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HIV research in South Africa: Advancing life

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South African (SA) researchers have made both national and global contributions to HIV prevention and treatment. Research conducted in SA has contributed markedly to improved survival in HIV-infected infants, children and adults. The translation of clinical research into practice has enabled the curtailment of paediatric HIV in SA. Along with international collaborators, SA has made pivotal contributions to biomedical prevention modalities including medical male circumcision and oral and topical microbicides, and is undertaking pivotal HIV vaccine research. Research into the structural and psychosocial drivers of HIV infection will be critical for sustaining biomedical interventions, and necessary to end AIDS.

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The graph of our region's life expectancy shows a peculiar dip in the 1990s that persists for a decade.[1] Those who were on the forefront – communities and their healthcare workers – can discern the cause of that dip through personal experience. HIV/AIDS went on to devastate South Africa (SA), overwhelming a fragile healthcare system not yet repaired from the damage of apartheid, killing the young and economically active in vast numbers, spreading stigma, leaving a generation of orphans and blotting the legacy of the political regime that rubber-stamped the avoidable deaths of over 300 000 South Africans by propagating AIDS denialism. By the mid-2000s, the graph begins to recover,[1] a testament to the human effort of the health activists, researchers and healthcare workers who contributed to alleviating the health crisis of our time. SA's force of HIV researchers can point to that recovery in the graph and say, 'We had a part to play in this.'

SA, with the largest HIV epidemic in the world, estimated at 7.52 million people living with HIV, still sees too many AIDS-related deaths: 115 167 people died of AIDS in 2018.[2] Although the death toll has substantially reduced, from 283 564 in 2006,[3] it is still too high for an era in which sophisticated treatments are available (Fig. 1).[4] New infections continue: the estimate of 231 000 new infections in 2017[5] is a rallying call toward strengthening preventive efforts.

Here we summarise the past, current and anticipated future contributions of HIV research in SA to help quell our epidemic.

How HIV affects life and death in SA

In 2005, the year after the public antiretroviral treatment (ART) programme had its limited launch, average life expectancy in SA reached a low point of 51.9 years for men and 55.5 for women.[4] By 2017, life expectancy was 61.2 and 67.4 years for men and women, respectively.[4] This dramatic progress is attributed to the decline in HIV-related mortality, specifically in young adults accessing treatment,[6] and in infants who avoided HIV infection thanks to ART-based prevention of mother-to-child transmission (PMTCT) strategies.[4]

Among adolescents and young adults, particularly women, HIV/AIDS has had a deadly effect in SA. The probability of a 15-year-old SA girl dying before the age of 25 was influenced by the country's response to HIV: this statistic peaked at the height of the untreated epidemic in 2004, and then significantly reduced in the era of ART availability

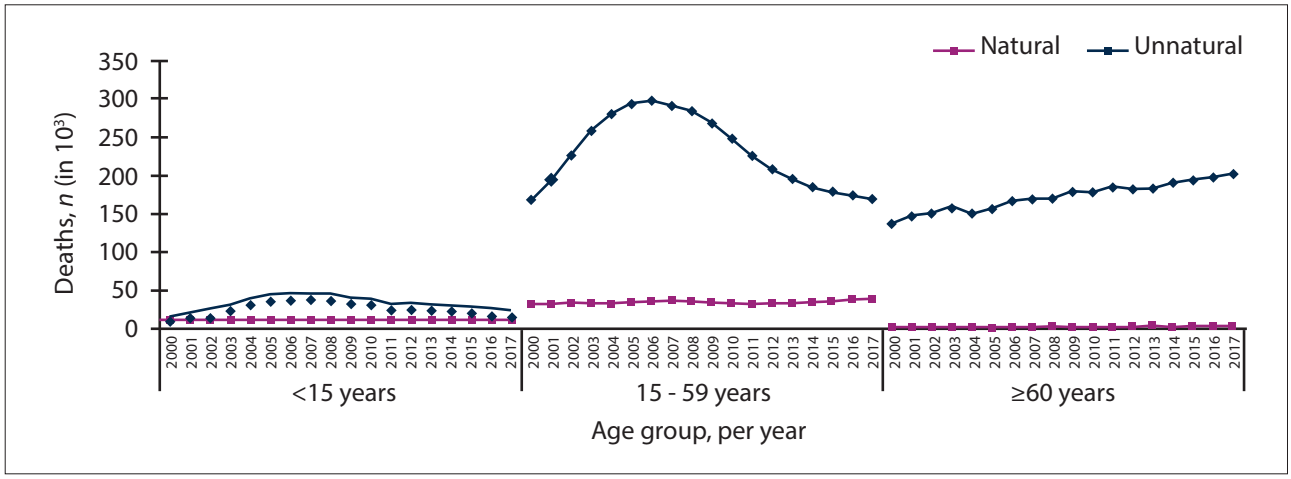

Fig. 1. Trend in the number of natural and unnatural deaths by broad age group, 2000 - 2017. (HIV-related deaths are classified as natural deaths.)[4]

(Table 1).[4] In parallel, infant and under-5 mortality rates are also declining in SA, and in 2017 were 23 and 32 per 1 000 live births, respectively – on track to meet the 2019 targets.[4]

Changing the trajectory of the HIV epidemic through research and implementation of ART

In 2004, SA launched what has since grown into the largest ART programme on the planet.[5] During this time, there have been significant advances in treatment science, which have been adopted in programmatic implementation. Key examples of the country's research-to-implementation model informing the success of the ART programme include (*i*) ART initiation eligibility for children and adults;[7,8] and (*ii*) task-shifting from an elite subset of 'HIV doctors' to HIV-trained nurses.[9,10]

Discovery of improved strategies for determining eligibility for ART initiation, and their implementation

Conducted in SA during a time when children had to meet steep immunological, virological and clinical criteria to start ART,[11] the Children with HIV Early Antiretroviral Therapy (CHER) study had startling findings: early HIV diagnosis and ART initiation reduced early infant mortality by 76%, and HIV progression by 75%.[7] The study influenced local and international clinical guidelines to treat children at diagnosis, translating into improved paediatric HIV outcomes globally.[11,12]

SA researchers also contributed to a study that influenced the change in adult treatment eligibility guidelines. The Strategic Timing of Antiretroviral Treatment (START) study, conducted in 35 countries including SA, showed that immediate ART initiation at CD4+ counts >500 cells/μL was superior to deferring ART initiation until the CD4+ count was <350 cells/μL.[8]

SA researchers, faced with a significant HIV/TB comorbidity problem, provided evidence for the timing of ART initiation after TB treatment. ART initiation within 4 weeks of TB treatment increased AIDS-free survival for patients with CD4+ counts <50 cells/μL. However, ART initiation ought to be deferred to the first 4 weeks of the continuation phase of TB treatment in those with higher CD4+ T-helper cell counts.[13,14]

The newest SA guidelines recommend a first-line dolutegravir-based regimen to replace the efavirenz component, minimising the side-effect profile and prolonging durable virological suppression.[15] Studies researching further ART regimen optimisation include WRHI 052,[16] which suggests that switching from a ritonavir-boosted lopinavir nucleoside-analogue-based regimen to a daily low-dose ritonavir-boosted darunavir nucleoside-analogue-based regimen after viral suppression might be safe and efficacious. The ADVANCE study is investigating a candidate universal ART regimen, including the replacement of tenofovir disoproxyl fumarate with tenofovir alafenamide.[17]

The evidence of good outcomes with task-shifting opens the way for ART scale-up

Researchers in SA conducted two landmark studies on task-shifting, one through the Comprehensive International Program for Research in AIDS in SA (CIPRA SA), and the other called the Streamlining Tasks and Roles to Expand Treatment and Care for HIV (STRETCH) study. Both proved that task-shifting was not deleterious to patient outcomes, thereby facilitating the scale-up of the SA ART programme to reach the millions of people living with HIV needing treatment initiation and lifelong monitoring.[9,10]

Table 1. Probability per 1 000 of a 15-year-old SA female dying before age 25 years[4]

Year	Probability
2000	35.1
2004	44.4
2017	17.0

SA = South African.

PMTCT: The SA commitment to protecting babies and mothers

SA has been at the forefront of PMTCT research. As evidence mounted from research in high-income settings about the effectiveness of ART for PMTCT, scientists in SA sought to determine whether such regimens were feasible for wide-scale implementation in low- and middle-income health-system contexts with breastfeeding populations. The multi-country PErinatal TRAnsmission (PETRA) trial (1996 - 2000),[18] which included two SA sites, assessed the efficacy of three different short-course antiretroviral (ARV) regimens. The PETRA trial showed that short-course ARV regimens effectively reduced intrapartum transmission, but that additional measures were needed to prevent postnatal breastmilk transmission.[18] After maternal-infant administration of single-dose nevirapine (sdNVP) was found to be moderately efficacious and affordable, SA scientists designed the South African Intrapartum Nevirapine Trial (SAINT) to evaluate whether an additional maternal dose of NVP could further reduce transmission rates. The trial demonstrated the efficacy of two inexpensive regimens given during labour in reducing intrapartum and early postpartum transmission.[19] However, the two maternal doses of NVP were found to increase the prevalence of NVP resistance. Given the high rates of non-nucleoside reverse-transcriptase inhibitor (NNRTI)-resistance mutations in most women and HIV-infected infants receiving NVP, including sdNVP, a study to assess adding a short course of zidovudine (AZT) and lamivudine (3TC) was designed and conducted in SA. This intervention was found to reduce emergent resistant mutations in both mothers and their infants, and was incorporated into clinical care.[20]

After the demonstration of short-course antiretroviral therapy for PMTCT, the WHO published technical notes on PMTCT stating that 'there was no longer any justification to restrict use of any of these regimens to pilot project or research settings'.[21] Following a Constitutional Court battle against the National Department of Health (NDoH) by the Treatment Action Campaign, the SA government began, in 2003, to scale up an NVP-based PMTCT programme from two pilot sites per province to reach national coverage.[22] Although early MTCT rates declined after the scale-up of single and short-course regimens in SA, the challenge remained as to how to prevent postnatal transmission through breastmilk, and how to improve maternal health.[23,24] Researchers in Soweto evaluated the role of post-exposure prophylaxis in preventing post-partum transmission, which led to the multi-centre HPTN 040 trial. This trial assessed three post-partum interventions to prevent HIV transmission[25] and changed clinical guidelines for post-partum prophylaxis for HIV-exposed infants whose mothers had been undiagnosed during pregnancy and labour.[26]

Research undertaken in SA, one of only a few African countries that provided free formula milk to HIV-infected mothers, provided evidence regarding HIV outcomes related to infant feeding choices.[27,28] A study conducted in KwaZulu-Natal Province found that exclusive breastfeeding carried a significantly lower risk of HIV-1 transmission than mixed feeding, and a similar risk to exclusive formula feeding.[29] These findings were confirmed in another study at the rurally-located Africa Centre, which also documented higher mortality among infants given replacement feeds compared with those exclusively

breastfed.[30] These two studies guided the 2009 WHO recommendations on HIV and infant feeding towards exclusive breastfeeding for 6 months, and continued breastfeeding until 12 months old, together with ART.[2,31]

PROMISE (2011 - 2015), a landmark multi-country trial that included sites in SA, investigated the benefits and risks of combination ART given to pregnant women with a CD4+ count of at least 350 cells/μL compared with short-course AZT and sdNVP. PROMISE proved that antenatal ART resulted in significantly lower rates of early HIV transmission than zidovudine alone,[32] which led to the decision by the SA government in 2015 to recommend starting lifelong ART for pregnant HIV-positive women, irrespective of CD4+ count. These evidence-informed policy changes led to dramatic improvements in the health and survival of women and children, such that by 2015, HIV was no longer the leading cause of under-5 deaths, and had declined significantly as a contributor to maternal deaths.[33] These successes have created an important area for current research, namely the health of HIV-exposed uninfected children, the focus of another article in this supplement.[34]

SA scientists have also contributed important health-systems research, undertaken across the continent, regarding strategies to improve the implementation of PMTCT policies in primary healthcare settings,[35-37] and the role of community cadres in strengthening linkages between households and health facilities.[38,39]

Future research in SA will be aimed at reducing the residual risk of breastmilk transmission, possibly including novel interventions such as passive immunisation with broadly neutralising antibodies or active vaccination strategies.

HIV prevention research and interventions in SA

From 2011 to 2016, there has been a 34% decrease in new HIV infections among 15 - 49-year-olds in SA.[40] Contributors to the decline include: (*i*) increased ART uptake;[41] (*ii*) the scale-up of voluntary medical male circumcision to 2.4 million procedures conducted between 2012 and 2016 alone;[40] (*iii*) increased condom distribution;[40,41] and (*iv*) increased availability of HIV testing services at over 4 500 public healthcare facilities, which tested 13 million South Africans within 18 months.[42,43] SA has contributed much research evidence on HIV prevention, including the protective effects of medical male circumcision on male HIV acquisition,[44] treatment of people living with HIV as prevention to HIV-uninfected partners[45] and the proven lack of efficacy of the diaphragm in preventing HIV acquisition.[46]

In 2016, SA began the rollout of pre-exposure prophylaxis (PrEP) to sex workers.[47] PrEP services were extended to men who have sex with men (MSM) and to adolescent girls and young women between 2018 and 2019,[40] with plans for provision to postpartum women, and for high-transmission areas. The effectiveness of oral and topical PrEP, which is closely tied to adherence, has varied across studies conducted in different populations. Generally, oral PrEP effectiveness has been high among MSM in high-income countries.[48,49] Studies conducted among women in SA have yielded different results. The effectiveness of oral Truvada as PrEP has ranged between –4% (VOICE)[50] and 6% (FEMPREP)[51] in African trials, and poor adherence has been implicated.[50,51] The effectiveness of topical tenofovir gel microbicide, an SA initiative, ranged between 0% (FACTS 001),[52] 15% (VOICE)[50] and 39% (CAPRISA 004).[53] Again, poor adherence was implicated. Such findings, shown in Table 2, highlight the ongoing need for a regionally acceptable method of HIV prevention, especially for young women in Africa, who are a most-at-risk population for HIV acquisition. The ASPIRE and RING trials found that the intravaginal dapivirine ring had modest efficacies of 27% and 31%, respectively.[54,55]

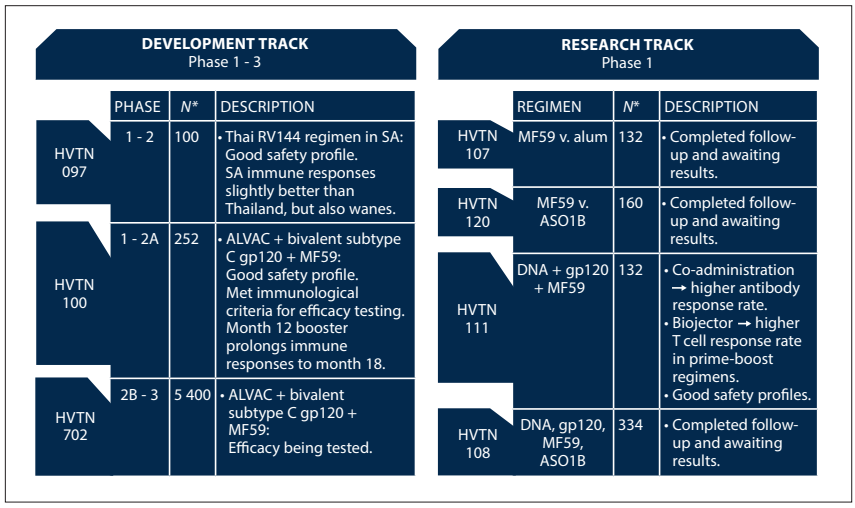

*Fig. 2. Study tracks of the Pox-Protein Public-Private Partnership (P5), which is investigating vaccines against HIV clade C (the South African Medical Research Council is one of the P5 partners). (SA = South Africa.) *Participants.*

Table 2. Summary of ARV-based PrEP trials in SA showing low to modest efficacy

Prevention trial	Trial name	Trial site	Participants	Effectiveness, %
Topical tenofovir gel, coital	CAPRISA 004	SA	Women	39
	FACTS 001	SA	Women	0
Topical tenofovir gel, daily	MTN003/VOICE	SA, Uganda, Zimbabwe	Women	15
Oral Truvada, daily	iPrex	Americas, Thailand, SA	MSM/transgender	44
	FeMPrEP	Kenya, SA, Tanzania	Women	6
	MTN003/VOICE	SA, Uganda, Zimbabwe	Women	–4
Oral tenofovir, daily	MTN003/VOICE	SA, Uganda, Zimbabwe	Women	–49
Dapivirine ring	RING	SA, Uganda	Women	31 (0 in 18 - 21 yrs)
	ASPIRE/MTN020	Malawi, SA, Uganda, Zimbabwe	Women	27 (0 in 18 - 21 yrs)

ARV = antiretroviral; PrEP = pre-exposure prophylaxis; SA = South Africa; MSM = men who have sex with men.

SA contributions to the search for a preventive HIV-1 vaccine

SA has adopted multiple HIV prevention tools into the public health system, including barrier methods, male medical circumcision and ARV prophylaxis strategies.[56] However, new infections continue to amass.[5] The challenges of current HIV prevention methods include resource constraints, reliance on daily adherence, patriarchal power imbalances and method unsuitability for women – the sex that experiences disproportionate infection risk.[57] As with other pathogens, a vaccine could cost-effectively deliver us to a tipping point in HIV control.[58,59]

For over 18 years, SA has contributed to the pursuit of a preventive HIV vaccine.[57] In collaboration with community, local and international stakeholders, the SA Medical Research Council (SAMRC), through the SA AIDS Vaccine Initiative (SAAVI), has pioneered studies of vaccines against the clade C HIV subtype responsible for the highest number of global HIV infections, such as the SAAVI-developed DNA.C and recombinant MVA vaccines.[60,61] The SAMRC-led SAAVI programme was a public-private partnership funded by the NDoH, Department of Science and Technology and Eskom, which, after a 9-year development period, created a pipeline of candidate HIV-1 subtype C vaccines. These included virus-like particles, novel DNA plasmid vaccines, capripoxvirus and Bacillus Calmette-Guérin (BCG)-vectored vaccines.[62]

The research of an HIV vaccine has required much persistence. In the evaluation of the MRK-Ad5 HIV vaccine, the SA HVTN 503/Phambili trial was stopped early after the declaration of futility of its companion study in the Americas, the HVTN 502/Step trial. A finding that halted further Adenovirus 5 platform development was that MRK-Ad5 increased the susceptibility to HIV in male volunteers, irrespective of circumcision and Ad5 serostatus.[63,64]

Since the 2009 milestone announcement in Thailand of the first vaccine regimen with some efficacy,[65] the SAMRC, as part of the Pox-Protein Public-Private Partnership, has collaborated in the development of a similar heterologous prime-boost regimen for clade C (Fig. 2). When South Africans were vaccinated with the Thai regimen, the initially robust cross-clade immune responses were not durable.[66] However, the addition of a booster to the clade-C adapted regimen prolonged immune responses.[67] The latter regimen has progressed to an efficacy trial, HVTN 702/Uhambo,[67] which is chaired by four female SA medical researchers. HVTN 702/Uhambo completed enrollment in July 2019 at its 14 SA sites. In parallel, results of other vaccine trials show that replacing the pox vector with a DNA plasmid vaccine prime can also induce relevant immune responses. The potential for easy and cheap manufacturing of DNA plasmid vaccines makes this avenue promising.[68]

SA researchers are also contributing to the clinical development of a global antigen HIV vaccine. An early-phase trial of a prime-boost vaccine strategy evaluating a mosaic adenovirus-26 vector and clade C gp140 protein conducted across three continents (Africa, Asia and North America) produced robust immune responses, comparable with those found to be efficacious in preclinical studies.[69] These findings led to the implementation of the HVTN 705/VAC89220HPX2008/Imbokodo phase 2b efficacy trial currently underway in sub-Saharan Africa (SSA), including 17 SA sites.[70]

Passive immunisation with monoclonal antibodies (mAb) is another promising strategy that has been shown to be protective in preclinical studies.[71,72] The first phase 2b human trial investigating preventive efficacy of the VRC01 mAb is underway in SSA. SA scientists have also identified a neutralising antibody, CAP256, which is highly potent against clade C HIV, and about to enter early clinical development.[73,74]

Future focus of research

We still need to find solutions to the underlying structural, psychosocial and behavioural drivers of the HIV epidemic. Key to epidemic control will be the engagement of young people and key populations such as sex workers, their clients and MSM, to ensure the uptake of biomedical interventions as well as address issues of intimate partner violence, intergenerational sex and patriarchy.[75-85] SA research has exposed gender-based violence as a key driver of HIV acquisition.[81] Gender-based violence is endemic across SA, driving mental health concerns,[75,84-86] both of which are associated with poor health-seeking behaviours and poor adherence to medications.[87-90]

Attention to designing interventions that ensure access to HIV prevention, treatment and care for adolescent girls and young adults may contribute to breaking the transmission cycle. Future research should also focus on understanding the HIV epidemic in men, and factors associated with transmission, such as intergenerational and transactional sexual partnerships.

Conclusion

The small community of SA researchers, supported by their communities, study participants, collaborations and sponsors, has made key scientific contributions that inform public programmes on changing the course of the HIV epidemic, and improving public health.

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