score (2) HIV viral loads and CD4 counts (3) Antidepressant prescription
Integration of TB care into ART services at infectious disease clinic	Local public health clinic(s) (unknown)	100 (at 1 site)	(1) TB treatment completion (2) TB treatment success (3) TB mortality
Integration of routine HIV testing and counselling into family planning services with gynaecologic and prenatal care services and psychosocial support	Hospital(s) (urban)	2,185 (at 1 site)	(1) Percentage of patients with HIV test in the last 12 months (2) Testing acceptance rate (3) New HIV cases identified (4) Feasibility and Acceptability
Integration of HIV testing and treatment services into outpatient care at a primary care facility	Outpatient-clinic(s) (urban)	80 (at 1 site)	(1) Patient waiting times
Opt-out testing for HIV into routine HCV testing during intake	Other (urban)	3,155 (at 1 site)	(1) Service uptake (2) New HIV/HCV cases identified
Integration of HIV testing and PrEP for partners at STI clinics	Local public health clinic(s) (urban)	(at 3 sites)	(1) Uptake of HIV services (2) Marginal costs per case
Integration of HIV self-testing into outpatient clinics	Local public health clinic(s) and hospitals (mixed)	5,885 (at 15 sites)	(1) Uptake HIV testing (2) Costs

Supplementary Table 2. Characteristics of studies that evaluated outcomes of HIV services integration with other health services. (*continued*)

Author(s) and year of publication	HIV services integration area	Target population	Location	Study period	Study design
Ezeanolue *et al.* (2015) [53]	Maternal and child healthcare; PMTCT	Women and infants who are HIV-positive or HIV-exposed	USA (Las Vegas, Nevada)	2007-12	Retrospective cohort study
Geelhoed *et al.* (2013) [54]	Maternal and child healthcare; PMTCT	HIV-positive women and their HIV-exposed infants	Mozambique (Tete Province)	2009-10	Cluster-randomised-controlled trial
Gilbert *et al.* (2018) [55]	Viral hepatitis; treatment for substance use disorders	HIV/HCV co-infected PWID: people using heroin or other opioids and their HIV/HCV-negative injection partners	Kazakhstan (Almaty)	2009-13	Randomised-controlled trial
Golovaty *et al.* (2018) [56]	Non-communicable diseases	General population: adult inhabitants of rural community	South Africa (KwaZulu-Natal)	2012-15	Cross-sectional study nested in prospective cohort study
Greig *et al.* (2012) [57]	Primary healthcare; tuberculosis; SRH and STIs	HIV-positive migrant and refugee patients on ART	Sub-Saharan Africa (9 countries)	2003-10	Retrospective cohort study
Guillaine *et al.* (2017) [58]	Maternal and child healthcare	HIV-positive mothers and their infants	Rwanda (Southern Kayonza and Kirehe Districts)	2012-13	Retrospective cohort study
Hankin *et al.* (2016) [59]	Primary healthcare	General population	USA	2008-13	Retrospective cohort study
Haraka *et al.* (2015) [60]	Tuberculosis	HIV-positive patients without prior history of TB	Tanzania (Ifakara, Morogoro)	2005-13	Pre-post study
Harding *et al.* (2012) [62]	Primary healthcare; non-communicable diseases	PLHIV presenting with pain symptoms	Tanzania (North East region)	2009-10	Prospective longitudinal controlled-intervention study

Intervention(s), comparison(s)	Healthcare setting	Sample size	Outcome measures
Integration of prenatal care and in-facility delivery services into HIV testing and treatment services	Local public health clinic(s) (urban)	131 (at 1 site)	(1) Adequacy of prenatal care (2) Appropriate ART use (3) caesarean section uptake (4) Mother-to-child HIV transmission rate
Reorganising HIV testing and counselling and ART provision and MCH services into one-stop shops	Local public health clinic(s) (rural)	2,559 (at 6 sites)	(1) Feasibility (2) Utilisation rates (3) Retention rates (4) Service Quality
Five-session couple-based HIV/HCV and overdose prevention intervention	Community-level (urban)	479 (at 1 site)	(1) Non-fatal overdose rates, heroin/opioid injection use (2) Drug treatment attendance rates, naloxone use (3) Overdose death rates
Integration of NCD screening and linkage to HIV care into home-based HIV testing and counselling	Community-level (rural)	570 (in one community)	(1) Incremental costs (2) Efficiency of utilised resources
Integration of ART programmes into general healthcare clinics (through Medicines Sans Frontiers services)	Community-level (rural)	15,403 (at 17 sites)	(1) AIDS-related mortality (2) Risk of loss to follow-up
Integration of maternal and child health services for HIV-positive women and their children – bi-directional	Local public health clinic(s) (rural)	185 (at 2 clinics)	(1) Service utilisation (2) Retention rates (3) Linkage to routine services (4) Clinical outcomes
Integration of non-targeted routine HIV screening into emergency triage process	Emergency clinic(s) (urban)	~120,000 (at 1 site)	(1) Number of HIV tests (2) New diagnoses (3) Feasibility
Integration of one-stop-shop TB testing and treatment into ART programmes (Kilombero Ulanga Antiretroviral Cohort, KIULARCO)	Community-level (rural)	5,123	(1) Incident TB cases among HIV patients (2) TB ascertainment
Integration of HIV outpatient palliative care into ART provision services	Outpatient-clinic(s) (unknown)	128 (at 1 site)	(1) Odds of reporting pain (2) Treatment success

Supplementary Table 2. Characteristics of studies that evaluated outcomes of HIV services integration with other health services. (*continued*)

Author(s) and year of publication	HIV services integration area	Target population	Location	Study period	Study design
Hemmer *et al.* (2015) [63]	Tuberculosis	TB and HIV patients	Cameroon (Littoral Province)	2007-09	Pre-post study
Herce *et al.* (2018) [64]	Tuberculosis	TB-positive PLHIV	Zambia (Lusaka)	2011-12	Pre-post study
Herlihy *et al.* (2015) [65]	Maternal and child healthcare	HIV-positive pregnant women visiting governmental ANC clinics	Zambia (Southern Province)	2011-13	Cohort study
Hermans *et al.* (2012) [66]	Tuberculosis	PLHIV presenting at large HIV clinic	Uganda (Kampala)	2007-09	Pre-post study
Hewett *et al.* (2016) [67]	Family planning; SRH and STIs	Adults accessing family planning, HIV testing and/or VMMC services	Zambia (Lusaka and Chipata)	2013-15	Randomised trial
Hung *et al.* (2016) [68]	Primary healthcare; treatment for substance use disorders	HIV-positive PWID and HIV-negative PWID	Vietnam (Ho Chi Minh City)	2013-14	Pre-post study
Jacobson *et al.* (2015) [69]	Tuberculosis	HIV/TB co-infected patients initiating treatment for TB	South Africa (KwaZulu-Natal)	2012-13	Retrospective cohort study
Johns *et al.* (2017) [70]	Primary healthcare	Population of Chernigiv, Northern Ukraine	Ukraine (Chernigiv Province)	2013-15	Pre-post study (difference-in-difference)
Kanyuuru *et al.* (2015) [71]	Maternal and child healthcare	Pregnant women and their infants	Kenya (Bondo District)	2010-12	Pre-post intervention study
Katz *et al.* (2016) [73]	SRH and STIs	Men who have sex with men presenting with STIs	USA (Washington)	2010-14	Cohort study

Intervention(s), comparison(s)	Healthcare setting	Sample size	Outcome measures
Integration of HIV services into national TB programmes	Local public health clinic(s) (urban, rural)	~16,000 (at 30 sites)	(1) HIV testing rates (2) Treatment prescribing rate for TB/HIV-patients (3) Mortality of newly recruited TB patients
Integration of HIV testing and treatment into one-stop-shop TB treatment and care	Local public health clinic(s) (urban)	473 (at 2 sites)	(1) Linkage to HIV care (2) Early ART uptake (3) TB treatment success
Integration of PMTCT into MCH services with community-based follow-up	Local public health clinic(s) (rural)	1,134 (at 1 site)	(1) CD4-testing rates (2) Proportion ART-eligible (3) HIV-exposed infant testing rates at 6 months
Integration of TB testing and treatment services into one-stop-shop ART programmes and outpatient care	Local public health clinic(s) (urban)	712 (at 1 site)	(1) ART initiation (2) CD4 counts (3) TB treatment success
Integration of HIV testing and counselling with SRH services, family planning, VMMC, cervical cancer screening – bi-directional models with referral to full integration	Local public health clinic(s) (urban)	3,963 (at 3 sites)	(1) Uptake of services (2) Cost-effectiveness
Integration of co-located voluntary HIV counselling and testing, treatment and methadone maintenance therapy using different integration models	Outpatient-clinic(s) (urban)	8,228 (at 7 sites)	(1) Linkage (2) ART initiation (3) Adherence
Integration of one-stop-shop HIV and TB treatment and care into primary health clinics or referral from HIV clinics – decentralised approach	Local public health clinic(s) (rural)	657	(1) TB treatment success (2) Retention in care
Integration of HIV testing and counselling into primary healthcare	Outpatient-clinic(s) (urban, rural)	86,000 (at 20 sites)	(1) Incremental costs (2) Number of newly detected HIV cases
Integration of MCH, HIV and immunisation services into routine community programmes	Local public health clinic(s) (unknown)	People from 329 villages	(1) Uptake of prenatal services (2) Uptake of HIV testing (3) Access to care
Integration of HIV testing and counselling for MSM with early syphilis, gonorrhoea or chlamydial infection and partner services into STI services in state hospitals	Outpatient-clinic(s) (urban)	8,133 (at multiple sites)	(1) HIV-testing rates for patients, partner services (2) New HIV cases identified (3) Proportion of new cases with concurrent STI diagnosis

Supplementary Table 2. Characteristics of studies that evaluated outcomes of HIV services integration with other health services. (*continued*)

Author(s) and year of publication	HIV services integration area	Target population	Location	Study period	Study design
Kerschberger *et al.* (2012) [74]	Tuberculosis	HIV/TB co-infected patients registered for TB treatment	South Africa (Cape Town)	2008-09	Pre-post study
Kimani *et al.* (2015) [75]	Family planning	Women receiving postnatal care	Kenya (Eastern Kenya)	2010	Non-randomised trial
Kinyua *et al.* (2019) [76]	Maternal and child healthcare	HIV-positive mothers and their HIV-exposed infants	Kenya (Kwale County)	2013-16	Pre-post intervention study
Kosgei *et al.* (2011) [77]	Family planning	HIV-positive women	Kenya (Western Kenya)	2005-09	Retrospective cohort study
Kufa *et al.* (2018) [78]	Tuberculosis	People seeking HIV and/or TB testing or treatment services	South Africa (Ekurhuleni District)	2010-13	Cluster-randomised trial
Lambdin *et al.* (2013) [80]	Primary healthcare	ART-naive PLHIV	Mozambique (Manica and Sofala Provinces)	2006-08	Retrospective cohort study
Leon *et al.* (2010) [81]	SRH and STIs	People presenting with STI(s)	South Africa (Cape Town)	2007	Cluster-randomised-controlled trial
Van Lettow *et al.* (2014) [82]	Maternal and child healthcare	Newly identified HIV-positive women	Malawi	2012	Cohort study
Mansoor *et al.* (2019) [84]	Family planning; PrEP	HIV-negative women	South Africa (KwaZulu-Natal)	2012-14	Randomised-controlled trial
Mantell *et al.* (2017) [85]	SRH and STIs	People seeking SRH care	South Africa (Cape Town)	2006-11	Cluster-randomised-controlled trial

Intervention(s), comparison(s)	Healthcare setting	Sample size	Outcome measures
Integration of one-stop-shop HIV and TB treatment and care into primary healthcare clinic	Local public health clinic(s) (semi-urban)	188 (at 1 site)	(1) ART uptake (2) Time to ART treatment initiation
Integration of HIV and family planning services into postnatal care at MCH clinics (Integra Initiative)	Local public health clinic(s) (semi-urban)	1,204	(1) Health services uptake (2) Effectiveness of integration
Integration of nutrition assessment, counselling and support into PMTCT services at HIV clinics through Ministry of Health programme	Local public health clinic(s) (rural)	837 (at 16 sites)	(1) Uptake of nutrition counselling and support (2) Retention of mother-baby-pairs
Integration of family planning into routine HIV services	Local public health clinic(s) (unknown)	1,031	(1) Uptake of family planning (2) Pregnancy outcomes
Integration of HIV and TB services into primary healthcare clinics	Local public health clinic(s) (unknown)	4,182 (at 18 sites)	(1) Incidence of hospitalisation and deaths among newly diagnosed HIV patients (2) Proportion of HIV patients newly diagnosed with TB
Integration of HIV care and treatment into primary healthcare	Local public health clinic(s) (urban, rural)	11,775 (at 17 sites)	(1) Attrition during early and late patient follow-up
Integration of provider-initiated (opt-out) HIV testing and counselling into primary healthcare clinics mainly offering SRH services	Local public health clinic(s) (urban)	9,080 (at 21 sites)	(1) Uptake of HIV testing and counselling (2) Consistency of testing across clinics
Integration of ART and ANC into MCH clinics (stand-alone, fully integrated in one of the clinics or referrals from MCH clinic to ART clinic)	Multiple settings (urban, rural)	41,203 (at 141 sites)	(1) Proportion of women tested for HIV (2) Retention rates
Integration of PrEP into family planning services (CAPRISA 004 trial)	Local public health clinic(s) (urban, rural)	372 (at 2 sites)	(1) Adherence rates (2) Retention rates, number of returned used gel applicators (3) HIV incidence rates
Integration of SRH into public sector HIV care services	Local public health clinic(s) (urban)	214 (at 1 site)	(1) Adherence to safer sex guidelines (2) Use of contraceptives among HIV-positive clients

Supplementary Table 2. Characteristics of studies that evaluated outcomes of HIV services integration with other health services. (*continued*)

Author(s) and year of publication	HIV services integration area	Target population	Location	Study period	Study design
Matulionyte *et al.* (2019) [86]	Other infectious diseases	General population: hospitalised patients and outpatients	Lithuania (Vilnius)	2010-14	Retrospective cohort study
Mavhu *et al.* (2020) [87]	SRH and STIs; mental health	HIV-positive adolescent girls and young women	Zimbabwe (Bindura and Shamva)	2016-17	Cluster-randomised-controlled study
Mayhew *et al.* (2017) [88]	SRH and STIs; other infectious diseases	Users of SRH services	Kenya	2009-13	Non-randomised trial
McBain *et al.* (2017) [89]	Primary healthcare	Newly enrolled HIV-positive patients	Malawi (Neno District)	2013-14	Population-based retrospective analysis
Mendelsohn *et al.* (2018) [90]	SRH and STIs; family planning	Adolescents visiting an integrated adolescent youth centre clinic or non-integrated public clinic	South Africa (Cape Town)	2015	Cohort study
Mgbemena *et al.* (2015) [91]	Primary healthcare	PLHIV with chronic pain	USA	2012-13	Prospective cohort study
Miller *et al.* (2018) [92]	Treatment for substance use disorders; mental health	HIV-infected PWID (with 1 uninfected injection partner) and their partners	Ukraine, Indonesia, Vietnam	2015-18	Randomised-controlled trial
Momplaisir *et al.* (2013) [93]	Primary healthcare; non-communicable diseases	HIV-positive and -negative patients seeking care in HIV-integrated, specialised HIV or general internal medicine facilities	USA (Pennsylvania)	2010-11	Cross-sectional study
Mudzengi *et al.* (2017) [95]	Tuberculosis	Adults living with TB and/or HIV	South Africa (Ekurhuleni)	2013	Cross-sectional study

Intervention(s), comparison(s)	Healthcare setting	Sample size	Outcome measures
Integration of rapid HIV testing into infectious disease units at hopitals	Hospital(s) (urban)	4,911 (at 1 site)	(1) HIV prevalence (2) Cost-effectiveness (3) Clinical effectiveness (4) Feasibility
Integration of adherence support, SRH, and mental health services into ART programmes (Zvandiri project)	Local public health clinic(s) (urban, rural)	496 (at 16 sites)	(1) ART adherence (2) Viral suppression
Integration of HIV testing and counselling into SRH and MCH services (Integra Initiative)	Local public health clinic(s) (urban, rural)	8,841 (at 17 sites)	(1) Uptake of services (2) Workload of healthcare staff (3) Contextual factors influencing sustainability of integration
Integration of HIV care and surveillance into social, community, and nutritional support programs	Local public health clinic(s) (urban, rural)	129,938 (at 682 sites)	(1) Survival rate (2) Cost for care (3) QALYs gained
Integration of sexual and reproductive health services into educational and recreational programmes	Local public health clinic(s) (urban)	2,235 (at 2 sites)	(1) SRH service uptake (2) HIV-counselling and testing uptake (3) Contraception use rates and adherence (4) HIV-case detection rates
Integration of chronic pain relief therapy into a primary care HIV clinic setting	Local public health clinic(s) (unknown)	27 (at 1 site)	(1) Pain score reduction (2) Costs
Integration of systems navigation, psychosocial counselling, and CD4-independent ART-initiation into ART and opioid replacement therapy (HPTN 074 Vanguard Trial)	Community-level (urban)	502 (at multiple sites)	(1) Retention rates (2) ART, opioid replacement therapy use rates, Viral suppression rates (3) Mortality (4) Injection Partner HIV incidence
Integration of colourectal and breast cancer screening into HIV- and general internal medicine clinics	Hospital(s) (urban)	762 (at 3 sites)	(1) Odds of getting cancer screening
Integration of TB-HIV services into public primary health care clinics (MERGE trial)	Local public health clinic(s) (urban, rural)	463 (at 18 sites)	(1) Costs of care

Supplementary Table 2. Characteristics of studies that evaluated outcomes of HIV services integration with other health services. (*continued*)

Author(s) and year of publication	HIV services integration area	Target population	Location	Study period	Study design
Musarandega *et al.* (2018) [96]	Maternal and child healthcare; PMTCT	Pregnant women	Zimbabwe (Hurungwe District)	2014-15	Pre-post study
Myer *et al.* (2018) [97]	Maternal and child healthcare; PMTCT	HIV-positive women eligible for ART in pregnancy, presenting with their infant(s) after delivery	South Africa (Cape Town)	2013-14	Randomised-controlled trial
Nance *et al.* (2017) [98]	Maternal and child healthcare	HIV-infected postpartum women and their children	Tanzania (Shinyanga Region)	2014-15	Cluster-randomised-controlled trial
Ndagijimana *et al.* (2015) [99]	Tuberculosis	Communities from Kicukiro and Rulindo Districts	Rwanda (Kicukiro and Rulindo Districts)	2006-10	Cohort study
Ngo *et al.* (2013) [100]	SRH and STIs; family planning	Adolescents (15-24) visiting integrated youth-friendly HIV/SRH services	Vietnam (five provinces)	2006-09	Pre-post study
Nsubuga-Nyombi *et al.* (2019) [101]	Maternal and child healthcare; PMTCT	HIV-positive mothers and their HIV-exposed infants visiting one of 22 facilities	Uganda (Ninja, Kisoro, Manafwa, Namutumba, Ntungamo, and Tororo)	2013-15	Pre-post study
Obure *et al.* (2015) [102]	SRH and STIs	Patients visiting one of 40 non-government and/or public health facilities	Kenya, Eswatini	2010-11	Non-randomised trial
Obure, Sweeney *et al.* (2016) [103]	SRH and STIs	Patients visiting one of 40 non-government and/or public health facilities	Kenya, Eswatini	2008-09 & 2010-11	Non-randomised trial

Intervention(s), comparison(s)	Healthcare setting	Sample size	Outcome measures
Integration of provider-initiated HIV testing into infant health services	Local public health clinic(s) (urban, rural)	12,556 (at 33 sites)	(1) Women tested for HIV (2) Infants tested for HIV (3) Proportion of HIV-infected infants
Integration of ART into postnatal MCH services	Local public health clinic(s) (urban)	471 (at 1 site)	(1) ART retention rate (2) Viral suppression rate (3) Transmission rate, child mortality, breastfeeding duration
Integration of CHW-linkage, ART-adherence counselling, tracing and provision of birth planning tools into PMTCT facilities	Community-level (urban, rural)	1,830 (at 32 sites)	(1) Retention in care at 60, 120 days (2) ART initiation rates, timing (3) ART adherence rate
Integration of HIV and TB testing, treatment and care	Community-level (urban, rural)	1,695 (at 12 sites)	(1) Utility (2) Quality (3) TB health outcomes
Integration of HIV-testing, outreach activities, referral and counselling into SRH and family planning services (gynaecological check-ups, STI, family planning and ANC services)	Outpatient-clinic(s) (urban)	1,314 (at multiple sites)	(1) Testing rates (2) Attitudes toward testing (3) HIV knowledge and risk perceptions (4) HIV-related risk behaviours
Integration of nutrition into PMTCT services	Local public health clinic(s) (urban, rural)	~2,000 (at 22 sites)	(1) Infant and young children feeding-counselling rate, adherence (2) Service utilisation rates (3) HIV-exposed infants alive at 18 months, infection rate
Integration of HIV counselling, testing, treatment and care into family planning, ANC, PNC, cervical cancer screening and STI screening services (Integra Initiative)	Multiple settings (urban, rural)	11,471 (at 40 sites)	(1) Costs per visit
Integration of HIV counselling, testing, treatment and care into family planning, ANC, PNC, cervical cancer screening and STI screening services (Integra Initiative)	Multiple settings (urban, rural)	11,471 (at 40 sites)	(1) Healthcare quality (2) Technical efficiency of integration

Supplementary Table 2. Characteristics of studies that evaluated outcomes of HIV services integration with other health services. (*continued*)

Author(s) and year of publication	HIV services integration area	Target population	Location	Study period	Study design
Obure, Jacobs *et al.* (2016) [104]	SRH and STIs	Patients visiting one of 40 non-government and/or public health facilities	Kenya, Eswatini	2008-11	Non-randomised trial
Owiti *et al.* (2015) [106]	Tuberculosis	HIV and/or TB patients presenting at one of 17 rural public health facilities	Kenya (Western region)	2010-12	Pre-post cohort study
Palma *et al.* (2018) [107]	Non-communicable diseases	PLHIV at risk of cardiovascular diseases	Eswatini (Manzini)	2015-16	Randomised-controlled trial
Rawat *et al.* (2018) [108]	Non-communicable diseases	PLHIV receiving ART in primary healthcare clinics	South Africa (Free State Province)	2009-13	Quasi-experimental study
Reza-Paul *et al.* (2019) [109]	SRH and STIs; HPV, cervical cancer	Female sex workers visiting a community-based clinic or partner private hospital	India (Mysore)	2013-16	Cohort study
Rosen *et al.* (2021) [145]	Mental health	Adolescents living with HIV	Zambia (Central and Eastern Provinces)	2017	Prospective cohort study
Van Rie *et al.* (2014) [110]	Tuberculosis	TB patients	Democratic Republic of Congo (Kinshasa city)	2007-09	Prospective cohort study
Roberts *el al.* (2019) [111]	Family planning; Maternal and child healthcare; SRH and STIs; PrEP	Adolescent girls and young women visiting family planning and MCH clinics	Kenya (Western counties)	2017-18	Cross-sectional study
Rodkjaer *et al.* (2017) [112]	Mental health	PLHIV: HIV patients with psychological challenges	Denmark (Aarhus)	N/A	Randomised-controlled trial

Intervention(s), comparison(s)	Healthcare setting	Sample size	Outcome measures
Integration of HIV counselling, testing, treatment and care into family planning, ANC, PNC, cervical cancer screening and STI screening services (Integra Initiative)	Multiple settings (urban, rural)	11,471 (at 40 sites)	(1) Technical, allocative efficiency (2) Service-specific economies of scale
Integration of HIV into TB-services using three models: 1) one-stop-shop 2) HIV+TB and non-HIV TB clinics and 3) under-one-roof TB/HIV clinics with separate staff for each	Local public health clinic(s) (rural)	824 (at 17 sites)	(1) Uptake of ART (2) Time to ART initiation (3) TB treatment success among co-infected patients
Integration of cardiovascular disease screening into HIV clinic visits	Hospital(s) (urban)	172 (at 10 sites)	Impact of screening on: (1) patient flow (2) HIV service delivery
Integration of HIV services into primary health care	Local public health clinic(s) (mixed)	57,958 (at 131 sites)	(1) Number of patients receiving ART (2) Number of new diabetes and hypertension patients
Integration of SRH (STI and cervical cancer testing/treatment) and HIV services (testing/counselling) into general population SRH services (DIFFER study)	Community-level (urban)	873 (at multiple sites)	(1) SRH service uptake (condom use, STI and cervical cancer testing/ treatment rates) (2) Proportion of female sex workers accessing services (3) HIV-testing rates
Integration of psychosocial, economic strengthening, and clinical services to HIV- affected households for adolescents (Zambia Family (ZAMFAM) Project)	Community-level (mixed)	494 house-holds	(1) Self-reported health status (2) HIV related stigma
Integration of nurse-centred TB and HIV services into a primary health clinic.	Local public health clinic(s) (unknown)	4,463 (at multiple sites)	(1) ART uptake/initiation (2) CD4 cell counts (3) TB-related mortality
Integration of PrEP into family planning and mother-child health services (PrIYA programme, DREAMS Innovation Challenge)	Local public health clinic(s) (semi-urban)	24,005 (at 16 sites)	(1) Average cost per patient month of supplied PrEP unsing different protocols (2) Unit costs and volume
Integration of a mental health intervention (mind-body approach) into care for HIV patients	Hospital(s) (urban)	29 (at 1 site)	(1) Feasibility (2) Change of depression risk (3) Level of coping self-efficacy, stress, and personal growth

Supplementary Table 2. Characteristics of studies that evaluated outcomes of HIV services integration with other health services. (*continued*)

Author(s) and year of publication	HIV services integration area	Target population	Location	Study period	Study design
Rosenberg *et al.* (2010) [113]	Viral hepatitis; mental health	General population; PWID – people from ethnic minorities attending mental health services	USA (Baltimore)	2006-08	Randomised-controlled trial
Rosenberg *et al.* (2018) [114]	SRH and STIs	Adolescent girls and young women	Malawi (Lilongwe)	2016-17	Cohort study
Rutaremwa *et al.* (2016) [115]	Family planning; SRH and STIs	Women (15+ years) using integrated or unintegrated HIV and SRH services during pregnancy and delivery of last child	Uganda	2011	Cross-sectional study
Schulz *et al.* (2013) [117]	Tuberculosis	TB/HIV co-infected patients presenting at TB hospital	South Africa (Western Cape)	2009-11	Cohort study
Shade *et al.* (2013) [118]	Family planning	Women attending HIV and/or family planning services	Kenya (Nyanza)		Cluster-randomised-controlled trial
Shade *et al.* (2020) [143]	NCDs	General population; PLHIV	Uganda	2015-16	Retrospective cohort study
Shenoi *et al.* (2017) [119]	Tuberculosis	Population with high burden of HIV and TB	South Africa (Msinga, KwaZulu-Natal)	2010-12	Retrospective cohort study
Shin *et al.* (2020) [146]	Maternal and child healthcare	Women, Children	India (Andhra Pradesh)	2014-16	2x2 factorial intervention trial
Siapka *et al.* (2017) [120]	Family planning	General population	Kenya	2009-11	Pre-post intervention study
Simeone *et al.* (2017) [121]	Treatment for substance use disorders	PLHIV with substance use disorders	USA (San Francisco)	2015	Cohort study

Intervention(s), comparison(s)	Healthcare setting	Sample size	Outcome measures
Integration of screening/testing for HIV and hepatitis, immunisation for hepatitis A and B, risk-reduction counselling, medical treatment referral and support into mental health services	Community-level (urban)	236 (at 4 sites)	(1) Cost per patient, breakdown (2) Participation, testing and immunisation rates (3) Referral (4) Knowledge and reduction in risk behaviour
Integration of previously stand-alone HIV testing, family planning, STI syndromic management and condom provision plus youth-friendly provision, peer-educators and behavioural intervention – bi-directional (Girl Power Malawi)	Local public health clinic(s) (urban)	1,000 (at 4 sites)	Uptake of (1) HIV-testing, including pre- and post-test-counselling (2) condoms (3) hormonal contraception (4) dual method contraception (5) medical STI consultations
Integration of HIV into SRH and "women" services (data from USAID Demographic and Health Surveys)	Multiple settings (urban, rural)	9,691 (at multiple sites)	(1) Service utilisation rates
Integration of ART into TB services and general HIV-care	Hospital(s) (urban)	271 (at multiple sites)	(1) TB treatment success (2) ART treatment success (CD4 counts)
Integration of family planning into HIV care and treatment clinics	Local public health clinic(s) (unknown)	4,135 (at 18 sites)	(1) Costs (2) Cost-efficiency (3) Cost-effectiveness
Integration of hypertension screening into HIV clinics for HIV-positive and HIV-negative people (SEARCH)	Community-level (rural)	2,425 (at 10 sites)	(1) Additional costs
Integration of TB intensive case finding into HIV intensive case finding and CD4 testing	Community-level (rural)	5,615 (at 322 sites)	(1) HIV testing uptake (2) CD4 cell counts (3) HIV yield (4) TB drug resistance
Integration of nutritional interventions for mother-child pairs living with HIV visiting HIV clinics	Community-level (rural)	600	(1) Body weight (2) CD4 counts
Integration of HIV services into family planning counselling and provision (Integra Initiative)	Multiple settings (mixed)	3,713 (at 24 sites)	(1) Duration of consultation (2) Staff workload
Integration of HIV-care-continuum patient monitoring and intervention-need recognition into opioid replacement therapy	Multiple settings (urban)	65 (3 sites)	(1) Retention rates (2) Viral suppression rates

Supplementary Table 2. Characteristics of studies that evaluated outcomes of HIV services integration with other health services. (*continued*)

Author(s) and year of publication	HIV services integration area	Target population	Location	Study period	Study design
Siregar *et al.* (2011) [122]	SRH and STIs	People accessing voluntary testing and counselling	Indonesia (Bandung)	2008-09	Cohort study
Solomon *et al.* (2019) [123]	Viral hepatitis; treatment for substance use disorders	PWID (and MSM)	India	2012-17	Cluster-randomised trial
Solomon *et al.* (2020) [124]	Viral hepatitis; treatment for substance use disorders	PWID; MSM	India	2013-16	Randomised-controlled trial
Stockton *et al.* (2020) [144]	Mental health	PLHIV	Malawi	2017-18	Pre-post intervention study
Sweeney *et al.* (2014) [125]	SRH and STIs	Patients visiting one of 40 non-government and/or public health facilities	Kenya, Eswatini	2010-11	Non-randomised trial
Talama *et al.* (2020) [139]	HPV, cervical cancer	Women living with HIV	Malawi (Neno)	2016-18	Pre-post intervention study
Tomlinson *et al.* (2014) [126]	Maternal and child healthcare; PMTCT	Pregnant women (17+ years) and their new-borns	South Africa (Umlazi)	2008-10	Randomised-controlled trial
Topp *et al.* (2010) [128]	Primary healthcare	Outpatient department patients	Zambia (Lusaka)	2008-09	Cross-sectional study
Topp *et al.* (2013) [129]	Primary healthcare	Outpatient department patients	Zambia (Lusaka)	2008-11	Cross-sectional study

Intervention(s), comparison(s)	Healthcare setting	Sample size	Outcome measures
Integration of voluntary testing and counselling into hospital, STI and prison clinic services compared to HIV services offered at a community clinic	Multiple settings (urban)	1,954 (at 4 sites)	(1) Service utilisation (2) Costs (3) Clinical HIV outcomes
Integration of HIV testing, prevention, and treatment into opioid replacement therapy and MSM health services	Other (urban)	12,726 (at 22 sites)	(1) Self-reported HIV testing (2) Exposure to HIV testing
Integration of HCV testing into HIV programmes (HIV testing, preventive services and linkage to ART programmes)	Other (urban)	~11,721 (at 12 sites)	(1) Self-reported HCV testing (2) HCV antibody prevalence (3) HCV treatment initiation
Integration of depression screening into routine HIV care	Local public health clinic(s) (unknown)	501 (2 sites)	(1) ART initiation (2) Retention in care (3) Viral suppression
Integration of HIV counselling, testing, treatment and care into family planning, ANC, PNC, cervical cancer screening and STI screening services (Integra Initiative)	Multiple settings (urban, rural)	11,471 (at 40 sites)	(1) Staff workload (2) Efficiency of service delivery
Integration of cervical cancer screening into a dual HIV and non- communicable disease clinic	Local public health clinic(s) (rural)	749 (at 1 site)	(1) Detected number of women with cervical cancer (2) Number of women first time screened for cervical cancer
Integration of a standard care package (PMTCT, lactation counselling, new-born care and systems navigation) into home-based MCH services	Community-level (semi-urban)	4,137 (at 30 sites)	(1) Exclusive breastfeeding rate (2) HIV-free survival at 12 weeks (3) Service utilisation (4) Infant weight-for-length z-scores at 12 weeks
Integration of ART into regular non-HIV outpatient department services	Outpatient-clinic(s) (urban)	~4,300 (at 2 sites)	(1) Acceptability (2) Uptake and adherence (3) Feasibility (4) Resource allocation
Integration of HIV services into outpatient department services in urban primary health care clinics	Outpatient-clinic(s) (urban)	~48,000 (at 12 sites)	(1) Resource and allocative efficiencies (2) Organisational advantages

Supplementary Table 2. Characteristics of studies that evaluated outcomes of HIV services integration with other health services. (*continued*)

Author(s) and year of publication	HIV services integration area	Target population	Location	Study period	Study design
Tran, Jacobs *et al.* (2012) [130]	Treatment for substance use disorders	HIV-positive drug users	Vietnam	2009	Cohort study, mathematical modelling study
Tran, Houston *et al.* (2012) [131]	Treatment for substance use disorders	HIV-positive drug users	Vietnam	2009	Cohort study
Turan *et al.* (2015) [132]	Maternal and child healthcare; PMTCT	HIV-positive pregnant women accessing ANC services	Kenya	2009-11	Randomised-controlled trial
Uebel *et al.* (2013) [133]	Primary healthcare	Patients receiving ART counselling and/or treatment	South Africa (Free State Province)	2007-08	Cohort study during a randomised-controlled trial study
Vodicka *et al.* (2017) [134]	HPV, cervical cancer	Adult women attending clinic for cervical cancer screening	Kenya (Nairobi)	2014	Cross-sectional study, qualitative study
Vodicka *et al.* (2019) [135]	HPV, cervical cancer	HIV-positive women with pre-cancerous cervical lesions	Kenya (Nairobi)	2014	Cross-sectional study
Wagner *et al.* (2021) [138]	Family planning	Serodiscordant couples	Uganda (Wakiso, Masaka, Mbale, Jinja, Rukugiri, Mbarara)	2017-19	Cluster-randomised-controlled trial
Wang *et al.* (2014) [136]	Maternal and child healthcare; PMTCT; viral hepatitis	Women visiting participating ANC clinics	China (multiple counties)	2010-13	Cluster-randomised trial
Wang *et al.* (2015) [137]	Maternal and child healthcare; other infectious diseases	Children below five years of age	Zambia (Southern Province)	2013	Cluster-randomised-controlled trial
Washington *et al.* (2015) [37]	Maternal and child healthcare; PMTCT	HIV-positive women visiting ANC clinics	Kenya (Nyanza Province)	2009-12	Cluster-randomised-controlled trial

Intervention(s), comparison(s)	Healthcare setting	Sample size	Outcome measures
Integration of ART into methadone replacement therapy (same site or different site)	Other (urban)	370 (at multiple sites)	(1) Cost per QALY gained (2) Incremental cost-effectiveness ratio
Methadone maintenance therapy integrated into ART programmes	Other (urban)	370 (at multiple sites)	(1) Health-related quality of life at baseline, 3, 6 and 9 months (2) Methadone therapy response Rates
Integration of PMTCT/ART into ANC clinics (SHAIP trial)	Local public health clinic(s) (rural)	1,172 (at 12 sites)	(1) Maternal HIV-care enrolment (2) HAART initiation rates (3) Three-month infant HIV-testing uptake
Integration of ART, HIV testing/ counselling, prevention services and monitoring into primary healthcare	Local public health clinic(s) (mixed)	9,252 (at ~200 sites)	(1) Risk of mortality (2) Coverage (3) Access
Integration of cervical cancer screening (different modalities) into HIV care clinics	Hospital(s) (urban)	148 (at 1 site)	(1) Marginal Costs per screening (2) Cost components
Integration of treatment of pre-cancerous cervical lesions into same-day HIV care	Hospital(s) (urban)	54 (at 1 site)	(1) Patient characteristics (2) Costs per procedure/ treatments, savings
Integration of family planning services into HIV clinics for serodiscordant couples (Our Choice)	Local public health clinic(s) (mixed)	189 (at 6 sites)	(1) Uptake of contraceptive methods (2) Costs
Integration of free tests for HIV, syphilis, hepatitis B and PMTCT into ANC clinics	Multiple settings (unknown)	4,529 (at 60 sites)	(1) Testing rates (2) Mother-to-child transmission rates
Integration of early infant HIV testing into an immunisation programme (diphtheria, pertussis, and tetanus vaccine) with or without operational assistance	Local public health clinic(s) (urban, rural)	~3,000 (at 60 sites)	(1) Vaccine doses distributed (2) HIV testing uptake (3) maternal re-testing for HIV
Integration of HIV services (including PMTCT) into antenatal care care clinics (SHAIP trial)	Local public health clinic(s) (rural)	1,172 (at 12 sites)	(1) Retention rates (2) ART initiation rates, timing (3) Maternal and child health outcomes

Supplementary Table 2. Characteristics of studies that evaluated outcomes of HIV services integration with other health services. (*continued*)

Author(s) and year of publication	HIV services integration area	Target population	Location	Study period	Study design
Young *et al.* (2019) [38]	Maternal and child healthcare; SRH and STIs; other infectious diseases	Women seeking MCH services in a high-volume dispensary	Kenya (Western region)	2014-15	Non-randomised trial, mathematical modelling study
Zang *et al.* (2016) [39]	Primary healthcare	Adults seeking outpatient care and screened positive for HIV	China (Guangxi)	2014-15	Modelling study based on a cluster-randomised-controlled trials
Zulliger *et al.* (2014) [40]	SRH and STIs	Pregnant women attending ANC	South Africa (Cape Town)	2011-12	Cohort study
Schackmann *et al.* (2011) [147]	Treatment for substance use disorders	HIV-positive patients with opioid-dependence	USA	2005-07	Cohort Study

Abbreviations: ANC = antenatal care; ART = antiretroviral therapy; CD4 = cluster of differentiation 4; CHWs = community health workers; EIMC = early infant male circumcision; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MCH = maternal and child healthcare; MSM = men who have sex with men; NCDs = non-communicable diseases; PMTCT = prevention-of-mother-to-child-transmission; PNC = postnatal care; PWID = people who inject drugs; PrEP = pre-exposure prophylaxis; SRH = sexual and reproductive health; STIs = sexually transmitted infections; TB = tuberculosis; VMMC = voluntary male medical circumcision.

Intervention(s), comparison(s)	Healthcare setting	Sample size	Outcome measures
Integration of point-of-care-testing (HIV, syphilis, malaria, anaemia) into MCH dispensaries	Multiple settings (urban, rural)	183 (at 1 site)	(1) Nurse utilisation (2) Waiting times
Integration of rapid point-of-care HIV screening, CD4 and viral load testing, linkage to care and ART counselling/ initiation into primary healthcare (CTN-0056 trial)	Outpatient-clinic(s) (urban)	478 (at 12 sites)	(1) QALY gained (2) Incremental cost-effectiveness ratio (3) ART access
Integration of rapid initiation ART into standard ANC care and testing (Rapid initiation of ART in Pregnancy (RAP) programme)	Local public health clinic(s) (semi-urban)	190 (at multiple sites)	(1) Cost per patient (2) Cost per QALY saved, cost-effectiveness (3) Perinatal infections averted
Integration of HIV screening into opioid replacement therapy	Community-level (unknown)	352 (at 12 sites)	(1) # of monthly provider encounters (2) Median monthly clinic/treatment costs (3) Cost breakdown

Supplementary Table 3. GRADE assessment of the quality of the included studies.

Author(s) and year of publication	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect size
Akinleye *et al.* (2017) [34]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Large (+1)
Akker *et al.* (2012) [35]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Large (+1)
Aliyu *et al.* (2016) [50]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Ameh *et al.* (2017) [61]	Likely (-1)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Ansa *et al.* (2012) [72]	Likely (-1)	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	N/A
Bailey *et al.* (2017) [83]	Likely (-1)	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Bergmann *et al.* (2017) [94]	Likely (-1)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Bindoria *et al.* (2014) [105]	Likely (-1)	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	Large (+1)
Broughton *et al.* (2016) [116]	Likely (-1)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Brunie *et al.* (2016) [127]	Likely (-1)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Brunie *et al.* (2017) [36]	Likely (-1)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Busza *et al.* (2019) [41]	Undetected (0)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Carrico *et al.* (2019) [42]	Likely (-1)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Chan *et al.* (2010) [43]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Chan *et al.* (2016) [44]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Large (+1)
Chen *et al.* (2020) [140]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Church *et al.* (2015) [45]	Undetected (0)	Undetected (0)	Likely (-1)	Likely (-1)	Undetected (0)	N/A
Ciampa *et al.* (2011) [46]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Click *et al.* (2012) [47]	Very likely (-2)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Coleman *et al.* (2012) [48]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Conradie *et al.* (2013) [49]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Large (+1)
Criniti *et al.* (2011) [51]	Undetected (0)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Deo *et al.* (2012) [52]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A

Quality	Justification
Low	Cross-sectional study downgraded due to (1) likely risk of bias from small timeslot of intervention, upgraded due to large effect sizes and large sample size
Low	Retrospective cohort study, downgraded due to risk of bias from type of date; extraction from medical records, upgraded due to large effect sizes
High	Cluster-randomised-controlled trial, high level of evidence
Low	Pre-post study downgraded due to (1) likely risk of bias from time and location differences (2) possible imprecision of evidence due to small sample sizes
Low	Pre-post study downgraded due to (1) risk of bias from non-random sample and pre-post set-up and (2) indirectness due to difference in intervention (different levels of integration)
Very low	Prospective cohort study downgraded due to (1) likely risk of bias from healthcare facility heterogeneity and (2) possible inconsistency due to included self-reported outcomes
Low	Pre-post study downgraded due to (1) likely risk of bias from time and location differences and (2) imprecision of evidence due to indirect cost estimation
Moderate	Pre-post study downgraded due to (1) risk of bias from different settings and (2) possible indirectness of evidence due to indirect comparison, upgraded due to large affect sizes
Low	Pre-post study downgraded due to (1) risk of bias from different settings (districts) and (2) possible imprecision of evidence due to small sample sizes
Low	Pre-post study downgraded due to (1) risk of bias from different settings (districts) and (2) possible imprecision of evidence due to small sample sizes
Low	Cluster-randomised-controlled trial downgraded due to (1) likely risk of bias due to different geographical regions of intervention and control groups and (2) imprecision of evidence due to largely qualitative outcomes
Moderate	Randomised-controlled trial downgraded due to likely imprecision of evidence due to qualitative nature of the outcomes
Low	Randomised-controlled trial downgraded due to (1) risk of bias from small sample size and (2) impression due to self-reported substance use
Low	Retrospective cohort study, low level of evidence
Low	Retrospective cohort study downgraded due to risk of bias from use of non-randomised clinic record data, upgraded due to large sample sizes and effect sizes
Low	Cross-sectional study, low level of evidence
Low	Non-randomised-controlled trial downgraded due to (1) likely indirectness of evidence from difference in intervention (degree of integration) and (2) possible imprecision due to qualitative nature of observations
Low	Cohort study, low level of evidence
Low	Pre-post study downgraded due to very likely risk of bias from (1) time effects and facility heterogeneity and (2) incomplete data
Very low	Retrospective cohort study downgraded due to (1) risk of bias from small number of responders and (2) likely inconsistency in controlling for relevant determinants
Low	Retrospective cohort study downgraded due to risk of bias from nonblinded study design (visitors of one integrated and one non-integrated clinic), upgraded due to large effect sizes
Very low	Cohort study downgraded due to likely imprecision of outcome measures
Low	Prospective cohort study, remains low level of evidence

Supplementary Table 3. GRADE assessment of the quality of the included studies. (*continued*)

Author(s) and year of publication	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect size
De la Flor *et al.* (2017) [79]	Likely (-1)	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	N/A
Digre *et al.* (2021) [141]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Dovel *et al.* (2020) [142]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Ezeanolue *et al.* (2015) [53]	Undetected (0)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Geelhoed *et al.* (2013) [54]	Undetected (0)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Gilbert *et al.* (2018) [55]	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Golovaty *et al.* (2018) [56]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Greig *et al.* (2012) [57]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Guillaine *et al.* (2017) [58]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Hankin *et al.* (2016) [59]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Haraka *et al.* (2015) [60]	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	Large (+1)
Harding *et al.* (2012) [62]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Hemmer *et al.* (2015) [63]	Likely (-1)	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	N/A
Herce *et al.* (2018) [64]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Herlihy *et al.* (2015) [65]	Likely (-1)	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	N/A
Hermans *et al.* (2012) [66]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Hewett *et al.* (2016) [67]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Hung *et al.* (2016) [68]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Jacobson *et al.* (2015) [69]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Johns *et al.* (2017) [70]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Kanyuuru *et al.* (2015) [71]	Likely (-1)	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	Large (+1)
Katz *et al.* (2016) [73]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Kerschberger *et al.* (2012) [74]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Kimani *et al.* (2015) [75]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A

Quality	Justification
Low	Pre-post study downgraded due to (1) likely risk of bias from time effect and (2) incomplete comparison
Moderate	Pre-post study downgraded due to likely risk of bias from time effects and use of routinely collected data
High	Cluster-randomised-controlled trial, high level of evidence
Very low	Cohort study downgraded due to small sample size likely leading to imprecise evidence
Moderate	Randomised-controlled trial downgraded due to qualitative nature of part of the primary evidence
Moderate	Randomised-controlled trial downgraded due partially self-reported outcomes
Low	Prospective cohort study, remains low level of evidence
Very low	Retrospective cohort study downgraded due to large heterogeneity of health facilities and implemented intervention
Low	Retrospective cohort study, low level of evidence
Very low	Retrospective cohort study downgraded due to large heterogeneity of implemented intervention
Low	Retrospective cohort study downgraded due multiple interventions, upgraded due to large effect sizes
Low	Prospective cohort study, low level of evidence
Low	Pre-post study downgraded due to (1) likely risk of bias from time effects and (2) facility-level heterogeneity
High	Pre-post study, high level of evidence
Low	Pre-post study downgraded due to (1) likely risk of bias from time effects and facility-level heterogeneity and (2) multiple tested interventions
Moderate	Pre-post study downgraded due to likely risk of bias from time effects and use of routinely collected data
High	Randomised-controlled trial, high level of evidence
Moderate	Pre-post study downgraded due to likely risk of bias from time effects and use of routinely collected data
Low	Retrospective cohort study, low level of evidence
Moderate	Pre-post study downgraded due to likely time effects and facility-level heterogeneity
Moderate	Pre-post study downgraded due to (1) likely risk of bias from time and location differences and (2) indirectness of evidence because of intervention differences, upgraded due to large effect sizes.
Low	Cohort study, low level of evidence.
Moderate	Pre-post study downgraded due to likely risk of bias from time effects and use of routinely collected data
Moderate	Non-randomised trial downgraded due to possible risk of bias from participant' preferences for integrated *vs.* non-integrated health facility

Supplementary Table 3. GRADE assessment of the quality of the included studies. (*continued*)

Author(s) and year of publication	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect size
Kinyua *et al.* (2019) [76]	Likely (-1)	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	Large (+1)
Kosgei *et al.* (2011) [77]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Kufa *et al.* (2018) [78]	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	N/A
Lambdin *et al.* (2013) [80]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Leon *et al.* (2010) [81]	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	N/A
Mansoor *et al.* (2019) [84]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Mantell *et al.* (2017) [85]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Matulionyte *et al.* (2019) [86]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Mavhu *et al.* (2020) [87]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Mayhew *et al.* (2017) [188]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
McBain *et al.* (2017) [89]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Mendelsohn *et al.* (2018) [90]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Miller *et al.* (2018) [92]	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Momplaisir *et al.* (2013) [93]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Mudzengi *et al.* (2017) [95]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Musarandega *et al.* (2018) [96]	Likely (-1)	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	N/A
Myer *et al.* (2018) [97]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Nance *et al.* (2017) [98]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Ndagijimana *et al.* (2015) [99]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Ngo *et al.* (2013) [100]	Very likely (-2)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Large (+1)
Nsubuga-Nyombi *et al.* (2019) [101]	Likely (-1)	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	N/A
Obure *et al.* (2015) [102]	Likely (-1)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Obure, Jacobs *et al.* (2016) [104]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A

Quality	Justification
Moderate	Pre-post study downgraded due to (1) likely risk of bias from time effects and (2) facility-level heterogeneity, upgraded due to large effect sizes
Low	Retrospective cohort study, low level of evidence
Moderate	Cluster-randomised trial downgraded due to facility-level heterogeneity
Low	Retrospective cohort study, low level of evidence
Moderate	Pre-post study downgraded due to likely heterogeneity between facilities and implementation of the intervention
High	Randomised-controlled trial, high level of evidence
High	Randomised-controlled trial, high level of evidence
Low	Retrospective cohort study, low level of evidence
High	Randomised-controlled trial, high level of evidence
Moderate	Non-randomised trial downgraded due to likely risk of bias from different types of clinics in intervention and comparison groups
Low	Retrospective cohort study, low level of evidence
Low	Cohort study downgraded due to likely risk of bias from non-randomised comparison of two very different types of health facilities
Moderate	Randomised-controlled trial downgraded due to self-reporting of outcomes by participants (ART use)
Low	Cross-sectional study, low level of evidence
Low	Cross-sectional study, low level of evidence
Low	Pre-post study downgraded due to (1) likely risk of bias from time differences and facility heterogeneity and (2) comparison of data from different sources
High	Randomised-controlled trial, high level of evidence
High	Randomised-controlled trial, high level of evidence
Very low	Cohort study downgraded due to (1) likely risk of bias from facility-level heterogeneity and (2) qualitative nature of the evidence
Moderate	Pre-post study downgraded due to very likely risk of bias due to non-standardised sample groups from survey data, upgraded due to large effect size
Low	Pre-post study downgraded due to (1) risk of bias from time differences and facility heterogeneity and (2) unclarity with regard to comparability of intervention
Low	Non-randomised trial downgraded due to (1) likely risk of bias from different types of clinics in intervention and comparison groups and (2) likely imprecision of estimated costs (conducted from health providers' perspective)
Moderate	Non-randomised trial downgraded due to likely risk of bias from different types of clinics in intervention and comparison groups

Supplementary Table 3. GRADE assessment of the quality of the included studies. (*continued*)

Author(s) and year of publication	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect size
Obure, Sweeney *et al.* (2016) [103]	Likely (-1)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Owiti *et al.* (2015) [106]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Palma *et al.* (2018) [107]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Rawat *et al.* (2018) [108]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Reza-Paul *et al.* (2019) [109]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Large (+1)
Rosen *et al.* (2021) [145]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Roberts *el al.* (2019) [111]	Undetected (0)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	Large (+1)
Rodkjaer *et al.* (2017) [112]	Undetected (0)	Likely (-1)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Rosenberg *et al.* (2010) [113]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Large (+1)
Rosenberg *et al.* (2018) [114]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Rutaremwa *et al.* (2016) [115]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Schackmann *et al.* (2011) [147]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Schulz *et al.* (2013) [117]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Shade *et al.* (2013) [118]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Shade *et al.* (2020) [143]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Shenoi *et al.* (2017) [119]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Shin *et al.* (2020) [146]	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	N/A
Siapka *et al.* (2017) [120]	Likely (-1)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Simeone *et al.* (2017) [121]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Siregar *et al.* (2011) [122]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Solomon *et al.* (2019) [123]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Solomon *et al.* (2020) [124]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Stockton *et al.* (2020) [144]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A

Quality	Justification
Low	Non-randomised trial downgraded due to (1) likely risk of bias from different types of clinics in intervention and comparison groups and (2) likely imprecision of estimated costs (conducted from health providers' perspective)
Moderate	Pre-post study downgraded due to likely risk of bias from time differences and facility heterogeneity
High	Randomised-controlled trial, high level of evidence
Moderate	Pre-post study downgraded due to likely risk of bias from time effects and use of routinely collected data
Moderate	Cross-sectional study, upgraded due to large effect size
Low	Prospective cohort study, low level of evidence
Low	Cross-sectional study downgraded due to likely imprecision of measured costs, upgraded due to large effect size
Low	Randomised-controlled trial downgraded due to (1) imprecision because of small sample size and (2) qualitative nature of some of the primary outcomes
Moderate	Cohort study upgraded due to nested study design within randomised-controlled trials and reported large effect sizes
High	Randomised-controlled trial, high level of evidence
Low	Cross-sectional study, low level of evidence
Low	Cohort study, low level of evidence
Low	Cohort study, low level of evidence
Moderate	Cluster randomised-controlled trial downgraded due to likely risk of bias from large facility heterogeneity
Low	Retrospective cohort study, low level of evidence
Low	Retrospective cohort study, low level of evidence
Moderate	Quasi-experimental study downgraded due to likely heterogeneity between facilities and implementation of the intervention
Low	Pre-post study downgraded due to (1) likely risk of bias from facility differences and different time points and (2) wide confidence intervals
Low	Cohort study, low level of evidence
Low	Cohort study, low level of evidence
High	Randomised-controlled trial, high level of evidence
High	Randomised-controlled trial, high level of evidence
High	Pre-post study, high level of evidence

Supplementary Table 3. GRADE assessment of the quality of the included studies. (*continued*)

Author(s) and year of publication	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect size
Sweeney *et al.* (2014) [125]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Talama *et al.* 2020) [139]	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	N/A
Tomlinson *et al.* (2014) [126]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Topp *et al.* (2010) [128]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Topp *et al.* (2013) [129]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Tran, Jacobs *et al.* (2012) [130]	Undetected (0)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Tran, Houston *et al.* (2012) [131]	Undetected (0)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Turan *et al.* (2015) [132]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Uebel *et al.* (2013) [133]	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Van Lettow *et al.* (2014) [82]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Van Rie *et al.* (2014) [110]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Vodicka *et al.* (2017) [134]	Undetected (0)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	Large (+1)
Vodicka *et al.* (2019) [135]	Undetected (0)	Undetected (0)	Likely (-1)	Likely (-1)	Undetected (0)	Large (+1)
Wagner *et al.* (2021) [138]	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	N/A
Wang *et al.* (2014) [136]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Wang *et al.* (2015) [137]	Undetected (0)	Undetected (0)	Undetected (0)	Likely (-1)	Undetected (0)	N/A
Washington *et al.* (2015) [37]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Young *et al.* (2019) [38]	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Zang *et al.* (2016) [39]	Undetected (0)	Likely (-1)	Undetected (0)	Undetected (0)	Undetected (0)	N/A
Zulliger *et al.* (2014) [40]	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	Undetected (0)	N/A

Quality	Justification
Moderate	Non-randomised trial downgraded due to likely risk of bias from different types of clinics in intervention and comparison groups
Moderate	Pre-post study downgraded due to likely heterogeneity between facilities and implementation of the intervention
High	Randomised-controlled trial downgraded due to likely risk of bias from facility heterogeneity, upgraded due to large effect sizes and indication of confounders that diluted the effect of HIV-free survival
Low	Cross-sectional study, low level of evidence
Low	Cross-sectional study, low level of evidence
Very low	Cohort study downgraded due to likely imprecision of cost estimates because of large range of assumptions
Very low	Cohort study downgraded due to likely imprecision of cost estimates because of large range of assumptions
High	Randomised-controlled trial, high level of evidence
Moderate	Randomised-controlled trial downgraded due to possible inconsistency in reported outcomes from different levels of integration as intervention and assessment if degree of integration by questionnaire
Low	Prospective cohort study, low level of evidence
Low	Prospective cohort study, low level of evidence
Low	Cross-sectional study downgraded due to likely imprecision of measured costs, upgraded due to large effect size
Very low	Cross-sectional study downgraded due to large set of assumptions for modelling component (higher likeliness of indirectness and imprecision of the evidence), upgraded due to large effect size
Moderate	Cluster-randomised trial downgraded due to facility-level heterogeneity
Moderate	Cluster-randomised-controlled trial downgraded due to likely risk of bias from unblinded intervention and control groups
Moderate	Cluster-randomised-controlled trial downgraded due to wide confidence intervals in service uptake
High	Randomised-controlled trial, high level of evidence
Moderate	Pre-post study downgraded due to likely risk of bias from time differences and facility heterogeneity
Moderate	Cluster-randomised-controlled trial downgraded due to non-empirical nature of some used data sources
Low	Retrospective cohort study, low level of evidence

Chapter 9

Evidence-based policymaking when evidence is incomplete: the case of HIV programme integration

Jan A.C. Hontelez[‡], Caroline A. Bulstra[‡], Anna Yakusik, Erik Lamontagne, Till Bärnighausen, Rifat Atun

[‡] *Shared first co-authorship*

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SUMMARY POINTS

- Sustainable Development Goal 3 aims to "ensure healthy lives and promote well-being for all at all ages" and has set a target of achieving global universal health coverage, representing a major policy shift away from mostly disease-specific "vertical programmes".

- While health service integration can be a promising strategy to improve healthcare coverage, health outcomes, and efficiency, the exact impact of integration in different settings is hard to predict, and policy makers need to choose from a large variety of integration strategies and opportunities with varying levels of scientific evidence.

- Using the case of health service integration for HIV in low- and middle-income countries, we outline implementation strategies for integration opportunities with lacking or scarce high-level causal evidence, based on existing frameworks and methodologies from within and beyond healthcare and implementation science.

- Proper use of scientific evidence in other contexts requires adequate and systematic assessments of the transportability of an intervention. Several methods exist that allow for judging transferability and comprehensively identifying key context-specific indicators across studies that can affect the reported impact of interventions.

- When (transferable) evidence is absent, we propose that by drawing on well-established design and implementation methodologies – underpinned by ongoing learning and iterative improvement of local service delivery strategies – countries could substantially improve decision-making even in the absence of scientific evidence.

- Reaching the goal of making the HIV response an integral part of a larger, universal, people-centred health system that meets the needs and requirements of citizens can be facilitated by applying lessons learned from implementation science and novel design methodologies.

INTRODUCTION

The Sustainable Development Goal (SDG) 3 aims to "ensure healthy lives and promote well-being for all at all ages" [1,2] and has a target of achieving universal health coverage by 2030 (UHC; SDG 3.8), where all people should have access to affordable and high-quality health services [3]. SDG 1, which aims to "end poverty in all forms everywhere", has a target (SDG 1.3) to "implement nationally appropriate social protection systems and measures for all", which requires availability of fiscal space for health and social programmes [2]. The SDGs represent a major policy shift away from mostly disease-specific and often Official Development Assistance-supported 'vertical programmes' in health, towards people-centred comprehensive approaches to healthcare [4]—where health systems are oriented towards promoting health equity by "leaving no one behind" while meeting all essential healthcare needs under the UHC umbrella [5].

Policy makers now face the daunting challenge of proposing, adapting, and implementing healthcare interventions tailored to specific contexts and population needs, often with limited high-quality scientific evidence on the impact of candidate interventions. Although evidence-based medicine remains the gold standard for decision-making in healthcare [6], randomised-controlled trials of health system interventions are extremely time-consuming and often have low external validity because their results are context-specific [7]. As part of the PLOS collection on UNAIDS HIV targets [8], we use the case of health service integration for HIV in low- and middle-income countries (LMICs) to outline existing frameworks and provide guidance on how to best utilise the existing evidence in policymaking and, in particular, how to design implementation strategies for integration opportunities where high-level causal evidence is scarce or lacking.

The current global evidence-base on HIV service integration

A recent comprehensive systematic review that was undertaken as part of the Joint United Nations Programme on HIV/AIDS (UNAIDS) 2021–2025 HIV/AIDS target estimations and resource needs exercise, analysed and synthesised the existing evidence on the impact of integration of HIV services with other health services [9]. The findings of this study indicate that integrated services were mostly associated with better outcomes across a wide range of cascades-of-care and health indicators, and provide a comprehensive new evidence base for policy. However, the wide variation of implementation design and contexts of implementations across the studies severely restricts the unadapted transfer of the findings to other settings, and reveal gaps in the evidence base for promising integration opportunities and in specific geographical settings.

Judging transferability of the existing evidence

Suitability of evidence for decision-making depends on both the quality of the evidence and the usefulness for a new context: results from experiments in one context may or may not be useful for policy decisions in another context. As a context is defined by different determinants, which can be measured and accounted for to some extend (*e.g.* geographical location, healthcare infrastructure, and economic, political, and social environments [10]), in the majority of situations, generalizability to the current location and situation needs to be carefully considered and study findings need to be adapted.

Different methods could be applied for judging overall transferability of the available evidence (**Table 1**). First of all, transferability should be judged by local policymakers, experts, and other stakeholders. How does the context in which the evidence for a certain intervention is generated differ from the context in which a policy decision needs to be made, *e.g.*, in terms of epidemiology and disease burden, target population, financial and human resources, health services in place, and targets for control? Mehrotra *et al.* (2019) propose a "transportability framework" to understand HIV programme effects in different contexts, to enable judgement of external validity of interventions and translate this into policy action and testable insight [11]. Second, qualitative or mixed-method studies could be conducted to explore how tested interventions need to be adapted to be successful in the new setting [12,13]. Such a process involves a sequence of steps, generally consisting of: (i) assessing the community and target population; (ii) evaluating the evidence base with local policymakers, experts, and other stakeholders; (iii) adapting the intervention for suitability in the local context; (iv) implementation; (v) monitoring and evaluation [12]. Third, recent statistical methods – developed under the heading of "transportability studies" – such as robust targeted maximum likelihood estimators [14,15] and inverse odds of sampling weights [16], allow for predicting the impact of an intervention in a new setting.

In attempting to understand, identify, and adapt interventions with problems of external validity simultaneously, Williams suggests "mechanism mapping" [17] – an approach in which the policy's theory of change is juxtaposed with the underlying contextual assumptions needed for each step of this mechanism to operate, and the actual characteristics of the policymaker's context. By identifying specific aspects of the policy that are likely to be affected by the difference in context, the approach also directly informs intervention adaptation processes. However, such efforts require studies of health service delivery to report on important underlying factors in detail, something that is not always done explicitly in the published literature. Standardised reporting guidelines like the STROBE guidelines for observational studies or the STARI guidelines for implementation studies do call for describing the setting and generalisability of the findings [18,19], but adaptation and re-interpretation of the findings to suit local contexts requires a more comprehensive understanding of the

contextual setting where the original study was performed [20,21]. For instance, Schloemer *et al.* (13) found that 44 different criteria influence the transportability of health interventions, divided over four overarching themes: (i) population in which the intervention was studied, (ii) intervention characteristics, (iii) environmental characteristics, and (iv) the transferability process [13]. Maximising transportability of context-specific interventions thus requires a comprehensive, systematic approach to reporting key context-specific indicators across studies.

Decision-making in the absence of scientific evidence

Transporting and adapting context-specific findings certainly enhances the usefulness of context-specific effect studies. Many promising integration opportunities, however, have limited to no quantitative scientific evidence on impact. This is especially true for key populations in the HIV response, such as transgender people, migrants, men who have sex with men, and sex workers; for particular geographic regions, such as Latin America, Southeast Asia and the Russian Federation; and for specific disease-based opportunities for integration, such as cervical cancer, mental health, or schistosomiasis. By drawing on well-established design and implementation methodologies – underpinned by ongoing learning and iterative improvement of local service delivery strategies – countries could substantially improve decision-making even in the absence of scientific evidence (**Table 1**).

The scope of claims that require evidence should be judiciously made. Cartwright and Stegenga (2013) propose to approach the issue from the policy makers' perspective and work backwards; assessing what the likelihood is that a proposed policy will be effective in achieving a pre-defined target, and what type of evidence would be relevant for the evaluation [22,23].

There are many examples in which integration opportunities are straight-forward, while the risks are likely negligible, allowing for implementation even without a solid evidence base. For instance, the integration of health services is often a sensible choice when the services are targeted at the same end-users, like integrating HIV services and gender-affirming therapies for transgender men and women [24] or integrating HIV services and cervical cancer screen-and-treat strategies for HIV-infected women [25]. Also, in cases of HIV service integration with social programmes, we know many examples of positive impacts, and we can question whether we truly need to await the lengthy process of formally testing impact before we can implement these elsewhere. For example, we know that adolescents can benefit from integration of youth-friendly health services with social programmes that include sex education and mental wellbeing awareness campaigns, like being done by the 'Youth Hub' in Malawi [26] and the Zvandiri project in Zimbabwe [27].

When scientific evidence is lacking, but the intervention of interest is already implemented in a given or a comparable context, expert evidence surveys can be administered to local experts to gather information about their unpublished observations and case series as a basis for developing recommendations that are as evidence-based as possible at a particular point in time [28].

When scientific evidence is lacking and comparable interventions have yet to be implemented, implementation and testing of understudied integration opportunities can be aided by lessons learned in other sectors, such as business or software design. Applying systems-thinking processes to integrating the HIV response, *e.g.*, by framing problem definitions and applying context analyses, ideation, creative thinking, prototyping, testing, and evaluation, could ensure that the right solutions to context specific problems are generated and iteratively refined [29]. Similarly, widely applied agile processes in service sectors, such as software development [30], which emphasise the need to collaborate with customers and respond to changes in demand in an agile way, seem to be highly relevant and applicable when redesigning health systems in the absence of clear scientific knowledge that reflects the rapidly changing contexts. Applying incremental, iterative development cycles, in which a system is gradually or radically improved as new evidence is emerging, could reduce the task of redesigning an entire health system to more manageable and feasible components that can be optimised individually [31].

How to arrive at an integrated HIV response

For people-centred approaches to health systems integration to be successful, deliberative inclusive processes [36]—in which stakeholders, from international donors to local policy makers, service implementers, civil society organisations, and end-users are involved as equal partners—should be at the core of decision-making. For example, human-centred design studies, in which the needs and requirements of the users are systematically analysed, could help ensure local needs and preferences are considered throughout the design and implementation process [37,38]. Co-creation, or co-design, is a deliberative process defined as the collaborative generation of knowledge by academics working alongside stakeholders from other sectors [38]. It builds on the foundation that key information and knowledge on underlying processes and determinants of success and failure are often well-known by implementers and consumers.

While redesigning the HIV response to meet the changing contextual needs, we should also ensure that we accelerate the sharing of knowledge within the public domain. Approaches, such as 'A/B testing' [33,34], *i.e.* experimental designs in which several variants of a new service are randomly offered to people and service uptake and effects are measured in real time, could rapidly result in knowledge on preferences, barriers, and enablers of specific

health service design choices. Furthermore, health system innovations could contain built-in trial elements, to ensure rapid impact assessment and knowledge generation alongside real-world implementation, *e.g.*, through stepped-wedge randomised trials [35,39,40].

Table 1. Conceptual framework for evidence-based decision-making on HIV service integration strategies by level of evidence.

Level of evidence	Evidence base, study types	Action
Context-specific evidence on integration interventions	• Local experimental study • Local implementation study	• Expert judgement • Epidemiological situation • Target population • Financial and human resources • Health systems in place
Evidence on integration intervention from other contexts	• Experimental studies from comparable context • Observational comparison studies from comparable contexts • Experimental or observational studies from distinctly different contexts and settings	• Assess likelihood that a proposed policy will be effective in achieving a pre-defined target, and what type of evidence would be relevant for the evaluation [22,23] • Mechanism mapping [17] • Use "transportability framework" to judge transferability of the existing evidence; suitability for the context of interest [11] • Test transportability • Robust targeted maximum likelihood estimators [14,15] • Intervention adaptation [21] • *E.g.*, service setting, target population, mode of delivery, cultural sensitivity
No scientific evidence on impact of integration intervention available	• Interventions implemented but no evidence of impact (yet)	• Hypothesise merit of intervention for local population • Deliberative ideation of promising integration opportunities based on local targets, populations, knowledge of barriers and enablers • Perform expert evidence survey to collect information about unpublished observations and case series for the context of interest [28]
	• Interventions not yet implemented and no experimental or observational studies from comparable contexts	• Agile design and implementation • Systems-thinking processes [29] • Prototyping • Agile software development [32] • A/B testing [33,34] • Step-wedged randomised trials [35] • Iterative development cycles [29]

DISCUSSION

Health policy makers and funders are tasked with the daunting challenge of redesigning the HIV response to meet the current complex epidemiological, financial and political chal-

lenges. By applying lessons learned and methods from a range of scientific fields – such as innovation models, systems dynamics models, implementation science, design research, and learning systems – policy makers, funders and practitioners could help accelerate and maximise the transfer of limited, and often context specific, knowledge on best practices for developing integrated HIV services. Furthermore, by expanding the evidence with results from widely-applied methods that are not randomised-controlled trials, policy makers could help ensure that the HIV response is an integral part of a larger, universal, people-centred health system that meets the needs and requirements of citizens. Such a shift in decision-making design could prove to be key in shaping the HIV response within the UHC agenda in rapidly changing contexts.

REFERENCES

1. United Nations. Political Declaration on HIV and AIDS: On the Fast-Track to Accelerate the Fight against HIV and to End the AIDS Epidemic by 2030. New York; 2016. doi:10.1093/oxfordhb/9780199560103.003.0005
2. United Nations. The Sustainable Development Goals Report. New York; 2020. Available: https://unstats.un.org/sdgs/report/2020/The-Sustainable-Development-Goals-Report-2020.pdf
3. Holmes CB, Rabkin M, Ford N, Preko P, Rosen S, Ellman T, *et al.* Tailored HIV programmes and Universal Health Coverage. Bull World Health Organ. 2020;98: 87–94. doi:10.2471/BLT.18.223495
4. World Health Organization (WHO). Framework on integrated, people-centred health services: Report by the Secretariat. World Health Assembly 2016 pp. 1–12. Available: http://apps.who.int/iris/bitstream/10665/174536/1/9789241564977_eng.pdf?ua=1,%0Ahttp://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_39-en.pdf?ua=1&ua=1%0Ahttp://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_39-en.pdf?ua=1
5. United Nations Sustainable Development Group (UNSDG). Leaving No One Behind: A UNSDG Operational Guide for UN Country Teams. Interim Draft; 2019. Available: https://unsdg.un.org/sites/default/files/Interim-Draft-Operational-Guide-on-LNOB-for-UNCTs.pdf
6. Guyatt G, Cairns J, Churchill D, Cook D, Haynes B, Hirsh J, *et al.* Evidence-based medicine: a new approach to teaching the practice of medicine. Jama. 1992;268: 2420–2425. doi:10.1001/jama.1992.03490170092032
7. Rothwell PM. External validity of randomised controlled trials:"to whom do the results of this trial apply?" Lancet. 2005;365: 82–93.
8. De Lay PR, Benzaken A, Karim QA, Aliyu S, Amole C, Ayala G, *et al.* Ending AIDS as a public health threat by 2030: Time to reset targets for 2025. PLOS Med. 2021;18: e1003649. doi:10.1371/journal.pmed.1003649
9. Bulstra CA, Hontelez JAC, Otto M, Stepanova A, Lamontagne E, Yakusik A, *et al.* Integrating HIV services and other health services: a systematic review and meta-analysis. PLOS Med. 2021.
10. Rogers L, De Brún A, McAuliffe E. Defining and assessing context in healthcare implementation studies: a systematic review. BMC Health Serv Res. 2020;20: 1–24. doi:10.1186/s12913-020-05212-7
11. Mehrotra ML, Petersen ML, Geng EH. Understanding HIV Program Effects: A Structural Approach to Context Using the Transportability Framework. J Acquir Immune Defic Syndr. 2019;82: S199–S205. doi:10.1097/QAI.0000000000002202
12. Escoffery C, Lebow-Skelley E, Udelson H, Böing EA, Wood R, Fernandez ME, *et al.* A scoping study of frameworks for adapting public health evidence-based interventions. Transl Behav Med. 2019;9: 1–10. doi:10.1093/tbm/ibx067
13. Schloemer T, Schröder-Bäck P. Criteria for evaluating transferability of health interventions: a systematic review and thematic synthesis. Implement Sci. 2018;13: 1–17. doi:10.1186/s13012-018-0751-8
14. Rudolph KE, van der Laan MJ. Robust estimation of encouragement-design intervention effects transported across sites.

J R Stat Soc. 2017;79: 1509. doi:10.1111/rssb.12213

15. Rudolph KE, Schmidt NM, Glymour MM, Crowder R, Galin J, Ahern J, *et al.* Composition or context: using transportability to understand drivers of site differences in a large-scale housing experiment. Epidemiology. 2018;29: 199. doi:10.1097/EDE.0000000000000774

16. Westreich D, Edwards JK, Lesko CR, Stuart E, Cole SR. Transportability of trial results using inverse odds of sampling weights. Am J Epidemiol. 2017;186: 1010–1014. doi:10.1093/aje/kwx164

17. Williams MJ. External validity and policy adaptation: From impact evaluation to policy design. World Bank Res Obs. 2021;35: 158–191. doi:10.1093/WBRO/LKY010

18. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014;12: 1495–1499. doi:10.1016/j.ijsu.2014.07.013

19. Pinnock H, Barwick M, Carpenter CR, Eldridge S, Grandes G, Griffiths CJ, *et al.* Standards for reporting implementation studies (StaRI) statement. BMJ. 2017;356.

20. Chambers DA, Norton WE. The adaptome: advancing the science of intervention adaptation. Am J Prev Med. 2016;51: S124–S131. doi:10.1016/j.amepre.2016.05.011

21. Escoffery C, Lebow-Skelley E, Haardoerfer R, Boing E, Udelson H, Wood R, *et al.* A systematic review of adaptations of evidence-based public health interventions globally. Implement Sci. 2018;13: 1–21. doi:10.1186/s13012-018-0815-9

22. Cartwright N, Stegenga J. A Theory of Evidence for Evidence-Based Policy. Evidence, Inference Enq. 2013; 289–319. doi:10.5871/bacad/9780197264843.003.0011

23. Cartwright N, Hardie J. Evidence-based policy: A practical guide to doing it better. Oxford University Press; 2012.

24. Sari L. Reisner, Perez-Brumer AG, McLean SA, Lama JR, Silva-Santisteban A, Huerta L, *et al.* Perceived barriers and facilitators to integrating HIV prevention and treatment with cross- sex hormone therapy for transgender women in Lima, Peru. AIDS Behav. 2017;21: 3299–3311. doi:10.1007/s10461-017-1768-8

25. Sigfrid L, Murphy G, Haldane V, Chuah FLH, Ong SE, Cervero-Liceras F, *et al.* Integrating cervical cancer with HIV healthcare services: A systematic review. PLOS ONE. 2017;12: e0181156. doi:10.1371/journal.pone.0181156

26. Jere E, Mafiala F, Jim G, Banda H, Nyasulu HM, Dambula I, *et al.* Growing Together: Multisectoral Investments in Malawi's Youth. Lilongwe; 2019. Available: https://www.prb.org/wp-content/uploads/2019/08/malawi-engage-presentation-guide.pdf

27. Grimsrud AT, Pike C, Bekker LG. The power of peers and community in the continuum of HIV care. Lancet Glob Heal. 2020;8: e167–e168. doi:10.1016/S2214-109X(19)30544-3

28. Mustafa RA, Garcia CAC, Bhatt M, Riva JJ, Vesely S, Wiercioch W, *et al.* GRADE notes: How to use GRADE when there is "no" evidence? A case study of the expert evidence approach. J Clin Epidemiol. 2021;137: 231–235. doi:10.1016/j.jclinepi.2021.02.026

29. Leslie HH, Hirschhorn LR, Marchant T, Doubova S V, Gureje O, Kruk ME. Health systems thinking: A new generation of research to improve healthcare quality. PLOS Med. 2018. doi:10.1371/journal.pmed.1002682

30. Flood D, Chary A, Austad K, Diaz AK, Garcia P, Martinez B, *et al.* Insights into global health practice from the agile software development movement. Glob Health Action. 2016;9: 29836. doi:10.3402/gha.v9.29836

31. Atun R, Moore G. Building a High-value Health System. New York: Oxford University Press; 2021.

32. Bulstra CA, Reddy CL, Atun R, Bärnighausen T, Hontelez JAC. Impact of the COVID-19-related global recession on the financing of the global HIV response. AIDS. 2021. doi:10.1097/QAD.0000000000002872

33. Gallo A. A Refresher on A/B Testing. Harvard Business Review. 2017. Available: https://hbr.org/2017/06/a-refresher-on-ab-testing

34. Laibson D, Keller PA, Halpern SD. A/B Testing Health Behaviour. NEJM Catal. 2017;3. Available: https://catalyst.nejm.org/doi/full/10.1056/CAT.17.0511

35. Bärnighausen T, Eyal N, Wikler D. HIV treatment-as-prevention research at a crossroads. PLOS Med. 2014;11: e1001654. doi:10.1371/journal.pmed.1001654

36. Berner-Rodoreda A, Bärnighausen T, Kennedy C, Brinkmann S, Sarker M, Wikler D, *et al.* From doxastic to epistemic: a typology and critique of qualitative interview styles. Qual Inq. 2020;26: 291–305. doi:https://doi.org/10.1177/1077800418810724

37. Pinho N, Beirão G, Patricio L, Fisk RP. Understanding value co-creation in complex services with many actors. J Serv Manag. 2014;25: 470–493. doi:10.1108/JOSM-02-2014-0055

38. Bucknall T, Hitch D. Connections, Communication and Collaboration in Healthcare's Complex Adaptive Systems: Comment on" Using Complexity and Network Concepts to Inform Healthcare Knowledge Translation". Int J Heal policy Manag. 2018;7: 556. doi:10.15171/ijhpm.2017.138

39. Yapa HM, De Neve J-W, Chetty T, Herbst C, Post FA, Jiamsakul A, *et al.* The impact of continuous quality improvement on coverage of antenatal HIV care tests in rural South Africa: Results of a stepped-wedge cluster-randomised controlled implementation trial. PLOS Med. 2020;17: 31–50. doi:10.1371/journal.pmed.1003150

40. Geldsetzer P, Bärnighausen K, Hettema A, McMahon SA, Dalal S, Chase RP, *et al.* A stepped-wedge randomized trial and qualitative survey of HIV pre-exposure prophylaxis uptake in the Eswatini population. Sci Transl Med. 2020;12. doi:10.1126/scitranslmed.aba4487

Chapter 10

General discussion

The overarching aim of this thesis is to describe and improve our understanding of the HIV epidemiology in various sub-Saharan African countries, and to provide insight into which health systems innovations could mitigate global challenges in the HIV response. Within this context, the previous chapters of this thesis expanded the evidence-base on HIV epidemic trends, in both the general population as well as in key populations, and on innovative strategies for optimising healthcare systems for HIV/AIDS in high-burden settings. This general discussion presents answers to the four research questions proposed in the general introduction, followed by my personal reflections on feasibility of reaching the 2030 global HIV targets. This chapter ends with conclusions and recommendations for policy and scientific research based on this thesis.

10.1 ANSWERING THE RESEARCH QUESTIONS

1) Where is the HIV burden highest in sub-Saharan Africa, the epicentre of the pandemic, and what drives the geographical heterogeneity in HIV transmission and prevalence on the subcontinent?

HIV prevalence among adults and young adults is geospatially heterogeneous at the subnational level in East and Southern Africa, with high transmission foci (i.e., areas with high levels of HIV transmission) mainly centred around areas with high economic activity and partially explained by an interplay of behavioural, socioeconomic, and environmental factors.

At the subnational level in East and Southern Africa, the two subregions with the highest HIV burden globally, we found areas with prevalence among young adults as high as 11% or 15% alternating with areas with prevalence levels between 0% and 2%, clearly demonstrating the existence of foci with high levels of transmission (**Chapter 2**). These high transmission foci are primarily located around major cities, mining areas, international border crossings, and large lakes – which are all areas with high levels of economic activity. We calculated that the geographical heterogeneity in HIV transmission could for about 16% be explained by an interplay of known (sexual) behaviour, socioeconomic, and environmental factors. Economic activity—approximated by the level of urbanisation, population density and the estimated global human footprint—was found to drive most of the geographical heterogeneity. People in high transmission foci more often were from a relatively high socioeconomic status and more often engaged in risky sexual behaviour (**Chapter 2**).

We also found that male circumcision is associated with geospatial heterogeneity in HIV prevalence among men in sub-Saharan Africa (**Chapter 2 and 3**). National-level male

circumcision prevalence among adult men on the subcontinent ranged from about 8% in Eswatini to nearly 100% in Sierra Leone with, overall, prevalence levels in West and Central Africa were much higher compared to in East and Southern Africa. We found that circumcised men had a 19% (11% - 27%) lower risk of living with HIV compared to uncircumcised men (**Chapter 3**). However, the estimated HIV risk reduction for circumcised men varied somewhat across regions, although smaller stratified samples for West and Central Africa prohibited precise comparison: estimates suggest a significant lower risk of living with HIV among circumcised men in East and in Southern Africa of 37% and 19% respectively, but a non-significant lower risk in West and in Central of 16% and 12% respectively.

Patterns of geographical heterogeneity in general population HIV prevalence, and risk- and protective factors associated with the observed heterogeneity, are comparable to the identified patterns and associated factors identified in other studies [1–6], despite being established using different geospatial methods. Geographical heterogeneity in HIV prevalence in Kenya, Malawi, Mozambique and Tanzania has previously been linked to sexual behaviour, education level, socioeconomic status, male circumcision status, population density and the level of urbanisation [1]. Geographic heterogeneity in HIV prevalence in Malawi was linked earlier to the sizes of high-risk groups present at locations—defined by the number of sex partners of individuals and overall population density levels—which were highest in urban settings [4]. These high-risk groups capture sex workers and their clients, which are known to drive up HIV transmission in sub-Saharan African populations [7–9]. Previous studies predominantly focused on mapping and explaining heterogeneities in HIV prevalence among the adult population, and suffered from the limitation that overall prevalence is a poor indicator of ongoing transmission, as many adults may have been infected years or even decades ago. By design, the cross-sectional nature of the Demographic and Health Surveys (DHSs) data prevents us from inferring whether the associated risk- and protective factors led to HIV infection, or if HIV infection actually preceded occurrence of those factors. By looking at HIV prevalence in young adults, however, we were better able to pinpoint areas with high levels of ongoing transmission, as young adults living with HIV are much more likely to have been infected relatively recently.

The previous studies were predominantly based on nationally representative cross-sectional survey data, sometimes supplemented by HIV or antenatal care clinic data, thus, mobile populations and key populations were likely underrepresented [10–12] and indicators related to sexual behaviour might have been biased due to the sensitive nature of such questions [13,14]. This could have led to biases in the observed HIV prevalence heterogeneity, where key populations are underrepresented, and to biases in the association between having HIV and engagement in risky sexual behaviour, where the observed association might be weaker due to misreporting or underreporting of indicators related to risky sexual behaviour. Fur-

thermore, the available dataset might miss data on other potentially relevant indicators explaining the variation in HIV prevalence. For instance, data on antiretroviral treatment (ART) coverage and on HIV preventive interventions is not included in the DHSs, and fine-scale reliable data on ART and other interventions is not yet widely available – hindering researchers from exploring the impact of HIV prevention and control interventions on geographical heterogeneity in HIV prevalence. Overall, the observed geospatial heterogeneity in HIV prevalence can likely never be fully captured by our and other predictive models, since there will always be random variation resulting from human individual behaviour [15].

The risk reduction due to men's circumcision status on HIV status as estimated in our study was lower than what could have been expected based on the three conducted randomised-controlled trials [16–18]. However, there are some important differences between our study and the randomised-controlled trials. First, we used HIV prevalence among the adult male population as outcome, while the trials all used HIV incidence as the end-point. The trials could determine efficacy in reducing HIV acquisition directly, because male circumcision always preceded HIV acquisition and randomisation allowed comparability of exposed and unexposed men. In contrast, our study uses current circumcision status and HIV prevalence, and uses household fixed-effects to account for confounding by all unobserved and observed factors shared by men living in the same household, but not for individual-level confounding. There might be unobserved or underreported factors that influence circumcision status among men in the same household and contribute to a different risk of having HIV, and thus act as confounders, such as factors related to sexual behaviour. Lastly, the cross-sectional nature of the data prevented us from knowing whether HIV acquisition preceded or succeeded circumcision. However, traditional male circumcision is often performed in boys before they reach the age where they become sexually active [19,20] and men planning to undergo voluntary medical male circumcision (VMMC) are often tested for HIV before the procedure is performed to ensure that they are HIV-negative [21]. Therefore, it is unlikely that HIV infection preceded male circumcision very often.

Our findings from **Chapter 3** should be interpreted with caution and in the light of other studies that estimated the population-level impact of male circumcision, including VMMC, within and across countries. For example, prospective cohort studies and cross-sectional studies estimating the impact of traditional circumcision [22–24] and medical circumcision [25–27] on risk of HIV infection, as well as a related systematic review [28], suggest that the HIV risk reduction is stronger among men at high risk of acquiring HIV— *e.g.* truck drivers, sex work clients, and STI clinic attendees (71% vs. 50% in the general population) [28]. In addition, the efficacy of VMMC is only slightly higher than of traditional circumcision [22–27], where time at circumcision seems to matter most: pre-pubertal circumcision significantly reduces HIV acquisition, whereas post-pubertal circumcision did not [22]. Based

on these findings, the observed differences in effect sizes of male circumcision between the randomised-controlled trials and our fixed-effects study might have been influenced by the type of circumcision performed (traditional versus medical) [22–24] and differences in sexual behaviour [29,30]. Another aspect that might have influenced efficacy in VMMC trials is risk selection; men who are more likely to engage in high-risk sexual behaviour might be more likely to undergo VMMC, although this assumption has never been proven. The authors of the three randomised-controlled trials [16–18] mention that they did not expect risk selection to affect their outcomes. Although male circumcision is hypothesised as one of the main contributors to the differences in HIV burdens between West and Central Africa and East and Southern Africa [31,32], based on our study, the impact of near-universal male circumcision on HIV incidence in East and Southern Africa might not be sufficient to reach epidemic control if implemented as a single-intervention approach.

The insights from our studies can help tailor and optimise the HIV response in the following ways. First, the identified high HIV prevalence and transmission foci, as well as insights into which factors are associated with the presence of these foci, can help optimising resource allocation [33]. Following this information, prevention and screening programmes can be scaled-up in high transmission foci, specifically for high-risk populations, and ART can be scaled-up in HIV prevalence foci with currently low treatment coverage [1,34–36]. Second, for sub-Saharan African countries or geographical areas where no or no reliable HIV data is available, indicators identified to be associated with the underlying dynamics of the HIV epidemic can be utilised to inform geospatial models for identification of HIV high-transmission or high-prevalence foci, such as recently done by Dwyer-Lindgren *et al.* [37]. Third, modifiable risk factors, such as those related to risky sexual behaviour, could be the focus of prevention programmes, especially for young populations. Fourth, VMMC delivery should predominantly be rolled-out in communities with the highest HIV burdens where male circumcision is not traditionally done and should be promoted alongside other HIV prevention interventions [34]. Finally, collecting fine-scale nationally representative data on ART uptake and cascade-of-care outcomes as well as on uptake of VMMC and PrEP could help to determine the real-life impact of such interventions on curbing the HIV pandemic in different regions and epidemic settings.

2) What is the HIV burden among key populations and how does this contribute to the HIV epidemiology in sub-Saharan Africa?

In both the concentrated epidemics of West and Central Africa as well as in the generalised epidemics of East and Southern Africa, the HIV burden among men who have sex with men (MSM), transgender women, and female sex workers is alarmingly high. However, while individual level indicators of sex work are associated with higher

HIV prevalence in the general population, sex work sites do not seem to directly affect HIV prevalence among the general population in surrounding areas.

We show that prevalence among MSM, male sex workers and female sex workers and transgender women is significantly higher compared to the general population in many African countries, also within countries marked as having 'generalised' epidemics (**Chapter 4 and 5**). In West and Central Africa, HIV prevalence is about 11-fold higher among MSM and about 8-fold higher among transgender women compared to the general population. In East and Southern Africa, prevalence is about 2-fold higher among MSM and among transgender women compared to among the general population. Finally, we found that prevalence among male sex workers is about 12-fold higher in Nigeria and about 9-fold higher in Kenya (**Chapter 4**) and prevalence among female sex workers in Zimbabwe is more than 3-fold higher compared to the general population (**Chapter 5**). Many sex work sites where female sex workers offer their services are located in or around areas with high levels of economic activity: cities, economic growth areas, international border crossings and transport routes (**Chapter 5**). However, we found no significant association between HIV seroprevalence and proximity to the nearest sex work site among the general population in Zimbabwe (**Chapter 5**). Nevertheless, key populations and sex work likely still play an important role in the African HIV epidemic, as individual-level indicators of engagement in sex work (*i.e.*, being a sex work client) and risky sexual behaviour (*i.e.*, having many sex partners, and having had an STI or STI symptoms over the past 12 months) were significantly associated with HIV seropositivity in our studies (**Chapter 2 and 5**).

Our and other studies have not been able to fully capture the complex transmission dynamics of the HIV pandemic in sub-Saharan Africa. In previous studies, sex work was univocally hypothesised as an important underlying driver of the geospatial HIV heterogeneity [4,38–40]. Our findings clearly demonstrate that at an individual level, indicators of practicing commercial sex as a client are significantly associated with increased risks for HIV, but they do not confirm that female sex work locations are associated with general population HIV transmission foci (or 'hotspots') in Zimbabwe and other settings with generalised epidemics. This might be due to the challenge to comprehensively capture the dynamic and complex nature of the HIV epidemic [12,41,42]; where especially key populations, including sex workers and their clients, are often underrepresented or not identifiable in nationally representative survey data. They are often mobile populations and may be missed in the cross-sectional survey data, which commonly rely on home-based surveys [10–12]. Furthermore, underreporting or missingness of factors that could help classify who belongs to certain key population groups hinders identification of those who do participate in these cross-sectional surveys [43]. More fine-scale geospatial mapping of key populations—including mobile populations [44]—could help to further understand the drivers of these areas with

high levels of transmission and help to determine how they fuel the generalised epidemics in sub-Saharan Africa.

Our findings substantiate that the focus of the HIV response over the next 5-10 years should shift more towards key populations when aiming to reach epidemic control. To this end, it is essential to obtain key population specific data, to further understand what puts different population groups at higher risk of HIV infection and to design population-tailored prevention and treatment services. While more data have become available on female sex workers and MSM in sub-Saharan Africa over the last 10-15 years [45–47], there is still very few data available on population size estimates, risk behaviours, HIV exposure and access to prevention, testing and care for other key populations in the sub-Saharan African HIV epidemics, including male and transgender sex workers [48,49]. An effective method to include key populations into data collection surveys is by involving members of the target key populations, such as done with CeSHHAR for female sex workers [50,51]. Peer female sex workers often know best where to find other sex workers in their community and can create trust to include new female sex workers into surveys.

While expanding the empirical evidence base on key populations, it is essential to, in the meantime, already design and implement interventions and healthcare services specifically tailored to the populations at risk. Empirical evidence demonstrates that interventions tailored to key population needs in African settings are effective in engaging them in prevention and care [52–55], but still to date, the majority of people belonging to key populations in sub-Saharan Africa do not have sufficient access to HIV services [49,56,57]. Following our work, we argue that, for instance, HIV interventions for MSM should, next to facilitating better ART uptake and adherence, also focus on improved uptake of PrEP [58,59] and interventions offered at sex work locations should primarily focus on sex workers and their clients, with special emphasis on including and retaining mobile sex workers and clients into services. There are many examples of successful interventions and healthcare programmes for key populations in sub-Saharan Africa, often offered by small grass roots organisations and other non-governmental organisations. They generally empower key populations themselves by having them play an essential role in in the design and implementation of the programs. For instance, CeSHHAR adapts service provision to the mobile nature of sex workers, by offering peer-led HIV services in mobile clinics at locations where sex workers work [60] and NorthStar Alliance offers HIV service for truck drives and sex workers at large truck stops and along busy transport routes [61]. Other small-scale organisations are offering community-guided HIV test-and-treat initiatives for female sex workers [62,63] or launching community-led peer-support programmes for adolescents [64,65].

Importantly, many people belonging to key populations still face structural barriers to healthcare, caused by stigma, discrimination, and criminalisation stigma and discrimination [66–68]. For example, in the past, US Congressional Republicans insisted that PEPFAR-funded programmes had to focus on abstinence-only until marriage and faithfulness in marriage in sub-Saharan Africa, with only limited support going to safe sex promotion and services for sex workers and lesbian, gay, bisexual, transgender, intersex (LGBTI) people in recipient countries [69]. Furthermore, 27 sub-Saharan African countries have anti-gay laws and/or prohibit sex work, posing a significant barrier for MSM and sex workers to access regular health services for HIV and other sexually transmitted infections [44,70,71]. These legislative and cultural contexts in many sub-Saharan African countries prevent the formal implementation of healthcare interventions specifically targeted at key populations and existing health services for key populations often still fall outside of the regular publicly financed healthcare systems [72]. The key to success of risk-group tailored interventions lies in overcoming those structural barriers: lifting discriminating laws and policies around the rights of LGBTI people and sex workers [73–75], designing needs-sensitive programmes for key populations, and restructuring of healthcare financing to specifically support such programmes for key populations.

3) Which service delivery and financing innovations could mitigate current global challenges in the HIV response?

Healthcare delivery innovations for HIV fall into four value-chain categories—service integration, elimination of point-of-care steps, task-shifting, and location-shifting—and broadly intend to enable HIV service scale-up, differentiation and efficiency. The economic consequences of the COVID-19 pandemic highlight the need to also innovate financing strategies.

In **Chapter 6** we describe five different service delivery models for ART: integrating ART with other required health services ("vertical ART plus", "partially-integrated ART" and "fully-integrated ART"); modifying steps in the ART value chain ("professional task-shifted ART", "people task-shifted ART" and "technology-supported ART"); eliminating steps in the ART value chain ("immediate ART" and "less frequent ART pick-up"); changing ART locations ("private-sector ART", "traditional-sector ART" and "ART outside the health sector"); and keeping the status quo ("vertical ART"). The models are intended to increase efficiency in ART delivery and to provide ART to more people without an increase in resources, while simultaneously differentiating care to offer a broader range of services adapted to the patients' needs. Suitability of the models will highly depend on national and subnational contexts, including existing health systems resources, available funding, and type of HIV epidemic. For instance, countries with generalised epidemics may continue to benefit from

a degree of 'verticality' in the delivery of ART, because in many communities within these countries there are sufficiently large numbers of HIV patients to keep vertical delivery structures fully and constantly occupied. In generalised epidemics with lower HIV incidence and prevalence levels, HIV services for the general population may be more efficiently provided as part of general internal medicine and family health services, or additional health services could be added onto existing HIV services to expand the scope of services offered in one place. In countries with more concentrated epidemics, among key populations such as sex workers and MSM, specific vertical services might be essential to be able to offer specialised care, tackle stigma, and promote easier access to health care for these vulnerable groups. The promise of ART delivery model innovations is large and implementation science, causal evaluation and mathematical modelling studies can help to identify which models are the best fit for different contexts.

Many of the outlined innovations for treatment services also apply to HIV prevention and testing services. For instance, HIV self-testing or by community healthcare worker-led testing can be offered at home or in the community, which could be integrated with testing for other common diseases and conditions, like tuberculosis, hypertension and diabetes [76–78]. Likewise, prevention interventions such as PrEP could be offered outside of regular clinical settings, such as in pharmacies, as currently done in Kenya [79,80]. Also here, suitability of the delivery interventions and overall effectiveness will depend on local contexts. Future implementation research needs to identify which models are the best fit for different contexts; and we suggested that delivery models should be put to the test in specific contexts before large-scale implementation. This could be done by prototyping and pilot studies [81,82], but also Delphi studies (*i.e.*, making systematic use of expert opinions) [83,84] and mathematical modelling studies (*i.e.* predicting health impact based on existing data and information on health systems and population context) can help to predict effectiveness of alternative service delivery models [85,86].

Innovative financing strategies are required to mitigate HIV funding gaps, among which most urgently the funding gaps potentially arising from the economic consequences of the COVID-19 pandemic. We estimate declines of as much as 5% to 11% for HIV funding in the 10 African countries with the largest ART programs, which could have devastating consequences for the scale-up of HIV prevention and treatment in sub-Saharan Africa (**Chapter 7**). These funding gaps further exacerbate other negative consequences of the COVID-19 pandemic on HIV control, *e.g.*, reallocation of HIV healthcare resources for covering COVID-19 testing, diagnosis and emergency care, and disturbances in HIV programs, access to facilities, and supply chains due to lockdowns and interruptions in international travel [87]. In retrospect, comparing our estimations to the current situation two-and-a-half years after the start of the COVID-19 pandemic, we observe that the initial funding gaps were smaller

than predicted. However, this is largely due to government-led financial emergency support programs, temporarily increased donor commitment by UNAIDS and some of the donor countries [88] and artificial economic regulation [89]. While the initial gaps seem limited, donor countries currently cope with the largest inflations since the 2008-09 economic crisis and unprecedented government debts. This might significantly impact government funding in the near future, as has been illustrated by the Global Fund which fell short of its $18-billion target [90].

We argue that strategies to mitigate the impact of COVID-19 on the HIV response could include: (1) the implementation of differentiated care, mainly enabling less frequent ART pick-ups, shifting tasks to community health workers, and integrating HIV/COVID-19 prevention; (2) pooling resources and sharing knowledge at the regional, national and international level; and (3) integration of HIV programmes with other health services to improve efficiency of service delivery and simultaneously force a conversation about reprioritisation across all health areas, which is essential to overcome the broader health system challenges introduced through the COVID-19 pandemic. Here, examples of successful financing innovations in healthcare and other industries could be implemented to optimise HIV financing, using available transferability frameworks.

Whereas COVID-19 caused immediate resource shortages on the short-run, it could, hopefully, ultimately result in an HIV response and general health system that is more integrated, efficient and sustainable, improving resilience to future crises, and bolstering efforts to end the HIV pandemic by 2030. This will require optimal application of available service delivery models, requiring knowledge on what determines suitability of certain models in different contexts, especially for contexts with the highest service needs and lowest resources. It also requires quantitative evidence on the effects of innovating HIV service delivery as well as qualitative evidence on patient experiences and preferences. Next to that, thus far, many countries struggle to turn universal health coverage (UHC) into reality, partly due to a lack of knowledge on feasible and effective ways to structurally improve the existing nationwide healthcare systems. Especially in the post-COVID-pandemic phase that we are in now, we urgently need studies that can guide the decision-making process on suitable health service delivery and health systems reforms for different settings and predict the concomitant health gains.

4) How can HIV service integration contribute to optimising the HIV response and reaching universal health coverage?

Integrating HIV services and other health services has the potential to improve HIV service uptake and cascade-of-care outcomes and outcomes for other diseases and

conditions. Policy makers, funders and practitioners, by sharing their knowledge and best practices, could help maximise the transfer of limited and often context specific evidence to ensure that the HIV response becomes an integral part of universal, people-centred health systems that meet the needs and requirements of citizens.

Our systematic review (**Chapter 8**) showed that HIV cascade-of-care outcomes tend to be better in integrated services: uptake of HIV testing and counselling (pooled risk ratio {RR} across 37 studies: 1.67 [1.41–1.99], p<0.001), ART initiation coverage (pooled RR across 19 studies: 1.42 [1.16–1.75], p=0.002), time until ART initiation (pooled RR across 5 studies: 0.45 [0.20–1.00], p=0.050), retention in HIV care (pooled RR across 19 studies: 1.68 [1.05–2.69], p=0.031), and viral suppression (pooled RR across 9 studies: 1.19 [1.03–1.37], p=0.025). In addition, treatment success for non-HIV-related diseases and conditions and the uptake of non-HIV services were commonly higher in integrated services. The most common forms of integration identified in the review were HIV testing and counselling added to non-HIV services and non-HIV services added to ART programs.

It is important to note that the studies identified in the systematic review were often highly context specific, and it remains unclear how transferable the findings are to other health systems contexts. However, we also argue that integration strategies could be implemented in some settings while high-level causal evidence is lacking or scarce, based on existing frameworks and methodologies from within and beyond healthcare and implementation science (**Chapter 9**). Countries cannot await the lengthy process of formally testing impact of potentially suitable interventions before subnational or national implementation. Policy makers, funders and practitioners could help accelerate and maximise the transfer of the limited—and often context specific—knowledge by discussing which interventions might improve healthcare in their local settings. Generally, implementation of integration and other service delivery interventions with limited evidence should be promoted if these interventions seem promising and come with neglectable risks. In those instances, a "learning-by-doing" approach can be useful and a good starting point is the use of co-creation stakeholder consultations valuable to share knowledge and best practices to optimise local HIV responses. The framework that we outline for the case of service integration also applies for other service delivery innovations, and potential suitability and effectiveness of certain interventions can be judged by reviewing patient needs, consulting expert opinion and learning about best practices from similar contexts.

Overall, integration should be seen as a tool to yield improvements both to HIV-related and to non-HIV related health outcomes. The focus should be on tailoring health services to local (sub)populations needs. In many contexts, existing health systems can be leveraged for providing integrated health services, for example by piggy-backing other services onto

existing health services at well-established clinics. For instance, in many settings in East and Southern Africa, well-functioning HIV clinics are in place, while services for non-communicable diseases (NCDs), such as hypertension and diabetes, are suboptimal despite their high and rising prevalences [91–93]. This offers an opportunity to strengthen and expand existing HIV health systems to address the increasing NCD burden, while also keeping track of the global HIV targets. The broader narrative of integration and health systems expansion is to improve UHC by meeting the different healthcare needs of the people they serve by creating capacity to address multiple health problems simultaneously [94–96].

Generally, a sustainable HIV response with successful implementation of integration strategies and alternative service delivery models will likely need broader health systems reform. Currently, healthcare delivery strategies are often designed and coordinated by the disease or healthcare domain [94], resulting in vertical clinics and highly specialised healthcare workers. In order to really make healthcare systems more sustainable, such structures need to evolve towards more flexible and integrative healthcare delivery strategies and platforms. A country that successfully managed to achieve this, is Brazil. Here, the Sistema Único de Saúde (SUS), created during the 1980s, is one of the largest universal healthcare systems in the world. It provides publicly funded healthcare to all citizens, without requesting out-of-pocket payments [97]. Digital health solutions could support the transition to integrated health systems and UHC, primarily by linking patient registries, mapping patient demand and ensuring the availability of essential diagnostics, medicines and medical equipment, and training healthcare workers to provide services tailored to their local populations needs [98,99].

Ultimately, truly integrated health systems will require healthcare financing reforms. Healthcare financing is now often earmarked for specific healthcare programs, to be able to measure disease-specific programme outcomes. Although effective for this purpose, disease-specific earmarking of funding limits the healthcare reform from vertical disease-based programmes to broader integrated people-centred programmes [100]. Hence, both donor agencies and recipient countries would have to look for alternative ways to finance healthcare programmes and enable the shift towards integrated healthcare and, ultimately, UHC. Suitable alternative financing models could be, for example, tax/levy–based primary healthcare insurance models [101] or social and development impact bonds (*i.e.*, public-private partnerships that fund effective healthcare programmes through performance-based contracts).

10.2 CAN THE HIV PANDEMIC BE ENDED BY 2030? A PERSONAL VIEW

The global HIV response of the last four decades has been an extraordinary journey. To date, the HIV pandemic consists of many unique local epidemics with different risk populations, transmission dynamics, and varying levels of success in local HIV control. Nevertheless, in all epidemic settings, two main epidemiological factors that influence HIV control will generally determine whether the current fifth decade will be the last decade of HIV: the share of people living with HIV who reach viral suppression and the share of HIV-negative people who have access to HIV prevention interventions. I propose that progress in reaching epidemic control relies on four key aspects: first, the availability and effectiveness of existing interventions for HIV prevention and treatment; second, the potential of innovations that could further curb the HIV pandemic, third, optimisation of health systems and health services to scale up and facilitate access to those interventions; and, fourth, continued commitment, in particular financial commitment, to ensure that suitable interventions can be offered to the people who need them, without financial hardship.

The availability and accessibility of evidence-based prevention and treatment interventions for HIV, including ART, and their real-world effectiveness, will largely influence our progress towards epidemic control. The ambition is to achieve the 95-95-95 targets by 2025 [102]. Achieving this target should accelerate substantial reductions in HIV incidence, by lowering viral loads in people living with HIV to undetectable levels and thus preventing onward transmission to seronegative partners, to ultimately "end AIDS" as a public health threat. The hope for significant reductions in HIV incidence from this "treatment as prevention" strategy are based on the individual-level effects of treatment on prevention of new HIV infections shown in randomised-controlled trials [103,104] and observational studies conducted among serodiscordant couples and high-risk communities [105–107], and confirmed by mathematical modelling studies [108]. However, even though about 75% of people living with HIV were accessing ART by the end of 2020 [72], the observed real-world population-level reductions in HIV incidence have been disappointing [109]. The disconnect between individual-level (as estimated by randomised-controlled trials) and real-world population-level effects of treatment (as estimated in cluster randomised trials and quasi-experimental studies) on HIV prevention might be explained by behavioural and biological heterogeneities influencing the infectiousness of and susceptibility to HIV infection across individuals and communities [110]. Whereas treatment remains a crucial pillar of the HIV response to improve the health and life-expectancy of people living with HIV, simultaneous emphasis should be placed on scaling up interventions for HIV prevention. Here, in generalised epidemic settings as well as in concentrated epidemics, the proven most effective strategy is combination prevention, *i.e.*, promoting a combination of biomedical, behavioural, and structural interventions

designed to meet the HIV prevention needs, including condom use, VMMC and PrEP, with broad population coverage [34].

Next to the already widely applied prevention, diagnosis and treatment interventions for HIV, there are several innovations in the pipeline that could help to further curb the HIV pandemic. Promising innovations that have been proven effective in recent pilot studies and could make a more short-term difference are, for instance, long-acting antiretrovirals for treatment [111] and prevention [112,113], HIV self-testing [114], and point-of-care viral load monitoring (similar to the widely used blood-glucose testing) [115]. Such interventions might be especially useful for harder-to-reach key populations, who could benefit from not having to go to health clinics regularly for their HIV services. Since over two decades, there is also the hope for discovering a cure for HIV as well as developing a vaccine to prevent HIV infection. Discovering a cure for HIV, if accessible to the majority of people living with HIV, could prevent many new infections, overcome the current limitations of antiretroviral treatment, and could lead to large reductions in required funding needed to reach epidemic control [116]. Although research to find a cure has been ongoing, a breakthrough discovery is not yet in sight [116]. The development of a vaccine could contribute substantially to curbing transmission, especially when (initially) targeted at people with a higher risk of HIV exposure, including seronegative people in serodiscordant relationships, sex workers and MSM [117]. An HIV vaccine might however not be the silver bullet we would like it to be, as substantial changes in prevalence would occur with a delay of one or two decades. Additionally, the scale-up of vaccination strategies requires time and substantial funding, and optimal implementation can be challenging, as became evident throughout the history of the HIV pandemic. Hence, while some believe that the invention of a vaccine will be the only way to end AIDS by 2030 [118], I suggest that over the next decade the focus should be on efficiently scaling up existing interventions to people who need them most. While a vaccine might not be developed and distributed in time to reach epidemic control by 2030, it could be a valuable intervention to sustain epidemic control afterwards.

Optimal utilisation of the available prevention, diagnosis and treatment interventions relies on efficient and equitable health systems design. In the next decade, the emphasis should be on offering people-centred, needs-sensitive health services, including tailored services for key populations (*e.g.*, opportunities for accessing services outside of regular clinics, anonymous services, differentiated-care packages [119]) and for people living with HIV (*e.g.*, services that integrate the management of tuberculosis, cardiovascular diseases [120,121]). As financial and human resources remain limited, widely available population-based survey data in combination with geospatial modelling and artificial intelligence methods should be leveraged to target the right populations at the right places with the right interventions. Applying this precision public health approach yields the potential of optimising healthcare

delivery [122,123]. Such analyses could, for instance, reveal national and local disparities in HIV incidence and prevalence as well as in access to currently available HIV treatment and prevention services, allowing to prioritise disadvantaged subpopulations to meet healthcare needs and optimally allocate resources. This is especially important when moving towards the 95-95-95 cascade-of-care targets, to ensure that high-risk populations, such as sex workers, MSM, and mobile populations such as truck drivers, are not left behind as the last, say, 5% of individuals not accessing the HIV services they need. Artificial intelligence methods and geospatial modelling of population-based survey data can also help to improve our understanding of changes in HIV transmission dynamics when moving towards epidemic control, which, in turn, can inform future HIV prevention and control programmes and their subsequent financing.

Sustained financial commitment at the global and national level will be essential to end the HIV pandemic. Currently, the world's economies are under pressure: climate change, new pandemics (such as COVID-19), armed conflict and geopolitical tensions, economic instabilities and shifting political landscapes will continue to affect overall funding priorities and might reduce fiscal space for health investments. This has important consequences for the funding of HIV treatment and prevention programmes and for the scientific research that should lead to new innovations in the HIV response. To address this challenge, pooling, streamlining, and equitably distributing global health resources, which currently largely come from official development assistance provided directly or indirectly by governments of high-income countries, could lead to a better alignment of financial resources and healthcare needs in different regions and populations [124]. To assess in which direction the available funding should flow, funding agencies should allow for country ownership in health system design and a bottom-up approach for deciding on priority areas, where political representatives and communities from low-income and middle-income economies in the Global South should determine funding priorities in their region, rather than decision-making led by high-income economies based on their local priorities and perspectives. In addition, building national scientific funding agencies and strengthening local research capacity could contribute to achieving and securing country ownership [125]. Furthermore, collaboration across disciplines and sectors—academia, policy makers, industry, and civil society—is essential to assure that the HIV response is aligned with other global health and development initiatives.

In conclusion, ending the HIV pandemic by 2030 might be within reach if we are able to utilise today's knowledge and technologies to bring suitable interventions to all places and all people needing access to HIV prevention and treatment. My hope is that in ten years from now, new HIV infections will be uncommon due to optimal use of interventions for HIV prevention and that AIDS will have become a rare disease as all people living with HIV will

have easy access to effective treatment. We have the opportunities at hand, but we are not there yet. Continued commitment to fighting this pandemic, in a world that is continuously changing, will be essential to reach the goal of ending HIV.

10.3 CONCLUSIONS AND RECOMMENDATIONS

Conclusions

1. HIV transmission is geographical heterogeneous at the subnational level in sub-Saharan Africa, with high-transmission foci largely centred around areas with high economic activity.
2. While HIV prevalence among key populations across sub-Saharan Africa is alarmingly high, including among key populations engaging in transactional sex, sex work sites do not seem to directly affect HIV prevalence among the general population in surrounding areas.
3. Innovations in HIV service delivery – integration, elimination of point-of-care steps, task-shifting, and location-shifting – can boost service scale-up, differentiation, efficiency, and sustainability.
4. Integrating HIV services and other health services could, by-and-large, improve HIV service uptake and cascade-of-care outcomes as well as outcomes for other diseases and conditions, and thus contribute to the goal of "ending AIDS by 2030" while simultaneously supporting progress towards UHC.

Recommendations for policy and scientific research

1. Strategies for prevention and control of HIV should take into account local variations in HIV burdens and underlying transmission dynamics to better target interventions, and should specifically scale-up tailored interventions for key populations.
2. Countries in sub-Saharan Africa that are affected by the HIV pandemic should strive towards more integrated HIV services and utilising suitable healthcare delivery innovations, based on current healthcare availability and tailored to local populations' needs, even when (local) evidence is limited.
3. Collecting fine-scale nationally representative data on ART uptake and cascade-of-care outcomes, as well as on uptake of (V)MMC and PrEP, could enable better quantification of the real-life impact of such interventions on curbing the HIV pandemic in different regions and epidemic settings.
4. Future research should focus on better understanding the role of key populations and population mobility (*e.g.*, by seasonal workers and truck drivers) in HIV transmission dynamics to better understand the clustering of HIV in geographical areas.

5. Continued collaboration between researchers, policy makers, healthcare providers and other stakeholders is essential to assess how broader healthcare systems and attached financing mechanisms should be reformed to match the needs of recipients of care while dealing with declining resources for global health.

REFERENCES

1. Cuadros DF, Li J, Branscum AJ, Akullian A, Jia P, Mziray EN, *et al.* Mapping the spatial variability of HIV infection in Sub-Saharan Africa: Effective information for localized HIV prevention and control. Nature. 2017;7: 1–11. doi:10.1038/s41598-017-09464-y

2. Dwyer-lindgren L, Cork MA, Sligar A, Steuben KM, Wilson KF, Provost NR, *et al.* Mapping HIV prevalence in sub-Saharan Africa between 2000 and 2017. Nature. 2019. doi:10.1038/s41586-019-1200-9

3. Sartorius B, VanderHeide JD, Yang M, Goosmann EA, Hon J, Haeuser E, *et al.* Subnational mapping of HIV incidence and mortality among individuals aged 15--49 years in sub-Saharan Africa, 2000--18: a modelling study. Lancet HIV. 2021;8: e363--e375.

4. Palk L, Blower S. Geographic variation in sexual behaviour can explain geospatial heterogeneity in the severity of the HIV epidemic in Malawi. BMC Med. 2018;16: 22. doi:10.1186/s12916-018-1006-x

5. Magadi M, Desta M. A multilevel analysis of the determinants and cross-national variations of HIV seropositivity in sub-Saharan Africa : Evidence from the DHS. Health Place. 2011;17: 1067–1083. doi:10.1016/j.healthplace.2011.06.004

6. Cuadros DF, Branscum AJ, Miller FD, Awad SF, Abu-Raddad LJ. Are geographical "cold spots" of male circumcision driving differential HIV dynamics in Tanzania? Front public Heal. 2015;3: 218.

7. Côté A-M, Sobela F, Dzokoto A, Nzambi K, Asamoah-Adu C, Labbé A-C, *et al.* Transactional sex is the driving force in the dynamics of HIV in Accra, Ghana. AIDS. 2004;18: 917–925.

8. Prüss-Ustün A, Wolf J, Driscoll T, Degenhardt L, Neira M, Calleja JMG. HIV due to female sex work: regional and global estimates. PLOS ONE. 2013;8: e63476.

9. Steen R, Hontelez JAC, Mugurungi O, Mpofu A, Matthijsse SM, de Vlas SJ, *et al.* Economy, migrant labour and sex work: interplay of HIV epidemic drivers in Zimbabwe over three decades. AIDS. 2019;33: 123.

10. Carr-Hill R. Missing millions and measuring development progress. World Dev. 2013;46: 30–44.

11. Mitlin D, Satterthwaite D. Urban poverty in the global south: scale and nature. Routledge; 2012.

12. Cassels S, Camlin CS. Geographical mobility and heterogeneity of the HIV epidemic. Lancet HIV. 2016;3: e339–e341. doi:10.1016/S2352-3018(16)30048-0

13. Kelly CA, Soler-Hampejsek E, Mensch BS, Hewett PC. Social desirability bias in sexual behaviour reporting: evidence from an interview mode experiment in rural Malawi. Int Perspect Sex Reprod Health. 2013;39: 14.

14. Mooney AC, Campbell CK, Ratlhagana M-J, Grignon JS, Mazibuko S, Agnew E, *et al.* Beyond social desirability bias: investigating inconsistencies in self-reported HIV testing and treatment behaviours among HIV-positive adults in North West Province, South Africa. AIDS Behav. 2018;22: 2368–2379.

15. Cleasby IR, Nakagawa S, Schielzeth H. Quantifying the predictability of behaviour: statistical approaches for the study of between-individual variation in the within-individual variance. Methods Ecol Evol. 2015;6: 27–37.

16. Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, *et al.* Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet. 2007; 643–656.

17. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, *et al.* Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007;369: 657–666. doi:10.1016/S0140-6736(07)60313-4

18. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 trial. PLOS Med. 2005;2: 1112–1122. doi:10.1371/journal.pmed.0020298

19. Wilcken A, Keil T, Dick B. Traditional male circumcision in eastern and southern Africa: a systematic review of prevalence and complications. Bull World Health Organ. 2010;88: 907–914.

20. Dunsmuir Wd, Gordon EM. The history of circumcision. BJU Int. 1999;83: 1–12.

21. World Health Organization (WHO). Preventing HIV through safe voluntary medical male circumcision for adolescent boys and men in generalized HIV epidemics: recommendations and key considerations. World Health Organization; 2020. Available: https://apps.who.int/iris/bitstream/handle/10665/350120/9789240039797-eng.pdf?sequence=1

22. Gray RH, Kiwanuka N, Quinn TC, Sewankambo NK, Serwadda D, Mangen FW, *et al.* Male circumcision and HIV acquisition and transmission: Cohort studies in Rakai, Uganda. AIDS. 2000;14: 2371–2381. doi:10.1097/00002030-200010200-00019

23. Shaffer DN, Bautista CT, Sateren WB, Sawe FK, Kiplangat SC, Miruka AO, *et al.* The protective effect of circumcision on HIV incidence in rural low-risk men circumcised predominantly by traditional circumcisers in Kenya: Two-year follow-up of the Kericho HIV Cohort Study. J Acquir Immune Defic Syndr. 2007;45: 371–379. doi:10.1097/QAI.0b013e318095a3da

24. Baeten JM, Richardson BA, Lavreys L, Rakwar JP, Mandaliya K, Bwayo JJ, *et al.* Female-to-male infectivity of HIV-1 among circumcised and uncircumcised Kenyan men. J Infect Dis. 2005;191: 546–553. doi:10.1086/427656

25. Davis S, Toledo C, Lewis L, Maughan-Brown B, Ayalew K, Kharsany ABM. Does voluntary medical male circumcision protect against sexually transmitted infections among men and women in real-world scale-up settings? Findings of a household survey in KwaZulu-Natal, South Africa. BMJ Glob Heal. 2019;4: e001389.

26. Amusa L, Zewotir T, North D, Kharsany A, Lewis L. Association of medical male circumcision and sexually transmitted infections in a population-based study using targeted maximum likelihood estimation. BMC Public Health. 2021;21: 1–10.

27. Amusa L, Zewotir T, North D, Kharsany ABM, Lewis L. Medical male circumcision and HIV prevention among men in Kwazulu-Natal, South Africa: A propensity score analysis. Sci African. 2021;11: e00683.

28. Weiss H a, Quigley M a, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. AIDS. 2000;14: 2361–2370. doi:10.1016/S1473-3099(09)70235-X

29. Wellings K, Collumbien M, Slaymaker E, Singh S, Hodges Z, Patel D, *et al.* Sexual behaviour in context: a global perspective. Lancet. 2006;368: 1706–1728.

30. Uchudi J, Magadi M, Mostazir M. A multilevel analysis of the determinants of

high-risk sexual behaviour in sub-Saharan Africa. J Biosoc Sci. 2012;44: 289–311.

31. Williams BG, Lloyd-Smith JO, Gouws E, Hankins C, Getz WM, Hargrove J, *et al.* The potential impact of male circumcision on HIV in Sub-Saharan Africa. PLOS Med. 2006;3: e262.

32. Weiss HA, Quigley MA, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. AIDS. 2000;14: 2361±2370 Keywords:

33. Meyer-Rath G, McGillen JB, Cuadros DF, Hallett TB, Bhatt S, Wabiri N, *et al.* Targeting the right interventions to the right people and places: the role of geospatial analysis in HIV program planning. AIDS. 2018;32: 957.

34. Anderson S-J, Cherutich P, Kilonzo N, Cremin I, Fecht D, Kimanga D, *et al.* Maximising the effect of combination HIV prevention through prioritisation of the people and places in greatest need: a modelling study. Lancet. 2014;384: 249–256.

35. Aral SO, Torrone E, Bernstein K. Geographical targeting to improve progression through the sexually transmitted infection/HIV treatment continua in different populations. Curr Opin HIV AIDS. 2015;10: 477.

36. Grantham KL, Kerr CC, Wilson DP. Local responses to local epidemics for national impact need advanced spatially explicit tools. AIDS. 2016;30: 1481–1482.

37. Dwyer-Lindgren L, Cork MA, Sligar A, Steuben KM, Wilson KF, Provost NR, *et al.* Mapping HIV prevalence in sub-Saharan Africa between 2000 and 2017. Nature. 2019. doi:10.1038/s41586-019-1200-9

38. Bulstra CA, Hontelez JAC, Giardina F, Steen R, Nagelkerke NJD, Bärnighausen T, *et al.* Mapping and characterising areas with high levels of HIV transmission in sub-Saharan Africa: A geospatial analysis of national survey data. PLOS Med. 2020;17: e1003042. doi:10.1371/journal.pmed.1003042

39. Dzomba A, Govender K, Mashamba-Thompson TP, Tanser F. Mobility and increased risk of HIV acquisition in South Africa: A mixed-method systematic review protocol. Syst Rev. 2018;7: 1–7. doi:10.1186/s13643-018-0703-z

40. Tanser F, de Oliveira T, Maheu-Giroux M, Bärnighausen T. Concentrated HIV sub-epidemics in generalized epidemic settings. Curr Opin HIV AIDS. 2014;9: 115.

41. Vearey J. Moving forward: why responding to migration, mobility and HIV in South(ern) Africa is a public health priority. J Int AIDS Soc. 2018;21: e25137.

42. Cassels S, Camlin CS, Seeley J. One step ahead: timing and sexual networks in population mobility and HIV prevention and care. J Int AIDS Soc. 2018;21.

43. Weir SS, Baral SD, Edwards JK, Zadrozny S, Hargreaves J, Zhao J, *et al.* Opportunities for enhanced strategic use of surveys, medical records, and program data for HIV surveillance of key populations: scoping review. JMIR public Heal Surveill. 2018;4: e8042.

44. Bershteyn A, Mutai KK, Akullian AN, Klein DJ, Jewell BL, Mwalili SM. The influence of mobility among high-risk populations on HIV transmission in Western Kenya. Infect Dis Model. 2018;3: 97–106.

45. Okal J, Geibel S, Muraguri N, Musyoki H, Tun W, Broz D, *et al.* Estimates of the size of key populations at risk for HIV infection: men who have sex with men, female sex workers and injecting drug users in Nairobi, Kenya. Sex Transm Infect. 2013;89: 366–371.

46. Baral S, Beyrer C, Muessig K, Poteat T, Wirtz AL, Decker MR, *et al.* Burden of HIV among female sex workers in low-income and middle-income countries: A systematic review and meta-analysis. Lancet Infect Dis. 2012;12: 538–549. doi:10.1016/S1473-3099(12)70066-X

47. Stannah J, Dale E, Elmes J, Staunton R, Beyrer C, Mitchell KM, *et al.* HIV testing and engagement with the HIV treatment cascade among men who have sex with men in Africa: a systematic review and meta-analysis. lancet HIV. 2019;6: e769--e787.

48. Viswasam N, Lyons CE, MacAllister J, Millett G, Sherwood J, Rao A, *et al.* The uptake of population size estimation studies for key populations in guiding HIV responses on the African continent. PLOS ONE. 2020;15: e0228634.

49. MacAllister J, Sherwood J, Galjour J, Robbins S, Zhao J, Dam K, *et al.* A comprehensive review of available epidemiologic and HIV service data for female sex workers, men who have sex with men, and people who inject drugs in select West and Central African countries. JAIDS J Acquir Immune Defic Syndr. 2015;68: S83--S90.

50. Fearon E, Chabata ST, Magutshwa S, Ndori-Mharadze T, Musemburi S, Chidawanyika H, *et al.* Estimating the Population Size of Female Sex Workers in Zimbabwe: Comparison of Estimates Obtained Using Different Methods in Twenty Sites and Development of a National-Level Estimate. J Acquir Immune Defic Syndr. 2020;85: 30–38. doi:10.1097/QAI.0000000000002393

51. Chabata ST, Hensen B, Chiyaka T, Mushati P, Mtetwa S, Hanisch D, *et al.* Changes Over Time in HIV Prevalence and Sexual Behaviour Among Young Female Sex - Workers in 14 Sites in Zimbabwe , 2013 – 2016. AIDS Behav. 2019;23: 1494–1507. doi:10.1007/s10461-019-02410-1

52. Chersich MF, Luchters S, Ntaganira I, Gerbase A, Lo Y-R, Scorgie F, *et al.* Priority interventions to reduce HIV transmission in sex work settings in sub-Saharan Africa and delivery of these services. J Int AIDS Soc. 2013;16: 17980.

53. Liu AY, Cohen SE, Vittinghoff E, Anderson PL, Doblecki-Lewis S, Bacon O, *et al.* Preexposure Prophylaxis for HIV Infection Integrated With Municipal- and Community-Based Sexual Health Services. JAMA Intern Med. 2016;176: 75–84. Available: https://jamanetwork.com/journals/jamainternalmedicine/articlepdf/2470593/ioi150079.pdf

54. Shannon K, Strathdee SA, Goldenberg SM, Duff P, Mwangi P, Rusakova M, *et al.* Global epidemiology of HIV among female sex workers: Influence of structural determinants. Lancet. 2015;385: 55–71. doi:10.1016/S0140-6736(14)60931-4

55. Macdonald V, Verster A, Baggaley R. A call for differentiated approaches to delivering HIV services to key populations. J Int AIDS Soc. 2017;20: 21658.

56. Rao A, Stahlman S, Hargreaves J, Weir S, Edwards J, Rice B, *et al.* Sampling key populations for HIV surveillance: results from eight cross-sectional studies using respondent-driven sampling and venue-based snowball sampling. JMIR public Heal Surveill. 2017;3: e8116.

57. Brookfield S, Dean J, Forrest C, Jones J, Fitzgerald L. Barriers to accessing sexual health services for transgender and male sex workers: A systematic qualitative meta-summary. AIDS Behav. 2020;24: 682–696.

58. Wahome EW, Graham SM, Thiong'o AN, Mohamed K, Oduor T, Gichuru E, *et al.* PrEP uptake and adherence in relation to HIV-1 incidence among Kenyan men who have sex with men. EClinicalMedicine. 2020;26: 100541.

59. Kimani M, van der Elst EM, Chiro O, Oduor C, Wahome E, Kazungu W, *et al.* Pr EP interest and HIV-1 incidence among MSM and transgender women in coastal Kenya. J Int AIDS Soc. 2019;22: e25323.

60. CeSHHAR Zimbabwe. What We Do At CeSHHAR. [cited 17 Aug 2022]. Available: http://ceshhar.org/

61. North Star Alliance. What we do. [cited 17 Aug 2022]. Available: https://www.northstar-alliance.org/

62. Maruyama H, Franks J, Laki D, Msumi O, Makyao N, Rwabiyago OE, *et al.* Bringing HIV services to key populations and their communities in Tanzania: from pilot to scale. J Int AIDS Soc. 2021;24: e25718.

63. Kerrigan D, Kennedy CE, Morgan-Thomas R, Reza-Paul S, Mwangi P, Win KT, *et al.* A community empowerment approach to the HIV response among sex workers: Effectiveness, challenges, and considerations for implementation and scale-up. Lancet. 2015;385: 172–185. doi:10.1016/S0140-6736(14)60973-9

64. Mavhu W, Willis N, Mufuka J, Bernays S, Tshuma M, Mangenah C, *et al.* Effect of a differentiated service delivery model on virological failure in adolescents with HIV in Zimbabwe (Zvandiri): a cluster-randomised controlled trial. Lancet Glob Heal. 2020;8: e264–e275. doi:10.1016/S2214-109X(19)30526-1

65. Grimsrud AT, Pike C, Bekker LG. The power of peers and community in the continuum of HIV care. Lancet Glob Heal. 2020;8: e167–e168. doi:10.1016/S2214-109X(19)30544-3

66. Stangl AL, Lloyd JK, Brady LM, Holland CE, Baral S. A systematic review of interventions to reduce HIV-related stigma and discrimination from 2002 to 2013: how far have we come? J Int AIDS Soc. 2013;16: 18734.

67. Starrs AM, Ezeh AC, Barker G, Basu A, Bertrand JT, Blum R, *et al.* Accelerate progress—sexual and reproductive health and rights for all: report of the Guttmacher– Lancet Commission. Lancet. 2018;391: 2642–2692. doi:10.1016/S0140-6736(18)30293-9

68. Barr D, Garnett GP, Mayer KH, Morrison M. Key populations are the future of the African HIV/AIDS pandemic. J Int AIDS Soc. 2021;24.

69. Girard F. Implications of the Trump Administration for sexual and reproductive rights globally. Reprod Health Matters. 2017;25: 6–13.

70. Duby Z, Nkosi B, Scheibe A, Brown B, Bekker L-G. 'Scared of going to the clinic': Contextualising healthcare access for men who have sex with men, female sex workers and people who use drugs in two South African cities. South Afr J HIV Med. 2018;19: 1–8.

71. Lyons CE, Schwartz SR, Murray SM, Shannon K, Diouf D, Mothopeng T, *et al.* The role of sex work laws and stigmas in increasing HIV risks among sex workers. Nat Commun. 2020;11: 1–10.

72. UNAIDS. Confronting inequalities: Lessons for pandemic responses from 40 years of AIDS. Geneva; 2021. Available: https://www.unAIDS.org/sites/default/files/media_asset/2021-global-AIDS-update_en.pdf

73. Beyrer C, Sullivan PS, Sanchez J, Dowdy D, Altman D, Trapence G, *et al.* A call to action for comprehensive HIV services for men who have sex with men. Lancet. 2012;380: 424–438. doi:10.1016/S0140-6736(12)61022-8

74. Hunt J, Bristowe K, Chidyamatare S, Harding R. 'They will be afraid to touch you': LGBTI people and sex workers' experiences of accessing healthcare in Zimbabwe—an

in-depth qualitative study. BMJ Glob Heal. 2017;2: e000168.

75. Scheibe A, Howell S, Müller A, Katumba M, Langen B, Artz L, *et al.* Finding solid ground: law enforcement, key populations and their health and rights in South Africa. J Int AIDS Soc. 2016;19: 20872.

76. Golovaty I, Sharma M, Heerden A Van, Rooyen H van, Baeten JM, Celum C, *et al.* Cost of integrating non-communicable disease screening into home-based HIV testing and counseling in South Africa. J Acquir Immune Defic Syndr. 2018;176: 139–148. doi:10.1097/QAI.0000000000001713

77. Chamie G, Kwarisiima D, Clark TD, Kabami J, Jain V, Geng E, *et al.* Leveraging rapid community-based HIV testing campaigns for non-communicable diseases in rural Uganda. PLOS ONE. 2012;7. doi:10.1371/journal.pone.0043400

78. Dememew ZG, Jerene D, Datiko DG, Hiruy N, Tadesse A, Moile T, *et al.* The yield of community-based tuberculosis and HIV among key populations in hotspot settings of Ethiopia: A cross-sectional implementation study. PLOS ONE. 2020;15: e0233730.

79. Ortblad KF, Mogere P, Roche S, Kamolloh K, Odoyo J, Irungu E, *et al.* Design of a care pathway for pharmacy-based PrEP delivery in Kenya: results from a collaborative stakeholder consultation. BMC Health Serv Res. 2020;20: 1–9.

80. Roche SD, Wairimu N, Mogere P, Kamolloh K, Odoyo J, Kwena ZA, *et al.* Acceptability and Feasibility of Pharmacy-Based Delivery of Pre-Exposure Prophylaxis in Kenya: A Qualitative Study of Client and Provider Perspectives. AIDS Behav. 2021; 1–12.

81. Nguyen VTT, Phan HTT, Kato M, Nguyen Q-T, Le Ai KA, Vo SH, *et al.* Community-led HIV testing services including HIV self-testing and assisted partner notification services in Vietnam: lessons from a pilot study in a concentrated epidemic setting. J Int AIDS Soc. 2019;22: e25301.

82. Zerbe A, Brittain K, Phillips TK, Iyun VO, Allerton J, Nofemela A, *et al.* Community-based adherence clubs for postpartum women on antiretroviral therapy (ART) in Cape Town, South Africa: a pilot study. BMC Health Serv Res. 2020;20: 1–12.

83. Tsui S, Denison JA, Kennedy CE, Chang LW, Koole O, Torpey K, *et al.* Identifying models of HIV care and treatment service delivery in Tanzania, Uganda, and Zambia using cluster analysis and Delphi survey. BMC Health Serv Res. 2017;17: 1–11.

84. McCombe G, Murtagh S, Lazarus J V, Van Hout MC, Bachmann M, Jaffar S, *et al.* Integrating diabetes, hypertension and HIV care in sub-Saharan Africa: a Delphi consensus study on international best practice. BMC Health Serv Res. 2021;21: 1–9.

85. Ying R, Sharma M, Celum C, Baeten JM, van Rooyen H, Hughes JP, *et al.* Home testing and counselling to reduce HIV incidence in a generalised epidemic setting: a mathematical modelling analysis. lancet HIV. 2016;3: e275--e282.

86. Campos NG, Lince-Deroche N, Chibwesha CJ, Firnhaber C, Smith JS, Michelow P, *et al.* Cost-effectiveness of cervical cancer screening in women living with HIV in South Africa: a mathematical modeling study. J Acquir Immune Defic Syndr. 2018;79: 195.

87. Lancet T. Maintaining the HIV response in a world shaped by COVID-19. Lancet (London, England). 2020;396: 1703.

88. UNAIDS. PRESS RELEASE: Governments step up to close the resource gap for UNAIDS work to end AIDS by 2030. 2022. Available: https://www.unAIDS.org/en/resources/presscentre/pressre-

leaseandstatementarchive/2022/november/20221118_funding

89. Allain-Dupré D, Chatry I, Michalun V, Moisio A. The territorial impact of COVID-19: managing the crisis across levels of government. OECD Policy Responses to Coronavirus. 2020;10: 1620846020–1909698535.

90. Padma T V. Lifesaving fund to fight AIDS, malaria and TB falls short of $18-billion target. Nature. 2022.

91. Atun R, Gale EAM. The challenge of diabetes in sub-Saharan Africa. Lancet Diabetes Endocrinol. 2015;3: 675–677. doi:10.1016/S2213-8587(15)00236-3

92. Teufel F, Seiglie JA, Geldsetzer P, Theilmann M, Marcus ME, Ebert C, *et al.* Body-mass index and diabetes risk in 57 low-income and middle-income countries: a cross-sectional study of nationally representative, individual-level data in 685 616 adults. Lancet. 2021;398: 238–248.

93. Geldsetzer P, Manne-Goehler J, Marcus M-E, Ebert C, Zhumadilov Z, Wesseh CS, *et al.* The state of hypertension care in 44 low-income and middle-income countries: a cross-sectional study of nationally representative individual-level data from 1·1 million adults. Lancet. 2019;394: 652–662.

94. Bekker LG, Alleyne G, Baral S, Cepeda J, Daskalakis D, Dowdy D, *et al.* Advancing global health and strengthening the HIV response in the era of the Sustainable Development Goals: the International AIDS Society—Lancet Commission. Lancet. 2018;392: 312–358. doi:10.1016/S0140-6736(18)31070-5

95. Goodwin N. Thinking differently about integration: people-centred care and the role of local communities. Int J Integr Care. 2014;14.

96. Organization WH, Others. Continuity and coordination of care: a practice brief to support implementation of the WHO Framework on integrated people-centred health services. World Health Organization; 2018. Available: https://apps.who.int/iris/bitstream/handle/10665/274628/9789241514033-eng.pdf

97. Castro MC, Massuda A, Almeida G, Menezes-Filho NA, Andrade MV, de Souza Noronha KVM, *et al.* Brazil's unified health system: the first 30 years and prospects for the future. Lancet. 2019;394: 345–356.

98. World Health Organization (WHO), Others. Global strategy on digital health 2020-2025. 2021.

99. Kickbusch I, Piselli D, Agrawal A, Balicer R, Banner O, Adelhardt M, *et al.* The Lancet and Financial Times Commission on governing health futures 2030: growing up in a digital world. Lancet. 2021.

100. Jay J, Buse K, Hart M, Wilson D, Marten R, Kellerman S, *et al.* Building from the HIV response toward universal health coverage. PLOS Med. 2016;13: e1002083.

101. Atun R, Silva S, Ncube M, Vassall A. Innovative financing for HIV response in sub-Saharan Africa. J Glob Health. 2016;6. doi:10.7189/jogh.06.010407

102. United Nations. Political Declaration on HIV and AIDS: Ending Inequalities and Getting on Track To End AIDS By 2030 United Nations General Assembly. Geneva, Switzerland; 2021. Available: https://www.unAIDS.org/sites/default/files/media_asset/2021_political-declaration-on-hiv-and-AIDS_en.pdf

103. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, *et al.* Antiretroviral therapy for the prevention of HIV-1 transmission. N Engl J Med. 2016;375: 830–839.

104. Group ISS. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;373: 795–807.

105. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, Van Lunzen J, *et al.* Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. Jama. 2016;316: 171–181.

106. Bavinton BR, Pinto AN, Phanuphak N, Grinsztejn B, Prestage GP, Zablotska-Manos IB, *et al.* Viral suppression and HIV transmission in serodiscordant male couples: an international, prospective, observational, cohort study. lancet HIV. 2018;5: e438--e447.

107. Tanser F, Bärnighausen T, Graspa E, Zaidi J, Newell ML. High Coverage of ART Associated with Decline in Risk of HIV Acquisition in Rural KwaZulu-Natal, South Africa. Science (80-). 2013;339: 966–972. doi:10.1177/1045389X05047210

108. Eaton JW, Johnson LF, Salomon JA, Bärnighausen T, Bendavid E, Bershteyn A, *et al.* HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. PLOS Med. 2012;9: e1001245.

109. Baral S, Rao A, Sullivan P, Phaswana-Mafuya N, Diouf D, Millett G, *et al.* The disconnect between individual-level and population-level HIV prevention benefits of antiretroviral treatment. lancet HIV. 2019;6: e632--e638.

110. Hontelez JAC, N.J.D N, S.J. de V. HIV Treatment as Prevention: Bound to Disappoint? Trop Med Int Heal. 2023;(in press).

111. Swindells S, Andrade-Villanueva J-F, Richmond GJ, Rizzardini G, Baumgarten A, Masiá M, *et al.* Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. N Engl J Med. 2020;382: 1112–1123.

112. Clement ME, Kofron R, Landovitz RJ. Long-acting injectable cabotegravir for the prevention of HIV infection. Curr Opin HIV AIDS. 2020;15: 19.

113. Landovitz RJ, Li S, Grinsztejn B, Dawood H, Liu AY, Magnus M, *et al.* Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial. PLOS Med. 2018;15: e1002690.

114. Hatzold K, Gudukeya S, Mutseta MN, Chilongosi R, Nalubamba M, Nkhoma C, *et al.* HIV self-testing: breaking the barriers to uptake of testing among men and adolescents in sub-Saharan Africa, experiences from STAR demonstration projects in Malawi, Zambia and Zimbabwe. J Int AIDS Soc. 2019;22: e25244.

115. Ochodo EA, Olwanda EE, Deeks JJ, Mallett S. Point-of-care viral load tests to detect high HIV viral load in people living with HIV/AIDS attending health facilities. Cochrane Database Syst Rev. 2022.

116. Dybul M, Attoye T, Baptiste S, Cherutich P, Dabis F, Deeks SG, *et al.* The case for an HIV cure and how to get there. Lancet HIV. 2021;8: e51--e58.

117. Chen S. Economics of HIV Vaccines and HIV Vaccine Research and Development. Harvard University. 2018.

118. Fauci AS, Lane HC. Four decades of HIV/AIDS—much accomplished, much to do. N Engl J Med. 2020;383: 1–4.

119. Wolf RC, Bingham T, Millett G, Wilcher R. Building the evidence base to optimize the impact of key population programming across the HIV cascade. J Int AIDS Soc. 2018;21.

120. Haldane V, Legido-Quigley H, Chuah FLH, Sigfrid L, Murphy G, Ong SE, *et al.* Integrating cardiovascular diseases, hypertension, and diabetes with HIV services: a systematic review. AIDS Care Psychol Socio-Med Asp AIDS HIV. 2018;30: 103–115. doi:10.1080/09540121.2017.1344350

121. Legido-Quigley H, Montgomery CM, Khan P, Atun R, Fakoya A, Getahun H, *et al.* Integrating tuberculosis and HIV services in low- and middle-income countries: a systematic review. Trop Med Int Heal. 2012/12/12. 2013;18: 199–211. doi:10.1111/tmi.12029

122. The Lancet Public Health. Next generation public health: towards precision and fairness. 2019.

123. Blower S, Okano JT. Precision public health and HIV in Africa. Lancet Infect Dis. 2019;19: 1050–1052.

124. Hanson K, Brikci N, Erlangga D, Alebachew A, De Allegri M, Balabanova D, *et al.* The Lancet Global Health Commission on financing primary health care: putting people at the centre. Lancet Glob Heal. 2022;10: e715--e772.

125. Noor AM. Country ownership in global health. PLOS Glob Public Heal. 2022;2: e0000113.

Chapter 11

Summary

Nederlandse samenvatting

SUMMARY

The HIV pandemic has been one of the most devastating public health threats in recent history, especially in sub-Saharan Africa. The overarching aim of this thesis is to describe and improve our understanding of the HIV epidemiology in various sub-Saharan African countries, and to provide insight into which health systems innovations could mitigate global challenges in the HIV response.

Chapter 1 provides a general introduction into HIV epidemiology, the rise of the global HIV/AIDS pandemic since the 80s, the discovery and roll-out of antiretroviral therapy (ART) and other key interventions in reducing transmission of the virus. We also describe the existence of geospatial variations in HIV prevalence and transmission, and the important role of key populations in the HIV pandemic. We further describe the history and current status of HIV service delivery and HIV financing in sub-Saharan Africa, the subcontinent hardest hit by the pandemic. We outline the global HIV targets and introduce two key challenges in reaching control of the pandemic: the persistent and increasing health systems and funding constraints, and the need for universal, more integrated care to adapt to the shifting population demographics and disease burdens. Chapter 1 concludes by introducing geospatial modelling and healthcare delivery innovations as potential solutions in reaching sustainable control of the HIV pandemic.

The research in this thesis gives answer to the following four research questions:

1. Where is the HIV burden highest in sub-Saharan Africa, the epicentre of the pandemic, and what drives the geographical heterogeneity in HIV transmission and prevalence on the subcontinent?
2. What is the HIV burden among key populations and how does this contribute to the HIV epidemiology in sub-Saharan Africa?
3. Which service delivery and financing innovations could mitigate current global challenges in the HIV response?
4. How can HIV service integration contribute to optimising the HIV response and reaching universal health coverage?

In **Chapter 2**, we map and characterise high-prevalence areas for young adults (15–29 years of age), as a proxy for areas with high levels of transmission in Eastern and Southern Africa, where 55% of people living with HIV reside. We use geolocated nationally representative survey data, including 113,000 adults from over 3,500 locations throughout Kenya, Malawi, Mozambique, Tanzania, Uganda, Zambia, and Zimbabwe, and open-source environmental data. We predict HIV prevalence levels at unmeasured locations and explore to what extent behavioural, socioeconomic, and environmental factors explain HIV prevalence at the

individual- and sample-location level. Findings suggest that, among young adults, micro-epidemics of relatively high HIV prevalence alternate with areas of very low prevalence, clearly illustrating the existence of areas with high levels of transmission. These areas are partially characterised by high economic activity, relatively high socioeconomic status, and risky sexual behaviour.

Chapter 3 describes a quasi-experimental study to quantify the 'real-life' impact of male circumcision, one of the key interventions in HIV prevention, on HIV status among men in sub-Saharan Africa. We pooled individual-level nationally-representative survey data from all sub-Saharan African countries that included information on male circumcision status and HIV status. Capturing data on 279,351 men from 29 countries, we estimated the effect of men's circumcision status on HIV-seropositivity. We used modified Poisson regression models with household fixed-effects, to control for heterogeneity in observed and unobserved factors that might confound the association shared by men living in the same household. In our analysis, the 'real-world', long-term impact of male circumcision equates to a 19% [95% CI: 11%-27%] reduction in the risk of HIV infection among men in sub-Saharan Africa. These findings underpin the importance of scaling up VMMC, alongside other HIV prevention interventions, as an important element of HIV control and elimination strategies.

Chapter 4 comprises a systematic review to assess the HIV burdens among men who have sex with men, transgender-women and -men, and male and transgender sex workers and compare their relative risks of having HIV with the general population in sub-Saharan Africa. We included peer-reviewed empirical studies that estimated HIV prevalence levels within sub-Saharan African contexts in these populations, which resulted in the inclusion of 44 articles. We found the prevalence among men who have sex with men, transgender women and male sex workers, the populations for whom data estimates were available, to be alarmingly high, and significantly higher than within the general population in both West and Central Africa as well as East and Southern Africa. Prevalence among MSM and transgender women was significantly higher compared to the general population, with prevalence ratios (PRs) of 11.3 [CI: 9.9-12.9] for MSM and 8.1 [CI: 6.9-9.6] for transgender women in Western and Central Africa, to respectively 1.9 [CI: 1.7-2.0] and 2.1 [CI: 1.9-2.4] in Eastern and Southern Africa. Prevalence among MSW was significantly higher in Nigeria (PR: 12.4 [CI: 7.3-21.0]) and Kenya (PR: 8.6 [CI: 4.6-15.6]). This high prevalence, coupled with the specific risks and vulnerabilities faced by these populations, highlights the urgent need for risk-group tailored prevention and treatment interventions across the subcontinent.

The association between distance to female sex work locations and HIV status in the general population is investigated in **Chapter 5**, for the Zimbabwean setting. We included data from 16,121 individuals (aged 15-49 years) from 400 sample locations and the locations

of 56 sex work sites throughout Zimbabwe (estimated to be 95% of all sex work sites). Univariate and multivariate analyses showed that no significant association exists between HIV seroprevalence and proximity to the nearest sex work site among the general population in Zimbabwe, regardless of which type of site was closest. The absence of an association could be explained by the mobile nature of both female sex workers and their clients, as individual-level indicators of sex work were significantly associated with HIV.

In **Chapter 6** we provide an overview of delivery model innovations that could support sustainable HIV treatment, by expanding access to treatment and improving efficiency of treatment programmes. We describe twelve models for ART delivery, which could be achieved through five categories of delivery innovations: integrating ART, modifying steps in the ART value chain, eliminating steps in the ART value chain, changing ART locations, and keeping the status quo of vertical treatment delivery. We conclude that suitability of the models will highly depend on local and national contexts, including existing health systems resources, available funding, and type of HIV epidemic. We emphasise that future implementation research needs to identify which models are the best fit for different contexts.

In **Chapter 7**, we estimate trends in HIV financing in the 10 countries with the largest ART programmes in sub-Saharan Africa over the next five years to illustrate potential gaps due to the COVID-19-related economic crises, and proposed mitigation strategies to ensure continued service delivery for HIV. We illustrated that the COVID-19 pandemic is putting acute pressure on HIV programmes in high burden countries and that – with potential declines in funding of as much as 5% or 11% – the scale-up of HIV prevention and treatment in sub-Saharan Africa could come to halt or even reverse. Our predictions indicate that it is imperative to start considering mitigation strategies for the ensuing financial gaps.

Chapter 8 presents the findings of a systematic review to quantify the impact of service integration on the HIV care cascade, health outcomes, and cost-effectiveness. The review is based on synthesis of the global empirical evidence of experimental and observational studies that featured both an HIV services integration intervention and a comparator. HIV cascade-of-care outcomes—uptake of HIV testing and counselling, ART initiation coverage and speed, retention in HIV care, treatment adherence, and viral suppression—tended to be higher in integrated services. Also, the uptake of non-HIV services was commonly higher, HIV-free survival was similar or higher, HIV and non-HIV mortality were lower, and the costs of HIV and non-HIV services tended to be lower in integrated services. We conclude that, overall, integration of HIV services and other health services tends to improve health systems and health outcomes.

Chapter 9 outlines a framework for evidence-based policymaking when evidence is incomplete, based on the case of HIV programme integration. Proper use of scientific evidence in other contexts requires adequate and systematic assessments of the transportability of an intervention. Several methods exist that allow for judging transferability and comprehensively identifying key context-specific indicators across studies that can affect the reported impact of interventions. We propose that, by drawing on well-established design and implementation methodologies, countries could substantially improve decision-making even in the absence of local scientific evidence.

We conclude in **Chapter 10** that ending the HIV pandemic by 2030 might be within reach if we are able utilise today's knowledge and technologies to bring suitable interventions to all places and all people needing access to HIV prevention and treatment. Continued commitment to fighting this pandemic, in a world that is continuously changing, will be essential to reach the goal of ending HIV.

NEDERLANDSE SAMENVATTING

De hiv-pandemie is één van de meest verwoestende bedreigingen voor de volksgezondheid uit de recente geschiedenis geweest, vooral in sub-Sahara Afrika. Het overkoepelende doel van dit proefschrift is het verbeteren van ons begrip over de hiv-epidemiologie in verschillende landen in sub-Sahara Afrika en het verschaffen van inzicht in welke innovaties in gezondheidssystemen de wereldwijde uitdagingen in de hiv-respons kunnen verminderen.

Hoofdstuk 1 geeft een algemene inleiding in de hiv-epidemiologie, de opkomst van de wereldwijde hiv/aids-pandemie sinds de jaren 80 en de ontdekking en het opschalen van antiretrovirale therapie (ART), en andere belangrijke maatregelen om de overdracht van het virus te verminderen. Het hoofdstuk beschrijft ook het fenomeen van waargenomen heterogeniteit in hiv-prevalentie en -overdracht en de rol van hoogrisicogroepen in de algehele hiv-pandemie. Verder beschrijven we de huidige status van hiv-zorgverlening en hiv-zorgfinanciering in sub-Sahara Afrika en de wereldwijde hiv-doelstellingen en introduceren we twee belangrijke uitdagingen om de pandemie onder controle te krijgen: de aanhoudende en toenemende financieringsbeperkingen, en tegelijk de behoefte aan universele, meer geïntegreerde zorg bij een veranderende bevolkingssamenstelling en ziektelast. Hoofdstuk 1 wordt afgesloten met de introductie van geospatiële modellering en innovaties in de gezondheidszorg als mogelijke oplossingen voor het bereiken van een duurzame beheersing van de hiv-pandemie.

Het onderzoek in dit proefschrift geeft antwoord op de volgende vier onderzoeksvragen:

1. Waar is de hiv-ziektelast het hoogst in sub-Sahara Afrika, het epicentrum van de pandemie, en wat drijft de geografische heterogeniteit in hiv-overdracht en -prevalentie op het subcontinent?
2. Wat is de hiv-last onder hoogrisicogroepen en hoe draagt die bij aan de hiv-epidemiologie in sub-Sahara Afrika?
3. Welke innovaties op het gebied van dienstverlening en financiering kunnen de huidige wereldwijde uitdagingen in de hiv-respons verminderen?
4. Hoe kan de integratie van hiv-diensten bijdragen aan het optimaliseren van de hiv-respons en het bereiken van een universele gezondheidsdekking?

In **Hoofdstuk 2** brengen we gebieden met een hoge hiv-prevalentie onder jongvolwassenen (15-29 jaar) in kaart en karakteriseren we deze gebieden als graadmeter voor gebieden met hoge hiv-overdracht in Oost- en Zuidelijk Afrika, waar 55% van de mensen met hiv woont. We gebruiken geogelokaliseerde, nationaal representatieve enquêtegegevens van ongeveer 113 duizend volwassenen uit meer dan 3.500 locaties in Kenia, Malawi, Mozambique, Tanzania, Oeganda, Zambia en Zimbabwe, en open-source milieugegevens. We

voorspellen hiv-prevalentieniveaus op niet-gemeten locaties en onderzoeken vervolgens in hoeverre gedrags-, sociaaleconomische- en omgevingsfactoren de hiv-prevalentie verklaren op individueel niveau en op steekproeflocatieniveau. De bevindingen laten zien dat onder jongvolwassenen micro-epidemieën met een relatief hoge hiv-prevalentie worden afgewisseld met gebieden met een zeer lage prevalentie, wat duidelijk het bestaan illustreert van specifieke gebieden met hoge transmissieniveaus. Deze gebieden worden gekenmerkt door een hoge economische activiteit, een relatief hoge sociaaleconomische status en risicovol seksueel gedrag.

Hoofdstuk 3 beschrijft een quasi-experimenteel onderzoek naar de kwantificering van de feitelijke impact van mannenbesnijdenis - een van de belangrijkste interventies in hiv-preventie - op de hiv-status onder mannen in sub-Sahara Afrika. We gebruikten nationaal representatieve enquêtegegevens uit alle landen in sub-Sahara Afrika waar gegevens over de besnijdenisstatus en de hiv-status van mannen zijn vastgelegd. Met de gegevens van in totaal 279.351 mannen uit 29 landen schatten we vervolgens het effect van de besnijdenisstatus van mannen op hiv-seropositiviteit. We gebruikten gemodificeerde Poisson-regressiemodellen met fixed-effects op niveau van het huishouden, om te corrigeren voor heterogeniteit in waargenomen en niet-waargenomen factoren die de associatie zouden kunnen verstoren die wordt gedeeld door mannen die in hetzelfde huishouden wonen. In onze analyse komt de langetermijnimpact van besnijdenis bij mannen overeen met een vermindering van 19% [95% betrouwbaarheidsinterval (BI): 11%-27%] van het risico op hiv-infectie bij mannen in sub-Sahara Afrika. Deze bevindingen onderstrepen het belang van het verder opschalen van medische mannenbesnijdenis, naast andere hiv-preventie-interventies, als een essentieel onderdeel van strategieën voor de bestrijding en uiteindelijk eliminatie van hiv.

Hoofdstuk 4 omvat een systematische review met als doel de hiv-ziektelast op populatieniveau te bepalen onder mannen die seks hebben met mannen, transgendervrouwen en -mannen, en mannelijke en transgender sekswerkers, en hun relatieve risico's op hiv te vergelijken met die van de algemene bevolking in sub-Sahara Afrika. We hebben in totaal 44 empirische studies geïdentificeerd die een schatting geven van de hiv-prevalentie in deze hoogrisicogroepen in sub-Sahara Afrika. De gerapporteerde hiv-prevalenties onder mannen die seks hebben met mannen, transgendervrouwen en mannelijke sekswerkers bleken alarmerend hoog in zowel West- en Centraal-Afrika als Oost- en Zuidelijk Afrika. De prevalentie onder mannen die seks hebben met mannen en transgendervrouwen was vele malen hoger in vergelijking met de algemene bevolking, met prevalentieratio's (PR's) van 11,3 [BI: 9,9-12,9] voor MSM en 8,1 [BI: 6,9-9,6] voor transgendervrouwen in West- en Centraal-Afrika, tot respectievelijk 1,9 [BI: 1,7-2,0] en 2,1 [BI: 1,9-2,4] in Oostelijk en Zuidelijk Afrika. De prevalentie onder mannelijke sekswerkers was significant hoger in Nigeria (PR:

12,4 [BI: 7,3-21,0]) en Kenia (PR: 8,6 [BI: 4,6-15,6]), de enige landen waarover data beschikbaar was. De hoge prevalenties, in combinatie met de specifieke risico's en kwetsbaarheden waarmee deze bevolkingsgroepen worden geconfronteerd, benadrukken de dringende behoefte aan preventie- en behandelingsinterventies op maat voor deze hoogrisicogroepen in sub-Sahara Afrika.

Het verband tussen de afstand tot sekswerklocaties van vrouwelijke sekswerkers en de hiv-status in de algemene bevolking is onderzocht in **Hoofdstuk 5**, voor de Zimbabwaanse setting. We hadden de beschikking over gegevens van 16.121 personen uit de algemene bevolking (leeftijd 15-49 jaar) uit 400 steekproeflocaties, en de locaties van 56 sekswerksites in heel Zimbabwe (ongeveer 95% van alle sekswerksites in het land). Univariate en multivariate analyses toonden aan dat er geen significant verband bestaat tussen hiv-prevalentie onder de algemene bevolking in Zimbabwe en de nabijheid van de dichtstbijzijnde sekswerklocatie, ongeacht het type locatie dat het dichtst in de buurt lag. De afwezigheid van een verband kan worden verklaard door het mobiele karakter van zowel vrouwelijke sekswerkers als hun klanten, aangezien indicatoren van het aanbieden en gebruiken van sekswerk op individueel niveau wel significant verband hielden met hiv.

In **Hoofdstuk 6** geven we een overzicht van innovaties in de dienstverlening die duurzame hiv-behandeling met ART kunnen ondersteunen, door de toegang tot behandeling te vergroten of de efficiëntie te verbeteren. We beschrijven twaalf modellen voor de toediening van ART, die kunnen worden gerealiseerd door middel van vijf categorieën van innovaties in de dienstverlening: ART integreren, stappen in de ART-waardeketen aanpassen, stappen in de ART-waardeketen wegnemen, ART-locaties wijzigen, en de status quo: het behouden van verticale behandelingslevering. We concluderen dat de geschiktheid van de modellen in hoge mate zal afhangen van de lokale en nationale context, inclusief de bestaande middelen van het gezondheidszorgsysteem, de beschikbare financiering, en het type hiv-epidemie. We benadrukken dat toekomstig implementatieonderzoek moet uitwijzen welke modellen het meest geschikt zijn voor verschillende contexten.

In **Hoofdstuk 7** schatten we trends in hiv-financiering voor de komende vijf jaar in de tien landen met de grootste ART programma's in sub-Sahara Afrika, om zo mogelijke hiaten als gevolg van de COVID-19-gerelateerde economische crisis te illustreren. Bovendien stellen we mitigatiestrategieën voor die ervoor kunnen zorgen dat de dienstverlening voor hiv wordt voortgezet. We laten zien dat de COVID-19-pandemie een acute druk legt op hiv-programma's in landen met een hoge ziektelast en dat – met mogelijke dalingen in financiering van maar liefst 5% of 11% – de opschaling van hiv-preventie en -behandeling in sub-Sahara Afrika tot stilstand kan komen of zelfs kan omkeren. Onze voorspellingen geven

aan dat het absoluut noodzakelijk is om mitigatiestrategieën voor de daaruit voortvloeiende financiële hiaten te overwegen.

Hoofdstuk 8 presenteert de bevindingen van een systematische review over de impact van het integreren van de hiv zorg met andere zorg op de hiv-zorgcascade, gezondheidsresultaten en kosteneffectiviteit. De beoordeling van de impact was gebaseerd op de synthese van het wereldwijde empirische bewijs van experimentele en observationele studies die zowel een interventie voor de integratie van hiv-diensten als een controle bevatten. De cascade-uitkomsten van hiv-zorg—gebruik van hiv-testen en -counseling, ART-initiatiedekking en -snelheid, behoud van hiv-zorg, therapietrouw en virusonderdrukking—waren over het algemeen gunstiger in geïntegreerde diensten. Ook was het gebruik van niet-hiv-diensten gewoonlijk hoger, was de hiv-vrije overleving vergelijkbaar of hoger, was de hiv- en niet-hiv-mortaliteit lager en waren de kosten van hiv- en niet-hiv-diensten over het algemeen lager in geïntegreerde diensten. We concluderen dat de integratie van hiv-diensten en andere gezondheidsdiensten over het algemeen leidt tot betere gezondheidssystemen en gezondheidsresultaten.

Hoofstuk 9 schetst een raamwerk voor op wetenschappelijk bewijs gebaseerde beleidsvorming in situaties waarin niet altijd duidelijk is of het integreren van zorg werkt, zoals bij integratie van hiv-programma's. Correct gebruik van wetenschappelijk bewijs in andere contexten vereist adequate en systematische beoordelingen van de overdraagbaarheid van een interventie. Er bestaan verschillende methoden die het mogelijk maken om de overdraagbaarheid te beoordelen en om de belangrijkste contextspecifieke indicatoren, die verschillen tussen studies, te identificeren. Wanneer (overdraagbaar) bewijs ontbreekt, stellen we voor dat landen gebruikmaken van gevestigde implementatie- en evaluatie methodologieën.

In **Hoofdstuk 10** concluderen we dat het beëindigen van de hiv-pandemie in 2030 mogelijk binnen bereik is indien we de kennis en technologieën van vandaag gebruiken om meest geschikte interventies aan te bieden aan alle mensen die toegang nodig hebben tot hiv-preventie en -behandeling wereldwijd. Aanhoudende toewijding voor de bestrijding van deze pandemie, in een wereld die voortdurend verandert, zal essentieel zijn om dit ultieme doel te kunnen bereiken.

Chapter 12

About the author

List of publications

Dankwoord / Acknowledgements

PhD portfolio

ABOUT THE AUTHOR

Caroline Annemarie Bulstra (born 1991 in Utrecht, The Netherlands) graduated from high school in 2009, after which she pursued her long-cherished dream of studying Veterinary Medicine at Utrecht University. Her enthusiasm for global public health was ignited after her BSc degree, during internships at the United Nations Food and Agriculture Organisation (Rome, 2013-14) and Dutch Ministry of Economic Affairs (The Hague, 2014). During her MSc degree, she participated in a Summer School on International Relations at the London School of Economics and Political Sciences (LSE), did a wildlife and exotics externship in Kruger Park, South Africa, and joined several annual assemblies of the World Health Organisation in Geneva as a student representative.

Caroline graduated as a veterinarian in 2017 with specialisation in Large Animal Medicine and Veterinary Public Health, after writing her MSc thesis at the Infectious Disease Control section of the Erasmus MC Department of Public Health. She was offered a PhD position in the same research group, under supervision of Prof.dr. Sake de Vlas and Dr. Jan Hontelez, where she worked as a PhD on geospatial modelling of infectious disease dynamics. In January 2019 she took on a Research Associate position at the Heidelberg Institute of Global Health next to her PhD, where she co-led several research projects on improving healthcare delivery for HIV/AIDS in low-income and middle-income settings under supervision of Prof. dr.dr. Till Bärnighausen. In 2020, she obtained a MSc degree in Epidemiology at the Netherlands Institute for Health Sciences (NIHES).

Caroline moved to the United States in August 2022 to start her new position of Health Systems Innovation Research Fellow at the Harvard T.H. School of Public Health, under supervision of Prof.dr. Rifat Atun. Here, she is working on designing and testing healthcare delivery innovations to integrate and optimise healthcare for HIV, hypertension and diabetes in areas in low-income and middle-income countries with the largest healthcare demands.

LIST OF PUBLICATIONS

This thesis

Bulstra CA, Dai X, Rosenberg S, Wamuti BM, J Salomon, Ngure K, Hontelez JAC, Ortblad K, Bärnighausen T. "The real-world effect of male circumcision on the risk of HIV infection in sub-Saharan Africa: a household fixed-effects analysis of 279,351 men from 29 countries". *Under review*. – Chapter 3 in this thesis

Kloek M, **Bulstra CA**, van Noord L, Al-Hassany L, Cowan FM, Hontelez JAC (2022). "HIV prevalence among men who have sex with men, transgender women and cisgender male sex workers in sub-Saharan Africa: a systematic review and meta-analysis". *Journal of the International AIDS Society*, 25(11): e26022; doi: 10.1002/jia2.26022. – Chapter 4 in this thesis

Kloek M[ǂ], **Bulstra CA**[ǂ], Chabata ST, Fearon E, Taramusi I, de Vlas SJ, Cowan FM, Hontelez JAC (2022). "No increased HIV risk in general population near sex work sites: A nationally representative cross-sectional study in Zimbabwe". *Tropical Medicine and International Health*, 27(8): 696-704; doi: 10.1111/tmi.13791. – Chapter 5 in this thesis

Bulstra CA, Hontelez JAC, Otto M, Stepanova A, Lamontagne E, Yakusik A, El-Sadr WM, Apollo T, Rabkin M, Atun R & Bärnighausen T (2021). "Integrating HIV services and other health services: a systematic review and meta-analysis". *PLOS Medicine*, 18(11): e1003836; doi: 10.1371/journal.pmed.1003836. – Chapter 8 in this thesis

Hontelez JAC[ǂ], **Bulstra CA**[ǂ], Bärnighausen T & Atun R (2021). "Evidence-based policymaking when evidence is incomplete: the case of HIV programme integration". *PLOS Medicine*, 18(11), e1003835; doi: 10.1371/journal.pmed.1003835. – Chapter 9 in this thesis

Bulstra CA, Reddy CL, Atun R, Bärnighausen T & Hontelez JAC (2021). "Impact of the coronavirus disease 2019-related global recession on the financing of the global HIV response". *AIDS,* 35(7), 1143–114; doi: 10.1097/QAD.0000000000002872. – Chapter 7 in this thesis

Bulstra CA[ǂ], Hontelez JAC[ǂ], Giardina F, Steen R, Nagelkerke NJD, Bärnighausen T & de Vlas SJ (2020). "Mapping and characterising HIV transmission hotspots in sub-Saharan Africa: a geospatial analysis of national survey data". *PLOS Medicine* 17(3), e1003042; doi: 10.1371/journal.pmed.1003042. – Chapter 2 in this thesis

Bulstra CA, Hontelez JAC, Ogbuoji O & Bärnighausen T (2019). "Which business model innovations can support HIV service delivery?" *African Journal of AIDS Research,* 18(4), 315–323; doi: 10.2989/16085906.2019.1686033. – Chapter 6 in this thesis

ǂ *Shared co-authorship position*

Other publications

Starck T, Dambach P, Rouamba T, Tinto H, Osier F, Oldenburg CE, Adam M, Till Bärnighausen, Jaenisch T and **Bulstra CA**. "The effect of malaria on childhood anemia in a quasi-experimental study of 7,384 twins from 23 sub-Saharan African countries". Forthcoming in *Frontiers of Public Health*.

Starck T, **Bulstra CA**, Tinto H, Rouamba T, Sie A, Jaenisch T & Bärnighausen T (2021). "The effect of malaria on haemoglobin concentrations: a nationally representative household fixed-effects study of 17,599 children under 5 years of age in Burkina Faso". *Malaria Journal*, 20(1), 416; doi: 10.1186/s12936-021-03948-z.

Le Rutte EA, van der Wilt L, **Bulstra CA**, Nieboer D, Kontoroupis P, de Vlas SJ, Richardus JH (2021). "Incidence and geographical distribution of canine leishmaniosis in 2016–2017 in Spain and France". *Veterinary Parasitology: Regional Studies and Reports*, 25(7), 100613; doi: 10.1016/j.vprsr.2021.100613.

Luz JGG, Leite Dias JV, de Carvalho AG, Piza PA, Chávez-Pavoni JH, **Bulstra CA**, Coffeng LE, Fontes CJF (2021). "Human visceral leishmaniasis in Central-Western Brazil: Spatial patterns and its correlation with socioeconomic aspects, environmental indices and canine infection". *Acta Tropica*, 221(5), 105965; doi: 10.1016/j.actatropica.2021.105965.

Bulstra CA, Blok DJ, Alam K, Butlin CR, Roy JC, Bowers B, Nicholls P, de Vlas SJ, Richardus JH (2021). "Geospatial epidemiology of leprosy in northwest Bangladesh: a 20-year retrospective observational study" *Infectious diseases of poverty*, 10(1), 1-12. doi: 10.1186/s40249-021-00817-4.

Bulstra CAǂ, Le Rutte EAǂ, Malaviya Pǂ, Hasker EC, Coffeng LE, Picado A, Singh OP, Boelaert MC, de Vlas SJ, Sundar S (2018). "Visceral leishmaniasis: Spatiotemporal heterogeneity and drivers underlying the hotspots in Muzaffarpur, Bihar, India". *PLOS Neglected Tropical Diseases*, 12(12), e0006888; doi: 10.1371/journal.pntd.0006888.

ǂ *Shared co-authorship position*

DANKWOORD / WORDS OF APPRECIATION

During the last five years, I had the privilege to conduct research at the Erasmus MC Department of Public Health (Rotterdam, the Netherlands) and at the Heidelberg Institute of Global Health (Heidelberg, Germany). This thesis only presents part of the work that has been done and all the people who made invaluable contributions to it.

Om te beginnen mijn promotor, Sake. Bedankt voor je vertrouwen in mij om de promotie aan te gaan. Toen ik begon hadden we nog geen idee van alle verschillende projecten die zouden gaan komen. Ik begon met een project over viscerale leishmaniase in India als onderdeel van mijn MSc onderzoek. Hier leerde je mij onder andere over datavisualisatie en het interpreteren van epidemiologische patronen. De opgedane kennis was cruciaal voor dit project en kon ik daarna mooi inzetten voor de verschillende daaropvolgende projecten over lepra, hiv en soil-transmitted helminths. Je bent een criticus en hebt oog voor detail, mijn geduld werd soms aardig op de proef gesteld, maar altijd ten gunste van het onderzoek. Ik heb enorm genoten van je enthousiasme tijdens de vele discussies die we hebben gevoerd.

Jan, een betere co-promotor had ik me niet kunnen wensen. Je leerde me ontzettend veel over onderzoek doen, maar daarnaast ook over het plannen, netwerken, omgaan met tegenslagen en stil staan en genieten van overwinningen. Je wist me te motiveren in het diepst van de pandemie, toen het onderzoek na maanden thuiswerken behoorlijk taai voor mij was. Hoogtepunten waren toch zeker wel onze trip naar Rio de Janeiro, waar we door de jungle naar de Cristo Redentor (het beeld Christus de Verlosser) wandelden, en onze trip naar Boston, waar we samen door downtown Boston huppelden en the most AMAZING lobster rolls aten.

Mijn paranimfen, Amber en Zoïe. Wat super lief en fijn dat jullie mij aan mijn zijde willen staan bij de verdediging! Jullie zijn een perfect team en ik had me geen betere support kunnen wensen!

Lieve Mariëlle, wat ben ik blij dat we samen onze promotietrajecten aan konden gaan! Ik bewonder jouw kennis en passie voor je werk enorm en heb ontzettend veel van je kunnen leren over onder andere definities van key populations, nuances in de interpretatie van onze kwantitatieve resultaten en samenwerking met mensen met een breed scala aan achtergronden. We glipten er regelmatig tussenuit voor een koffietje bij Parqiet, een wandeling of een biertje in de zon. Ook reisden we samen met Jan af naar Zimbabwe, waar ik afspraken met de Ministery of Health had terwijl jij een nieuw programma voor dataverzameling onder sekswerkers opzette. Ons reisje naar de Victoria Falls daarna, waar we bij twee supergezellige hosts verbleven en giraffen, nijlpaarden en neushoorns spotten, zal ik niet snel vergeten. Ik bewonder je doorzettingsvermogen en weet zeker dat er hele mooie volgende stappen in het verschiet liggen!

Till, you gave me the opportunity to join the Heidelberg Institute of Global Health and expand my focus to health systems research. You are a very inspiring person to work with and I am very grateful that our paths have crossed. Thank you for the vivid discussions, sharing many new research ideas, and for offering me the opportunity to conduct research at Harvard with Prof. Rifat Atun's team. I look forward to continue collaborating together in the future.

Jan Hendrik, ik ben dankbaar voor de kans om samen te werken aan het lepra onderzoek. Onze trip naar Nilphamari, Bangladesh was ongelooflijk waardevol en zal ik nog vaak aan terugdenken. De motivatie van het team en de ontzettend gastvrije mensen, ondanks de uitdagingen in het land, hebben veel indruk op me gemaakt. Je mensenkennis, kalmte en nieuwsgierigheid hebben me geïnspireerd.

Epke, samenwerken met jou was een feest! We kenden elkaar al van diergeneeskunde en waren de twee enige dierenartsen op de afdeling. Zonder jou had ik de afdeling en het onderzoek naar de verspreiding van Neglected Tropical Diseases en andere infectieziekten misschien wel nooit ontdekt!

Luc, David, ik heb genoten van onze samenwerking tijdens de projecten over soil transmitted helminths en lepra. Ook al zit het werk uiteindelijk niet in dit boekje, ik heb enorm veel geleerd van de projecten en van jullie.

I am grateful for all my colleagues of the Infectious Disease Control Section and Department of Public Health at Erasmus MC and at the Heidelberg Institute of Global Health. During the past years I have learned from all of you, could always walk into your offices (when we were not working from home) to ask quick questions about our work, and I appreciated the open and critical discussions during meetings. Next to that, I hold great memories of all the fun events we had together. I especially cherish great memories of my time at the Social Committee of the Erasmus MC Department of Public Health.

Lieve vrienden: de Billies, de Stappers, Lowlands maatjes, dierenartsen zonder grenzen, de runderen en alle andere lieve vrienden om me heen. Zonder jullie had ik de finish van deze marathon niet gehaald!

De Billies, hoe bijzonder is het dat we elkaar al zo lang kennen! En wie had gedacht, toen we onze eindeloze liefde voor paarden bespraken in groep 8 of stiekem rebelleerden in de brugklas op de Werkplaats, dat ik hier ooit zou staan. Bedankt dat jullie er altijd voor mij zijn, ook als ik weer eens zo nodig op reis moest en pas na maanden weer terugkwam… Lieve

Marguerite, Anne, Anne en Esmee: Ik hoop dat we samen nog heel veel champagne drinken, op onze hechte vriendschap!

Lieve Stappers, toen ik mijn leven in de koeienstallen en knuffelend met puppy's verruilde voor het onderzoek, waren jullie toch wel een tikkeltje teleurgesteld. Wat moest er dan komen van al die spannende verhalen? Gelukkig levert een promotieonderzoek in de volksgezondheid ook de nodige avonturen op. Ik vind het bijzonder hoe we, alle 18, ons eigen unieke pad bewandelen en kijk ernaar uit elkaar weer veel te zien zodra ik in Nederland ben!

Lieve dierenartsen zonder grenzen, Amber, Charlotte, Esther, wij zijn uit hetzelfde hout gesneden, zoals iemand dat laatst zo mooi zei. Jullie begrijpen mij als geen ander, als mede-dierenartsen die daarnaast dolgraag de wereld willen ontdekken! Ik kan niet wachten binnenkort weer samen onze grenzen te verleggen.

Liselotte, mijn liefste tweelingzusje, jij stond al eerder hier te shinen en hebt inmiddels je bul binnen! Ik begon mijn avontuur in Rotterdam bij jou op de Maashavenkade en dat was toch wel heel gezellig. Ook al praten we niet elke dag, we begrijpen elkaar door en door en zijn er altijd voor elkaar. Ik kijk ernaar uit je straks weer meer te zien in Nederland. Maarten, ik geloof dat je soms geen idee hebt waar ik nou al die tijd aan gewerkt hebt, maar je bent altijd in voor een drankje op het terras of samen een hapje eten in Amsterdam, reuze gezellig! Ik ben supertrots op jullie!

Allerliefste pap en mam, jullie zijn een onbeschrijfelijke support geweest gedurende de afgelopen jaren. Toen ik jullie belde om te vertellen dat ik een promotietraject met nog onvolledige funding had aangenomen, moesten jullie wel even slikken, maar gelukkig pakte alles uiteindelijk goed uit. Bedankt voor jullie betrokkenheid, jullie bevlogen interesse in mijn werk en het enthousiasme waarmee jullie anderen vaak over mijn onderzoek vertellen. Zonder jullie had ik dit onzekere onderzoeksbestaan waarschijnlijk niet aangedurft. En zonder jullie had ik nooit kunnen staan waar ik nu sta, ik ben jullie super dankbaar en realiseer me heel goed wat een mazzel ik heb met zulke ouders en familie.

Felix. Mijn liefde. You have been the greatest support, together we can do anything. Both being ambitious and being in international careers already brought us to many different places, and sometimes separated us in space: you in Heidelberg and me in Amsterdam, you in Cape Town, me in Sri Lanka, and now you in Atlanta and me in Boston. Erasmus once said that "space separates the bodies but not the minds" and for us that always holds true. Luckily there's unlimited phone connection… I am so grateful for all the insightful and supportive conversations we have, while being together or in different places. I cannot wait for the next adventures ahead with you!

PHD PORTFOLIO

Name PhD student:	Caroline Annemarie Bulstra
Erasmus MC Department:	Public Health
Research school:	Netherlands Institute for Health Sciences (NIHES)
PhD period:	2018-2022
Promotor:	Prof.dr. S.J. de Vlas
Copromotor:	Dr. J.A.C. Hontelez
Mentors:	Prof.dr. J.H. Richardus
	Prof.dr.dr. Till Bärnighausen
	Dr. E.A. Le Rutte
	Dr. D.J. Blok

1. PhD training

Research skills	Date	Workload
Master of Science in Health Sciences, specialisation Epidemiology, Netherlands Institute for Health Sciences (NIHES), Erasmus University, Rotterdam	Sep 2018 – Aug 2020	70 ECTS
Erasmus Summer Programme 2018		
Introduction to Global Public Health		
Methods in Public Health Research		
Fundamentals of Medical Decision Making		
Principals of Research in Medicine		
Primary and Secondary Prevention Research		
Social Epidemiology		
Erasmus Summer Programme 2019		
Causal Mediation Analysis		
Causal Inference		
Advances in Clinical Epidemiology		
Health Economics		
Core curriculum		
Study Design		
Biostatistical Methods I: Basic Principles		
Biostatistical Methods II: Classical Regression Models		
Principals in Causal Inference		
Introduction to Medical Writing		
Master Thesis		
Elective courses		
Using R for Decision Modelling		
Public Health Research: Analysis of Population Health		
Public Health Research: Analysis of Determinants		

Public Health Research: Intervention Development and Evaluation		
Repeated Measurements in Clinical Studies		
Public Health in Low- and Middle-Income Countries		
General academic skills		
Time and project management course for PhD students	2018	0.3 ECTS
Biomedical English writing and communication	2019	1.0 ECTS
Systematic literature retrieval in PubMed, Erasmus MC, Rotterdam	2019	0.3 ECTS
Systematic reviews and meta-analyses for economic evidence of health interventions, Heidelberg University, Heidelberg, Germany	2020	1.0 ECTS
Research integrity	2021	0.3 ECTS
Other skills		
Roland Berger Business Course 'The Pitch'	2017	1.0 ECTS
The Health Effects of Climate Change, Harvard University and Heidelberg Institute of Global Health	2020	1.0 ECTS
R.I.O.T club seminars on open and reproducible science	2020, 2021	0.6 ECTS
The Science of Well-Being, Yale University	2020	1.0 ECTS
COVID-19 Challenge 3-day hackathon, Massachusetts Institute of Technology (MIT)	2020	0.6 ECTS
McKinsey & Company Next Generation Women Leaders Business Programme	2020	0.6 ECTS
NWO Insight Out – Inspiring Women in STEM career seminar series	2021	0.6 ECTS
Participant THRIVE PhD Academy Purpose Accelerator, Think Tank for Societal Impact	2020-2021	3.0 ECTS

2. Presentations

Oral presentations at (inter)national conferences	**Date**	**Workload**
WEON Dutch Epidemiological Conference 2018, Utrecht	Jun 2018	0.5 ECTS
Spring meeting Nederlandse Vereniging voor Parasitiologie, Utrecht	May 2018	0.5 ECTS
20th International Leprosy Congress, Manilla, Philippines	Sept 2019	1.0 ECTS
European Congress for Tropical Medicine and International Health (ECTMIH) 2019, Liverpool, UK	Sept 2019	1.0 ECTS
Neglected Tropical Diseases (NTD) Modelling Consortium Science Day Flash Talks, online	Apr 2021	0.5 ECTS
Oral presentations during seminars and other events		
Research seminars of the Infectious Disease Control research group of the Department of Public Health, Erasmus MC, Rotterdam	6x 2018–2021	2.0 ECTS
Research presentation at USAID, Zimbabwean Ministry of Health, Harare, Zimbabwe	Feb 2018	1.0 ECTS
Presentation on geospatial modelling methods at Leprosy Relief (Leprastichting) event, Amsterdam	Mar 2018	0.5 ECTS
Design and introduction 3-day training programme for data collection coordinators and 40 field staff members, Nilphamari, Bangladesh	Oct 2018	2.0 ECTS
Research meetings of the Department of Public Health, Erasmus MC, Rotterdam	Jun 2019, Feb 2021	1.0 ECTS

3-day Joint United Nations Programme on HIV/AIDS (UNAIDS) Expert Meeting 2025 Target Settings (7 presentations), Rio de Janeiro, Brazil	Mar 2020	3.0 ECTS
Poster presentations		
Conference on Retroviruses and Opportunistic Infections (CROI), Boston, USA	Mar 2020	1.0 ECTS
AIDS Conference, San Francisco, USA (virtual due to COVID-19)	Jul 2020	1.0 ECTS

3. Attended conferences, seminars, workshops and other events

(Inter-)national conferences	Date	Workload
AIDS Conference 2018, Amsterdam	Jul 2018	1.0 ECTS
GIS R Conference UK: Applications of GIS and R in environmental and health sciences, Newcastle, UK	Apr 2019	1.0 ECTS
NTD Modelling Consortium Science Day, online	Mar 2020	0.3 ECTS
Global Health Summit 2021, Berlin and online	Oct 2021	1.0 ECTS
Seminars		
Weekly research seminars of the Department of Public Health, Rotterdam	2017–2021	3.0 ECTS
Biweekly meetings of the Infectious Disease Control research group of the Department of Public Health, Erasmus MC, Rotterdam	2017–2021	3.0 ECTS
Workshops		
5-day course "Use of Geographical Information Systems for Infectious Disease Control", data visualisation and interpolation methods, mid-level, Tropical Institute, Antwerp, Belgium	Sept 2017	1.0 ECTS
5-day course "Use of Geographical Information Systems for Infectious Disease Control", geospatial statistics and satellite imaging, advanced-level, Tropical Institute, Antwerp, Belgium	Jul 2018	1.0 ECTS
Erasmus MC PhD Day	Sept 2018	0.3 ECTS
Mathematical modelling of Sexually Transmitted Infections, RIVM, Utrecht	Apr 2019, Sept 2020	0.6 ECTS
HIV Policy Lab symposium and hackathon, Georgetown University, online	Dec 2021	0.6 ECTS
Expert meetings		
Invited participant 3-day UNAIDS meeting sustainability of the HIV health care systems, Geneva, Switzerland	Apr 2019	0.6 ECTS
Invited participant 3-day soil transmitted helminths modellers meeting, Neglected Tropical Diseases Modelling Consortium, Lancaster, UK	Jun 2019	0.6 ECTS
Invited participant 1-day UNAIDS meeting HIV/AIDS 2025 Target Settings, Geneva, Switzerland	Jan 2020	0.3 ECTS

4. Teaching and supervision activities

Educational activities and lecturing	Date	Workload
Teaching assistant NIHES elective course Public Health in Low- and Middle-Income Countries	May 2018	1.0 ECTS
Guidance of medical students – 'community projects', 3rd year curriculum Medicine, Erasmus MC, Rotterdam	Sep 2019 – Mar 2020	2.0 ECTS
Guidance of medical students – 'community projects', 3rd year curriculum Medicine, Erasmus MC, Rotterdam	Sep 2020 – Mar 2021	2.0 ECTS

Supervision		
Doctoral student (Heidelberg University), topic: studying the impact of Malaria on anaemia among children below 5 years of age in high endemic regions.	2019–2021	1.0 ECTS
Two research assistants (Heidelberg University), topic: providing assistance with the study selection and data extraction process for a systematic review on HIV services integration.	2019–2020	1.0 ECTS
PhD student (Heidelberg University), topic: studying client satisfaction of utilising HIV services in sub-Saharan Africa.	2019–2021	1.0 ECTS
Master thesis student (Erasmus University), topic: extracting cross-sectional HIV prevalence data to complement a systematic review on HIV prevalence among key populations.	2020	1.0 ECTS
Doctoral student (Heidelberg University), topic: reviewing national health benefit packages and inclusion of HIV service delivery for low-and-middle-income countries.	2021–2022	1.0 ECTS

5. Other activities

Ad-hoc peer-reviewing for scientific journals		
Nature Scientific Reports, PLOS Neglected Tropical Diseases, PLOS ONE, BMC Infectious Diseases, Spatial and Spatio-temporal Epidemiology, Journal of Tropical Medicine and International Health, Health Affairs, BMJ Open	2019–2022	2.0 ECTS
Non-research activities at the department		
Social committee member of the Department of Public Health	2018	1.0 ECTS
Initiator 'Sharing best practices' workshops with monthly sessions for junior researchers of the Department of Public Health	2020	1.0 ECTS
Organisation committee of 50-year anniversary of the Department of Public Health	2020	0.6 ECTS

6. Awards, scholarships and personal grants

Awards	Date	Amount
AIDS Conference International Scholarship Award, American International AIDS Society	2020	€2500
Next Generation Women Leaders Award, McKinsey & Company	2020	-
CROI Conference New Investigator Award, American International AIDS Society	2020	€2500
Young Talent Awards, Prins Bernhard Cultuurfonds	2021	€12,000
(Co-)acquired research support		
The Joint United Nations Programme on HIV/AIDS (UNAIDS), "Costs, benefits and efficiency gains from integration of HIV with other health services", role: co-PI	2019–2020	US$ 67,000
The Joint United Nations Programme on HIV/AIDS (UNAIDS), "HIV Financing and UHC in The Emergency and Recovery Phase of the COVID-19 Pandemic", role: co-investigator	2020–2021	US$ 430,000

7. Further research experience

Other project grants		Time investment
Bill and Melinda Gates Foundation, "NTD Modelling Consortium: filling the gaps - operational research to ensure the success of NTD control and elimination programs", PI: Prof.dr. Sake de Vlas, role: Junior Researcher	2017–2018	5 months
World Bank, "Modelling the possible benefits of combination HIV prevention in Zimbabwe", PI: Dr. Jan Hontelez, role: Research Assistant	2017–2018	4 months
Nationale Postcode Loterij, "Effects of Single-dose Rifampicin for Leprosy control", PI: Prof.dr.dr. Jan Hendrik Richardus, role: PhD Researcher	2018–2019	10 months
Bill and Melinda Gates Foundation, "NTD Modelling Consortium: moving towards elimination", PI: Prof.dr. Sake de Vlas, role: Junior Researcher	2020–2021	6 months