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Combination Prevention: New Hope for Stopping the Epidemic

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Abstract HIV research has identified approaches that can be combined to be more effective in transmission reduction than any 1 modality alone: delayed adolescent sexual debut, mutual monogamy or sexual partner reduction, correct and consistent condom use, pre-exposure prophylaxis with oral antiretroviral drugs or vaginal microbicides, voluntary medical male circumcision, antiretroviral therapy (ART) for prevention (including prevention of mother to child HIV transmission [PMTCT]), treatment of sexually transmitted infections, use of clean needles for all injections, blood screening prior to donation, a future HIV prime/boost vaccine, and the female condom. The extent to which evidence-based modalities can be combined to prevent substantial HIV transmission is largely unknown, but combination approaches that are truly implementable in field conditions are likely to be far more effective than single interventions alone. Analogous to PMTCT, "treatment as prevention" for adult-to-adult transmission reduction includes expanded HIV testing, linkage to care, antiretroviral coverage, retention in care, adherence to therapy, and management of key co-morbidities such as depression and substance use. With successful viral suppression, persons with HIV are far less infectious to others, as we see in the fields of sexually transmitted infection control and mycobacterial disease control (tuberculosis and leprosy). Combination approaches are complex, may involve high program costs, and require substantial global commitments. We present a rationale for such investments and cite an ongoing research agenda that seeks to determine how feasible and cost-effective a combination prevention approach would be in a variety of epidemic contexts, notably that in a sub-Saharan Africa.

Keywords HIV · Prevention · Combination approaches · Treatment as prevention · Africa · Circumcision · Behavior change · Global epidemic · HIV transmission · Antiretroviral therapy (ART) · Prevention of mother to child HIV transmission (PMTCT) · Combination prevention

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Introduction

Many infectious diseases have required a combination of approaches to reduce transmission [1]. Tuberculosis control relies on case detection, treatment, and contact tracing to find yet more cases for prophylaxis or treatment (Table 1). Malaria control may incorporate bed nets, vector control, intermittent presumptive treatment, case finding and treatment, and we hope in the not-too-distant future, a malaria vaccine. Nosocomial infections may use rigorous multi-component protocols to ensure the full array of preventive strategies in health care settings. Helminth infections may be controlled with combinations of sanitation, vector control, mass chemotherapy, and surveillance to assess where the major impact may be seen (Table 1). HIV is a sexually transmitted infection (STI), propagated by human sexual behavior. Other STIs have required combinations of case finding and treatment, behavior change (eg, fewer sexual partners), risk reduction (eg, condoms), and even structural changes (eg, 100 % condom use policies in brothels) to achieve successful control. The inability to cure HIV with current therapies renders its effective control much more challenging.

A feature of many STIs is the replenishment of an at-risk pool of persons as children age into adolescence and

Table 1 Examples of infectious diseases for which combination prevention approaches are essential for reducing transmission: Tuberculosis, Malaria, Nosocomial infections, Helminths [325–328]

Infection and key strategy	Key elements for control strategies using tools available in 2013 (note that many elements listed under 1 disease might well apply to other diseases)
Tuberculosis: Directly Observed Treatment, Short Course	• Political commitment and adequate financing • Case detection with high quality diagnostics, including drug sensitivities • Standardized treatment with patient support to maximize adherence • Effective drug supply and management system • Monitoring and evaluation to measure impact
Malaria: Reducing the basic reproduction rate	• Reduction of human infectivity with early diagnosis and effective treatment • Reduction in vectorial capacity with effective, sustained mosquito control • Avoidance of mosquito bites through consistent use of bed-nets • Intermittent presumptive treatment • Measures to reduce global warming • Partially protective vaccine
Nosocomial infections: Reducing patient exposures	• Enhanced real-time surveillance and immediate feedback • Implementation of clinical protocols based on evidence-based interventions, eg, ○ Hand hygiene, vaccines, clean environment, prudent prescribing • Training, audit, and performance management focus (targets, legislation) ○ Management commitment to rigorous protocols, eg, flu vaccine
Helminths: Control of poly-worm infections	• Vector control, eg, specific species of snails, mosquitoes, black flies • Reduce exposures, eg, laundries away from streams, dispose fecal waste • Case finding and treatment; mass drug administrations • Disease surveillance with concentrated effort on highest intensity infections

adulthood. About half of the world's global population is under age 25 and it is estimated that nearly half of all HIV infections are also among persons under age 25, most ages 15-24 [2]. The intensity of risk for adolescents and youth is especially high in sub-Saharan Africa once they become sexually active, given the likelihood of a sexual partner being HIV-infected [3–7]. Over a third of infected persons globally live in just 10 nations of southern Africa where the epidemic is driven by heterosexual contact [8, 9]. Injection drug use and male-to-male sexual contact seem to be increasing in this region, and are the major drivers of the epidemic in other parts of the world [10–31]. Iatrogenic spread is also prevalent [32, 33].

While individual approaches to HIV prevention have had some success, most interventions are of limited, partial, or unproven effectiveness. Any single intervention is unlikely to be sufficient to achieve the steep reductions in incidence that is needed to bring the epidemic under control, especially in sub-Saharan Africa where high rates of transmission in the general population are the norm.

Elements of Combination Prevention

Evidence for efficacy of elements of combination prevention can come from observational data (as with male condoms or reduction in partner numbers) or from randomized clinical trials (RCTs; as with male circumcision or early treatment as prevention). What elements might be considered essential for successful combination prevention are a matter of debate, but can be elucidated with decision-analysis and HIV transmission models (Table 2). A consensus is emerging that combination prevention should be anchored on the use of combination antiretroviral therapy (cART) given that infected persons who receive and are adherent to cART regimens can suppress HIV replication and reduce their infectiousness [34, 35, 36•, 37]. As of this writing (late 2012), Ministries of Heath of low and middle income countries (LMIC) typically limit their start of cART at the World Health Organization (WHO) recommended threshold of CD4+ cell counts <350/μL or WHO clinical status 3 or 4 [37]. Some of the most resource-limited nations continue to authorize the start of cART at a lower threshold like <250 cells/μL, despite overwhelming evidence that this is too late for optimal clinical response [38]. A large proportion of transmissions occur before patients reach the usual thresholds for ART initiation, however, a rationale for treating at earlier CD4+ cell counts (or even universal ART for all HIV-infected persons).

The HIV Prevention Trials Network 052 protocol (HPTN 052) was an RCT that assessed early initiation of cART at CD4+ cell counts of up to 550/μL, demonstrating both reduced transmission of HIV to sexual partners as well as clinical benefits to their infected partners on cART [40••].

Table 2 Elements of combination prevention likely to synergize to improve the effectiveness of prevention programs for HIV infection [184•, 329•, 330, 331•, 332–335]

	Goal(s) to be achieved
Personal elements	
Treatment as prevention	Increased HIV testing, linkage to care, coverage with cART, retention and adherence; lower viral load and infectiousness
Voluntary medical male circumcision	In high prevalence areas driven by heterosexual transmission dynamics, increase circumcision among men
Abstinence	Encourage delayed sexual debut among adolescents
Partner reduction	Encourage mutual monogamy and reduced sexual partners
Physical barriers	Market male condoms widely, and where appropriate, female condoms
Chemical barriers	Pre-exposure prophylaxis with antiretroviral drugs, both oral and topical (ie, microbicides)
STI control	Reduce both ulcerative and non-ulcerative STIs via diagnosis, treatment, and partner notification (contact tracing)
Prevention of mother to child transmission	Universal testing of pregnant women and protocol-driven ART for mother and newborn child
Nosocomial and iatrogenic transmission	Clean needle use for all medical encounters; use of infection-screened blood products with modern blood-banking techniques
Societal elements	
School attendance	Maximal school attendance by children and youth
Workplace policies	Enable workers to live with their families
Human rights and legal protections	Protect the rights of HIV-infected persons, widows, minority populations such as men who have sex with men, women/girls, vulnerable populations
Structural changes	100 % condom policies in brothels and universal availability in public places, hotels, and key venues where high risk sex occurs
Community mobilization	Engage communities in HIV control; reduce stigma, increase disclosure of status, increase coverage and adherence
Program elements	
Health workforce development	Increase substantially the numbers of health care providers for both rural and urban settings; Efficient allocation of tasks
Integration of services	Nest HIV/AIDS care and treatment within sustainable primary care and reproductive care services, including family planning
Physical infrastructures	Provide basic electricity, water, medical waste disposal, and space for health centers
Pharmacy logistics systems	Ensure that inventory management, shipping, and storage systems avoid supply (eg, test kits) and drug stock-outs
Laboratory development	Decentralize laboratory work, as much as possible and affordable, with point-of-care diagnostic tests
Quality of care and iterative evaluation	Build sustainable quality improvement research and systems improvement efforts into HIV care programs
Hub-and-spoke models of care	Bring primary and HIV/AIDS care closer to people who are remote from major clinical services; home-based HIV testing
Data management systems	Build sustainable, affordable electronic medical record systems to harmonize the myriad of systems now extant
Community engagement to support programs	Implement innovative community models of outreach, retention, and adherence support, including patient-to-patient and family-to-patient
Cultural changes in the health sector	Train staff and reform procedures to protect patient confidentiality/privacy, provide more respectful, client-friendly services in familiar local languages
Management and administration	Train and capacitate health systems to use modern business practices for financial and logistical management

Hence it is disappointing that only 19 %–28 % (range of estimates) of Americans infected with HIV were on cART with successful suppression of HIV viral load [40••, 41••, 42•, 43•]. Even if these are overly pessimistic estimates due to some "lost-to-follow-up" patients possibly being in therapy elsewhere, the true rates of ART coverage and viral suppression are disappointing, in both high and low income nations [44–47, 48•, 49•, 50–53, 54•, 55•]. In selected venues, ecological evidence of prevention benefits from cART is emerging [56•, 57••, 58]. Ecological analyses in San Francisco, Vancouver, China, Taiwan, and KwaZulu-Natal have suggested that higher cART coverage may

correlate with lower seroincidence rates [56–61]. However, it is unknown whether these correlations represent success of TasP or whether other factors are contributing [62, 63].

Vancouver is a case in point. Investigators and public health officials have addressed prevention of HIV with needle/syringe exchange and opiate substitution therapy among Vancouver IDUs at the same time that cART was being made available [64]. Hence, it is hard to disaggregate the prevention impact of needle/syringe exchange and expanded heroin addiction therapy from cART expansion or other factors. Western Europe is also a region of interest [65]. It is easy to speculate that easy access to HIV testing and widespread cART use within national health systems may have resulted in lowering HIV incidence rates in Western Europe, but it is hard to know whether other sociocultural factors or prevention efforts also made impacts. However, in the United Kingdom where access to testing and treatment is facilitated by the National Health System (NHS) with free services available to all, no reduction in the incidence of new infections in MSM has been noted to date, so interpreting European experiences is not always clear-cut.

The option of moving to *immediate* offering of ART—irrespective of CD4+ cell count-is being supported by public health policy in San Francisco, Vancouver, New York City, and elsewhere. If HIV testing were expanded markedly and all persons were treated shortly after diagnosis and successful virally suppressed, then fewer infectious persons would be transmitting to others and the epidemic might decline. Whether this is possible is the topic of intense current investigation.

Suboptimal cART Coverage and Viral Suppression

Patient management issues are complex for HIV disease (Table 2). Rather than the lethal diagnosis for so many in the pretreatment era, HIV disease is now a chronic, manageable disease. It requires HIV testing, linkage to care, cART availability, national guidelines permitting cART administration, and adherence to lifelong therapeutic regimens. In the US, current systems fail to meet the full need of HIV-infected patients, many of whom have co-morbidities that inhibit full viral suppression [41••, 42•, 43•]. These may include substance use (eg, drugs and/or alcohol), mental health problems, financial and health care insurance challenges, transportation issues, and stigma/disclosure challenges [66–87]. In LMICs, it is plausible that less than 10 % of all infected persons are successfully virally suppressed. Stigmatized persons who do not "come out" may not reach medical care or be retained in care, as is the case with Black men who have sex with men (MSM) in the US [88–99]. Adolescents with HIV infection have demonstrated abysmal adherence rates in some studies [100–108]. Children with HIV are dependent on their parents or guardians; many children have not had their HIV status disclosed to them and may not be participating actively in their ongoing care [109–115].

The gulf between current guidelines for high income countries where all HIV-infected persons are typically offered cART vs WHO and LMIC Ministries of Health guidelines that offer a smaller proportion of HIV-infected persons cART (typically persons under 350 CD4+ cells/μL) is worth highlighting. By definition, the latter policies have a larger pool of infected persons who remain virally unsuppressed. If resources were obtained to treat all HIV-infected individuals (ie, universal, immediate cART), the proportion of infectious persons would decline. If a large enough pool of infectious persons were made non-infectious, mathematical models suggest a decline in new infections. It is not certain that a test-and-treat prevention strategy is feasible, acceptable, sustainable, and affordable. The most resource-limited LMICs depend on the programmatic resources available from the President's Emergency Program for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria; local Ministries of Health rarely have the resources to find, link, and retain HIV-infected persons in cART-based care, with optimized adherence [116–120]. The long-term management of chronic diseases in LMICs is challenging; HIV investments may serve as a backbone for also addressing a wide variety of diseases requiring chronic management [39, 47, 52, 121–131, 132•, 133–138].

We also do not know whether a test-and-treat approach will have the postulated benefits in a real world circumstance. Whether we can further enhance its benefits with other prevention modalities without overwhelming the public health and clinical systems is also unknown. While behavior change is a component of all approaches, some combined interventions only make sense in certain epidemic circumstances, as with male circumcision in generalized epidemics and needle exchange where IDU drives transmissions.

Adapting for Local Epidemics

HIV is a disease based on patterns of human behavior; hence, it is affected and modulated by stigma, discrimination, prejudice, fear, stress, depression, denial, and ignorance [80, 139]. Many have compared AIDS to the leprosy of the Bible when infected persons were shunned and even banished. Since HIV is transmitted similarly to patterns for other sexual and blood-borne agents, it is subjected to the same societal distress surrounding other STIs. HIV transmission is more likely in the face of multiple sexual partners (ie, high mixing rates) and failure to use condoms, so persons acquiring infection are typically judged by others [8]. However, we must put stigma into its modern perspective. While a major problem in most areas, especially perhaps in concentrated epidemics in marginalized risk-groups, there are also signs of "normalization" of HIV as a public health problem in both higher income and LMICs, including in southern Africa. We speculate that wider access to cART

has contributed to an improving social environment for many persons living with HIV.

Much progress has been made in the avoidance of iatrogenic and occupational parenteral transmission unclean syringes and needles through single use technologies, serological screening of blood or blood products, and policies to reduce inadvertent needle sticks in an occupational health care setting. Progress, too, has been made in offering universal screening of pregnant women and the offering, uptake, and adherence to 1 of a variety of antiretroviral therapy options, pre-partum, intra-partum, or post-partum, to avoid mother-to-child transmission that can take place in utero, during delivery, or from breastfeeding, respectively [140–144]. Yet too often, successful programs are not integrated and potential synergies for combination prevention are lost. If testing/treatment successes in PMTCT, say, could be expanded into the analogous treatment as prevention cascade for adults, we might well combine components of prevention into an integrated whole, with the kind of impact on incidence not often seen in the global pandemic.

Hepatitis B virus (HBV) is spread in ways reminiscent of HIV, though HBV is typically more communicable [145, 146]. Our tools for HBV control include active and passive immunization, tools that are not yet available for HIV control. In addition, HIV infection is not yet curable, such that persons whose viral loads are not suppressed can transmit the infection for many years. Other STIs can also be spread via blood-borne routes (eg, syphilis, hepatitis C virus [HCV], and human T-lymphotropic virus type 1 [HTLV-1]), but sexual routes are the dominant mode of transmission for most STIs, as with HIV. The CD4+ T-lymphocyte tropism of HIV makes it unique among the STIs and its penchant for deep lymphoid tissue invasion and quiescence are the roots of it incurability.

Stigma, Discrimination, Poverty, and Human Rights

HIV spread is steeped in gender inequality, poverty, discrimination based on sexual preference and identity, and perverse public policies that exacerbate the epidemic, rather than control it. One's perspective on the role of stigma in fueling the epidemic must recognize both the fear that an HIV diagnosis still engenders among many, and the fact that increased HIV testing and adherence to cART-based care represent signs of "normalization" of HIV as a public health challenge in many countries, including some in southern Africa, where wider access to cART has probably contributed to HIV being seen to be more like other diseases.

Russia's failure to legalize and promulgate clear needle distribution and opiate substitution therapy, the continued demonization of MSM in many African countries, and the insistence on ineffective "abstinence only" educational investments in the US are all examples of policy gone awry [4, 26, 147–155]. In the face of the politicization of HIV/AIDS, policymakers failing to use existing tools to prevent HIV transmission are responsible for much preventable infection [156]. Failure to protect the blood supply early in the epidemic led to the infection of tens of thousands of blood and blood product recipients worldwide, especially persons with hemophilia. The taboo of politicians, religious leaders, teachers, or even health care providers discussing sexual risk reduction frankly and clearly keeps issues of HIV prevention from being fully integrated into political, religious, and social discussions. This is unfortunate since some themes — delaying adolescent coital debut and reducing numbers of sexual partners, for example — are widely supported goals in nearly all circles and political philosophies. While condoms are opposed by some due to a conviction that they may lead to higher risk sexual activities and/or that they may violate certain religious proscriptions against contraception, there is no strong evidence for the former view and support for the latter may be waning. For example, a major global religious leader who previously opposed condom use stated in a 2010 book that "there may be a basis in the case of some individuals, as perhaps when a male prostitute uses a condom, where this can be a first step in the direction of a moralization, a first assumption of responsibility." [157]. The religious leader later indicted that he also was referring to female prostitutes when he suggested that condom use may actually be a morally superior choice to prevent transmission to others. Such changes in attitude can be influential in empowering at-risk persons to protect themselves without going counter to religious views to which they may subscribe.

Failures in public policy have consequences. Modelers have quantified public policy failures, particularly the failure to provide clean needles and syringes for IDUs in the US from 1987–1995, estimating that an excess of between 4394 and 9666 infections, representing a third of incident IDU cases, was the result [158]. The attendant excess costs to the US were US$244 to $538 million. It will be a major stride in the HIV field if public health advocacy for evidence-based prevention could be the basis for HIV control policy and investment [26].

Behavior Change

Even in the face of biomedical interventions such as TasP or voluntary medical male circumcision, behavior change is an essential component of prevention interventions; for example, persons must agree to and adhere to the given intervention. All by itself, however, behavior change to reduce HIV incidence has not proven robust [159]. In studies designed to enhance adherence to ART, for example, the impact of behavioral interventions has often be very contextual or transient [160]. The HIVNET 015 Project EXPLORE

protocol in MSM in the US sought to lower HIV incidence with an intensive 10-visit educational program that included reinforcement sessions [161–163]. Investigators were disappointed with the 18.2 % reduction (95 % CI: -4.7 %, 36.0 %) in HIV incidence in the intervention group compared with a control group receiving a short intervention [163]. However, given that the benefits were even lower in substance users and persons with mental health problems, this underscored the importance of attending to these co-morbidities in order to reduce HIV transmission [164–166].

For TasP, willingness to test for HIV, be linked to care, and adherence to cART to reduce infectiousness all require behavioral support. Pre-exposure prophylaxis (PrEP) using cART in seronegative persons to prevent infection, and increased testing and linkage to cART require high levels of adherence to be successful. "Serosorting" is when HIV seropositive persons have sex only with other infected persons, and HIV-seronegatives seek other uninfected persons for sex; this obviously requires a great deal of self-efficacy and motivation. Substance abuse treatment, including needle exchange, alcohol treatment, and opiate substitution therapy, as needed, depend on motivated and able clients. Contingency cash transfers are rewards for lowering risk behaviors, and depend on behavior change and political support.

Classic "ABC" approaches of **A**bstinence/**B**e faithful/**C**ondom advocacy are fully dependent upon behavioral change [42•, 167–176]. The US Centers for Disease Control and Prevention (CDC) has published its evidence-based interventions for risk reduction in the US; they are heavily behaviorally-based [177–181]. Abstinence-only education has been unsuccessful in reducing risk and was paradoxically associated with higher pregnancy rates than more comprehensive educational approaches that included STI prevention advocacy based on abstinence, partner reduction, and condom use [150, 153, 182]. It is the consensus in the HIV scientific community that "ABC" principles are vital guides for public health intervention, but are better bundled with biomedical prevention approaches; lone behavioral change approaches are not likely to stop the global pandemic [42•, 89, 183, 184•].

Linked to behavior change, but worthy of separate consideration are the so-called "structural interventions". This involves changing laws, policies, or other societal norms to reduce risk behavior. Raising cigarette taxes to reduce tobacco use among youth or banning cigarette smoking in indoor spaces where the public has access are examples of structural interventions. If schools were improved, school fees eliminated as obstacles to full attendance, and after-school opportunities for youth were promulgated, this might be considered a structural change to seek to reduce substance abuse in higher income nations and the exchange of sexual services for money to attend school as happens in many LMICs. A law requiring all commercial transient lodgings (hotels, etc.) to provide in-room condoms would be another example of a structural intervention. Large scale programs to offer universal testing in saturation volumes, incentives to link persons with HIV to care, near-universal use of cART for all HIV-infected persons, and community partnerships to maximize clinic attendance and cART adherence are the backbone of TasP programs that, while still depending on behavioral adherence, would be enhanced considerably if a structural context could be promulgated by policymakers of routine, widespread, opt-out testing.

Packages of Tools for Combination Prevention

"Magic bullets" have not worked to control the epidemic on their own, with the possible exceptions of needle exchange for IDUs and blood screening for blood banks. Even if we had a proven, effective vaccine for HIV, vaccination would still require multiple voluntary visits to optimize immunization along with large-scale population mobilization and program expansion for children, adolescents, and/or adults, depending on vaccine characteristics (durability of protection, for example). Combination prevention packages must vary to target those at-risk persons who are at highest risk in a given epidemiologic context [185]. If the local epidemic is being driven by IDU, then needle exchange and addiction treatment will be the best strategies, along with primary prevention of drug abuse. If sex work is a principal driver of a local epidemic, community and political mobilization of sex workers and their employers (eg, brothel owners, pimps, madams) will be needed to ensure effective STI screening and treatment, to promote universal condom use, and perhaps to provide PrEP. Other efforts to offer sex workers a way out of the profession through protection and job retraining and job placement, as well as to control sexual trafficking, can help protect the women who are aided, and may or may not reduce prostitution or HIV incidence overall.

Some interventions have far stronger levels of evidence of efficacy to reduce HIV transmission (infectiousness) or acquisition (susceptibility) than others. Among these are voluntary medical male circumcision (VMMC) with compelling observational data supported by 3 definitive and remarkably consistent RCTs [186–189]. ART for prevention was begun as a concept with the definitive demonstration of prevention of maternal-to-child transmission (PMTCT) with ART dating from 1994 [190]. Observational data from 2000–2001 and an incidental finding in a clinical trial in 2010 suggested that cART would reduce sexual transmission [191, 192, 193•]. Finally, the HPTN 052 RCT, over a decade in the making, demonstrated early use of cART as a major tool to reduce infectiousness and sexual transmission to partners, while clinically benefiting the infected persons as well [40••].

Other strategies are logical as adjunctive tools for HIV prevention, but are less consistently beneficial in RCTs. STI control based on syndromic management worked very well in one Tanzanian epidemic context to reduce HIV transmission,

but has failed in other epidemic contexts and other treatment [194]. PrEP has had a mixed success: Tenofovir-containing PrEP (cART among HIV-seronegative at-risk persons) was successful in CAPRISA 004 (topical microbicide for women), iPrEx (MSM) and Partners PrEP, and TDF-2 studies (heterosexual men and women), but not in the large VOICE trial (heterosexual women), or the FemPrEP studies (heterosexual women) [195•, 196•, 197, 198]. The Thai vaccine prime-boost strategy published in 2009 was partially effective; however, the vaccine companies did not seek licensure for marketing of either the prime or boost products, given their very modest effects [199•, 200]. Nonetheless, as better oral and vaginal PrEP/microbicide and vaccine products are developed, they may be added as future components to the therapeutic armamentarium. Given that PrEP is a tool for use in seronegative persons and TasP a tool for use in seropositive persons, work is needed to assess how these might be combined to maximize potential HIV impact at the community level.

When RCT data are not available, observational data are used to make judgments as to likely efficacy. Evidence of male condom efficacy is confirmed by effectiveness studies [184•]. Evidence for efficacy and effectiveness of female condoms is inconsistent, but they have been reported helpful in selected contexts [201–204]. Of certain utility, but not backed up by RCT evidence are needle exchange for drug users and opioid substitution therapy for IDUs [64, 205–223]. Also convincing are the use of contraception for HIV-infected women to reduce unintended pregnancies and HIV infection in infants [224–253]. A variety of behavioral and structural interventions that reduce HIV-related risk behaviors are of possible, but uncertain utility, due to conflicting trial and study evidence [175, 254–267].

Testing and Linkage to Care as a Core Strategy

The person who knows his or her own HIV serostatus is in a position to access HIV prevention or care services as they are provided in a given community; thus, testing is a first gateway [266–288]. While persons testing HIV seronegative may not change their risky behaviors, persons testing HIV seropositive tend to reduce their sexual transmission risk behaviors significantly [289–291]. Persons who do not know their own or their partners' serostatus are far less likely (range of 50 %–66 %) to use condoms [292, 293]. It is estimated that <20 % of adults in sub-Saharan Africa have been tested for HIV, yet the HPTN 043 NIMH Project ACCESS study demonstrated in a community RCT how community mobilization can increase testing rates up to 10-fold [294, 295]. The best HIV testing access includes provider-initiated, routine or opt-out testing, and voluntary home-based HIV counseling and testing (HBCT) [194, 290]. HBCT may be cost-effective for population-level scale-up in generalized epidemics, despite its higher programmatic costs [296].

Once a person is tested for HIV, those testing positive must be linked to cART-based care. In the HPTN 052 trial, excellence in cART care and adherence reduced viral replication and reduced HIV transmission to sexual partners by 96 %, termed a "game-changer" by the director of UNAIDS [40••]. HIV-infected persons with 350–550 CD4+ cells/μL were assigned randomly to receive ART either immediately (early therapy) or after a decline in the CD4 count to 250–350 cells/μL or the onset of HIV-1-related symptoms (delayed therapy). Given the success of TasP in HPTN 052 when persons with high CD4+ cell counts were the target, the option of immediate treatment for all HIV-diagnosed persons, regardless of immunological status is ideal, if resources are available. Still, a combination of interventions is inherently needed to make TasP a reality in public health terms: HIV testing has to be brought to scale, effective linkage to care must be a key priority for primary care programs, and high coverage and adherence to cART must be nurtured. WHO's estimate of a 23 % yearly ART attrition rate in Africa illustrates the tremendous challenge faced by the public health community in this regard [297]. It is plausible that a universal testing and treatment approach (regardless of CD4+ cell count) could reduce stigma in communities where testing is common and infection is simply treated in everyone, as with other infectious diseases or chronic disease conditions.

Given this need for expanded HIV testing, accessing the service, and willingness to adhere to the prevention modality (eg, VMMC, future HIV vaccine or microbicide, cART regimen, consistent and correct condom use), behavioral co-interventions are essential. Prevention for positives to reduce risky behaviors with counseling focused on building motivation and developing skills is promising [298]. Interventions based on sound behavioral theory, such as the Health Belief model, can help address mental health and substance use issues, with a focus on adherence [67]. Condom use will continue to be emphasized as an adjunctive tool for HIV/STI risk reduction [292, 299, 300]. The biomathematics of combining methods for prevention are compelling, but intimidating at the same time; substantial coverage will be needed to succeed in bringing the basic reproductive rate to <1 thereby offering the potential prospect of eventual elimination of HIV as a public health problem [34, 301–309, 310•, 311–313].

The PopART Intervention

Led by one of us (RJH), our protocol team is launching a trial, HPTN 071/PopART, designed to measure the impact on HIV incidence of an intervention package that combines TasP, VMMC, STI control, PMTCT, and key behavioral approaches

Table 3 Key elements of the combination prevention community randomized clinical trial, HPTN 071: population effects of antiretroviral therapy to reduce HIV transmission (PopART): a cluster-randomized trial of the impact of a combination prevention package on population-level HIV incidence in Zambia and South Africa (to begin in 2013), Conceptual reference [331•]

Study Purpose and Design: To determine the impact of two community-level combination prevention packages on population-level HIV incidence. Both interventions are based on universal HIV testing and intensified provision of combination antiretroviral therapy (cART) and care, one with cART for all HIV infected persons and one only for persons meeting national treatment guidelines (CD4+ cells ≤350/μL and/or WHO clinical groups 3 or 4. PopART is a three-arm, cluster-randomized, longitudinal study to be implemented in 21 clusters (communities).

Study Population and Size: The prevention packages will be implemented throughout the communities randomized to the intervention arms. Main study outcomes will be measured in a randomly-selected group drawn from the adult population of the communities: a Population Cohort. The combined population of all 21 clusters is approximately 1.2 million individuals. The interventions will be implemented in 14 of the 21 clusters with a combined population of approximately 800,000 individuals (adults and children) in the intervention arms. The approximate sizes of the randomly-selected groups for main study outcome assessments are:

- Population Cohort: 52,500 individuals
- Case–control Studies: 2400 individuals
- Qualitative Studies: ≈2000 individuals

Study Sites: The study communities in Zambia are spread across 4 provinces and 5 districts. Each community is the catchment population of a government health facility. The study communities in South Africa are located in the Cape Metro District and Cape Winelands District of the Western Cape Province. The communities are defined by the catchment population of a government health facility. For a list of all sites, see: http://www.hptn.org/research_studies/hptn071.asp.

Study Duration: The planned duration of the entire study will be approximately 6 years, with enrollment and follow-up of communities and delivery of the intervention occurring over 4 years.

Intervention Packages:

Arm A - Universal testing with immediate cART.

- •House-to-house deployment of:
  - •Universal HIV counseling and testing;
  - •Active linkage to care for persons diagnosed as HIV-infected, with immediate cART eligibility
  - •Promotion of male circumcision and prevention of mother to child transmission (PMTCT); and
  - •Provision of condoms.
- •Strengthening of HIV testing and services at health facilities and other venues.
- •Strengthening of male circumcision and prevention of mother-to-child transmission of HIV services available in the community.
- •Treatment of sexually transmitted infections (STIs) and provision of condoms at health units.

Arm B - Universal Testing with cART Eligibility According to National Guidelines Package includes all of the Arm A interventions, except cART eligibility according to national guidelines.

Arm C - Standard of Care (Control Arm).

- •Strengthening of HIV testing and cART services according to national guidelines at health facilities and other venues.
- •Strengthening of male circumcision and PMTCT available at health facilities and other venues in the community.
- •Treatment of STIs and provision of condoms at health facilities and other venues in the community.

Primary Objectives: To measure the impact of the 2 intervention packages on HIV incidence by enrolling and following a random sample of adults (Population Cohort) in the trial communities.

Secondary Objectives:

- •Measure the impact of the 2 intervention packages on the following:
  - •HIV incidence over the first, second, and third years of follow-up;
  - •Community viral load, cART drug resistance, and cART adherence and viral suppression (if funding is identified);
  - •HSV-2 incidence; Sexual risk behavior; HIV-related stigma;
  - •Uptake of HIV testing and retesting over the entire study period;
  - •cART screening and uptake; cART toxicity based on clinic records;
  - •Time between HIV diagnosis and initiation of care; Uptake of PMTCT;
  - •Retention in care; HIV disease progression and death;
  - •Case notification rate of tuberculosis;
  - •Uptake of male circumcision.
- • Carry out case–control studies to examine factors related to:
  - •Uptake of HIV testing during the first round of home-based testing in Arms A and B;
  - •Uptake of immediate treatment in Arm A;
  - •Uptake of HIV testing during the second round of home-based testing in Arms A and B.
- •Use qualitative methods to:
  - •Assess popular understanding of testing/treatment at study initiation and during implementation;

- •Evaluate the acceptability/functioning of the Community HIV-care Providers in Arms A and B;
- •Evaluate the acceptability of interventions and barriers to access in Arms A and B;
- •Document the effect of the interventions on social networks, stigma, sexual behavior, alcohol use, gender-based violence, HIV identity, other HIV prevention options and community morale;
- •Evaluate the process and challenges of community consultation and applying ethical principles.
- •Measure burden experienced by local health centers from implementation of the community intervention.
- •Systematically record costs in all communities to measure incremental costs of intervention packages.
- •Estimate the effectiveness and cost-effectiveness of interventions by fitting mathematical models based on the empirical data from the trial, including data related to cost.

to reduce infection at the community level (Table 3). There are other small and large clinical and community research efforts to access the impact of various TasP and combination prevention approaches [36•, 313–318].

Conclusions

There is substantial heterogeneity in the global HIV epidemic, with the drivers of the epidemic differing substantially by mode of transmission (eg, heterosexual, homosexual, IDU) [319]. Regardless of the mode of transmission, the HIV pandemic can be confronted with a combination of approaches, anchored by the deployment of cART that can reduce infectiousness as well as the clinical boon of turning a previously fatal disease into a chronic, manageable one. Complementary preventive approaches must differ. For example, needle/syringe exchange is important for IDU-related prevention, voluntary medical male circumcision addresses heterosexual transmission in high prevalence areas like sub-Saharan Africa, and PrEP has potential to help prevent male-to-male transmission. The promise of combination prevention depends on the long-term resolution of huge health services gaps in LMICs. Yet as we have more tools for HIV prevention, "HIV-fatigue" in donor nations combined with concern from economic downturns from 2008 onwards may result in cuts in HIV programs. Past experience suggests, however, that failures in HIV prevention or early treatment will simply cost society more in the long run, given the high direct costs of illness and indirect costs of disability, suffering, and death [320–324]. Prevention, including testing and early cART treatment, is a good societal and economic investment.

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- • Of importance,
- •• Of major importance

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