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Is the HIV vaccine our best shot? - Why the answer to HIV prevention will be found in South Africa

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The state of the South African epidemic

South Africa is the unenviable epicentre of the HIV pandemic with 0.7% of the global population sadly amassing 18% of the global prevalence (1). The epidemic is widely acknowledged to be generalised and predominantly heterosexual in transmission.

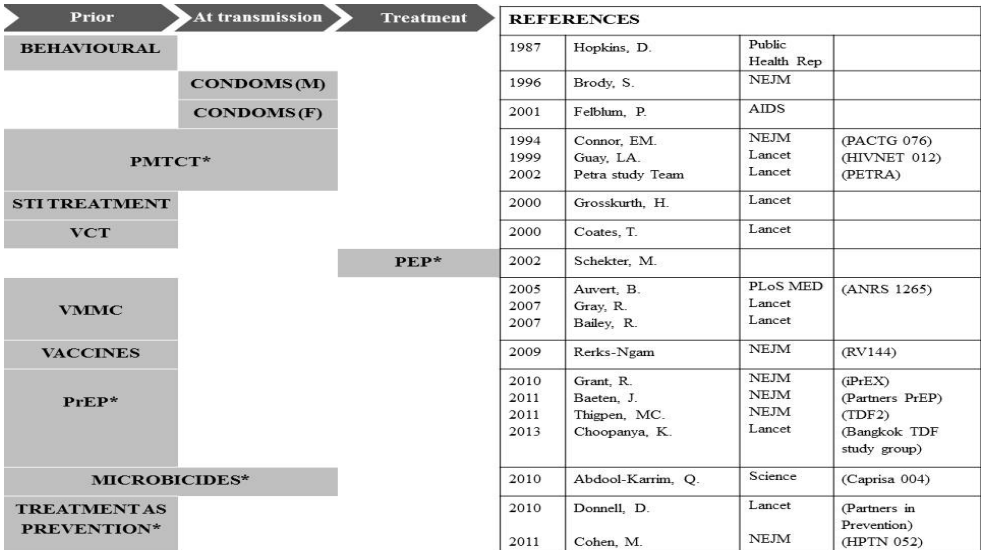
What has South Africa achieved?

The government has expanded interventions over the years to quell the epidemic. In 2010, the national HIV counselling and testing (HCT) campaign was launched increasing the numbers of people that tested by over 15% between 2008 and 2012 (2). Modelling estimates suggest that universal implementation of HCT among South Africans aged 15 years and older would result in a reduction in prevalence to less than 1% in the next 50 years (3). Prevention of mother-to-child transmission (PMTCT) HIV services was being offered at 98% of health facilities since 2010 resulting in the decline of new infections to 2.2% in 2013/2014 (4). Further to this, South Africa has developed the most established condom distribution programme in the world with 506 million male condoms distributed in 2013/2014 alone (4). HIV and AIDS education has become integrated into the primary and high school curriculums through a Life Skills Education Programme aimed at averting new infections and providing support to those children already living with HIV. Lastly, South Africa has orchestrated the largest ARV rollout programme in the world accounting for a third of new ARV drug recipients globally between 2010 and 2013 (1).

Sadly however, 58% of South Africans eligible for ARV treatment remain unable to access it (1). Despite the strides made by government to alleviate the HIV burden, high HIV incidence rates of 16% were reported in 2013 (1). We can gauge from this that the current prevention and treatment processes are failing. The question is: what alternatives do we have at our disposal? And could we gauge the potential success of these?

Successes, near-misses and hopes in HIV prevention

Global research into evidence based HIV prevention strategies has yielded some success. (Figure 1).



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2009	Rerks-Ngam	NEJM	(RV144)
2010 2011 2011 2013	Grant, R. Baeten, J. Thigpen, MC. Choopanya, K.	NEJM NEJM NEJM Lancet	(iPrEX) (Partners PrEP) (TDF2) (Bangkok TDF study group)
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**ARV based intervention*
PMTCT – Prevention of mother to child transmission, STI – sexually transmitted infection, VCT – voluntary counselling and testing, PEP – post exposure prophylaxis, VMMC – voluntary male medical circumcision, PrEP – pre exposure prophylaxis
Figure 1. HIV prevention strategies by implementation stage

Anti-retroviral prophylaxis

Microbicides for women

Microbicides are formulated for application to the vagina or rectum with the aim of reducing the acquisition of STIs including HIV. An effective microbicide holds immense potential for impacting the course of the HIV epidemic, particularly among women unable to negotiate condom use with their partners. There have been significant advancements in microbicide development following decades of disappointment (6 candidate products have failed to show effectiveness in 11 clinical trials conducted in the last 20 years). CAPRISA 004 was the first study to provide proof of concept for microbicides. Assessing the effectiveness and safety of a 1% vaginal gel formulation of Tenofovir (TDF), the product conferred an estimated 39% overall reduction in HIV acquisition (5). In women demonstrating higher adherence to the gel, the reduction was 54%. Gel adherence, however, became a critical focal point. The results of MTN-003/VOICE study further underscored the impact of adherence when all three VOICE arms were stopped prematurely because there was no effect (6). While the evidence established in the CAPRISA 004 work supported pericoital vaginal application of TDF in a proof on concept study, additional data (the FACTS 001 study) was required to strengthen the application if licensure was being considered (6). Sadly, the FACTS 001 findings announced at CROI this year did not find the gel effective in preventing HIV acquisition, with adherence once again the key finding behind the poor outcomes. This brings into question the future use of this prevention modality, with perhaps its use being reserved for self-motivated populations of women.

Oral pre-exposure prophylaxis

Pre-exposure prophylaxis (PrEP) involves the use of a pharmacological agent prior to a potential HIV exposure to prevent infection. Antiretroviral chemoprophylaxis has been shown to be a promising approach to prevent HIV acquisition. In 2010, the iPrEx study demonstrated the initial encouraging work in this field with a 44% reduction in HIV incidence noted among males having sex with males (MSM) on daily doses of TDF (7). This convincing data forms the basis for the standard of care regarding MSM antiretroviral chemoprophylaxis in South Africa. By 2012, Baeten showed comparable results in serodiscordant heterosexual couples in Kenya and Uganda in the Partners PrEP study (8). Chemoprophylaxis for heterosexual transmission was validated by Thigpen et al. in the TDF2 study conducted in Botswana (9). Following the impact of ARV chemoprophylaxis in the reduction of sexual transmission of HIV, the Bangkok Tenofovir Study Group established similar positive findings among injection drug users in Thailand (10). Despite these promising findings, PrEP efficacy (like microbicides) is limited by poor adherence levels. The FemPrEP and two arms of the VOICE trial were halted early owing to futility associated with poor adherence. Conversely, participants exhibiting high adherence experienced 90% protection (6, 11). In the PrEP trials, poor adherence was mostly identified among younger female participants at high risk of HIV acquisition, the group mostly likely to be targeted for the intervention (12). Apart from adherence, concern has been raised around the development of drug resistance, potential sexual disinhibition due to perceived protection, accessibility and acceptability by the hardest to reach and most at risk populations and stigmatization and negative attitudes by peers and healthcare providers. Used as prescribed, PrEP can provide up to a 99% level of protection which would render this intervention highly cost-effective. But cost-effectiveness does not translate to affordability and the potential risks associated with PrEP have to be weighed against the cost of upscaling ARV coverage.

Treatment as prevention

Combination antiretroviral therapy decreases the replication of HIV-1. Thus, the sexual transmission of HIV in serodiscordant couples can be limited by the infected partner's use of ARVs to decrease blood concentrations and genital secretions of HIV. The Partners in Prevention HSV/HIV Transmission Study was conducted at 14 sites in 7 African countries including South Africa. They documented a 92% reduction in HIV-1 transmission risk following ARV initiation among heterosexual couples, likely attributed to markedly reduced plasma HIV-1 levels. The greatest relative prevention benefit from ARV was identified among couples where the HIV-1 infected partner had low CD4 counts (<200 cells/mm^3) or high plasma HIV-1 RNA concentrations (50,000 copies/mL) (13). In 2011, a landmark study, HPTN 052, showed early initiation of antiretroviral treatment (in people with a CD4 count between 350 and 550 cells/mm^3) for the HIV-positive partner in a serodiscordant couple reduced HIV transmission to the HIV-negative partner by 96% (14). The HPTN 052 findings prompted the World Health Organisation (WHO) to recommend ARV treatment to all serodiscordant couples to reduce HIV transmission. The general consensus, however, is that ARV treatment as prevention would result in high risk behaviours, likely from decreased condom use. Adherence is again a prime concern with South African data indicating that only 64% of those initiated between 2002 till 2007 were still on treatment 3 years later (15). The greater challenge in the South African HIV landscape is whether we can justify curtailing funds directed at HIV treatment in favour of HIV prevention efforts. In a country with the greatest

global burden of HIV and 58% of those afflicted still unable to access treatment, the scenario seems rather implausible.

Voluntary male medical circumcision

Voluntary male medical circumcision (VMMC) has been proven to reduce female to male sexual transmission of HIV by 60%. Based on landmark studies, the WHO launched the unprecedented public health initiative in 2009 calling for 80% coverage of voluntary, safe, culturally appropriate and affordable male circumcision by 2016 (16). Heeding this call, South Africa had conducted 3,3 million VMMCs by 2012 (2). Initially, the South African VMMC services were limited as they were performed by doctors exclusively with the programme being marred by poor quality of facilities and surgical care (17). The recent introduction of PrePex in South Africa (an elastic ring device requiring no local anaesthetic that can be placed and removed by a mid-level health care worker) holds the promise of accelerating the rollout while relieving the demands placed on the limited numbers of healthcare workers. VMMC has limited value in key populations such as MSM, injection drug users and sex workers, but should rather be directed at countries with high HIV prevalence occurring primarily via sexual transmission, like South Africa. VMMC is highly cost-effective. It is a once-off procedure that potentially has benefit for the rest of a man's' life and is significantly associated with averting new HIV infections.

HIV vaccines

South Africa is unlikely to treat its way out of the current HIV epidemic. Apart from the financial implications of scale up and expansion the ARV programme, there are several valid reasons why a HIV vaccine is imperative. In the South African context, the issue of adherence would be rendered moot unless booster vaccine doses were required. Vaccination would be independent of behaviour change (abstinence) and would not require the consent of both partners as with condom use. Children can be targeted at schools prior to exposure and allow for potential development of herd immunity should coverage reach appropriate thresholds. However, HIV vaccines should not be viewed in isolation. The HIV vaccine would complement the current evidence based strategies of HCT, access to condoms, PrEP, STI treatment and treatment as prevention together with behavioural and structural interventions of sexual health education, outreach and support services.

HIV vaccine development presents a dynamic set of challenges to the scientist. There is no documented recovery in HIV infected humans, so no natural immune mechanism to emulate, nor is there a comparable successful animal model. HIV destroys the immunity – the very cells needed to mount a response. Following infection, HIV is integrated into the human genome, relatively hidden from detection. There are several subtypes, each of which is constantly varying.

Research into broadly neutralizing antibodies against HIV, capable of neutralizing high percentages of HIV has shifted the focus of vaccine development. Much can be gleaned from the HIV vaccine trail. The first Phase III trial candidate AIDSVAX, initiated among American homosexual males (1998) and Thai injection drug users (IDU) (1999) respectively, ended in 2003 showing no benefit. Further disappointment followed when 2 Phase IIb trials (STEP and Phambili) were halted prematurely in 2007 due to futility (18, 19). In fact, more infections were linked to vaccine recipients which essentially put paid to the use of the adjuvant adenovirus type 5 (Ad5). Finally in 2009, the results of the RV144 trial conducted in Thailand demonstrated human immunogenicity to a HIV vaccine, the first study to do so. The combination of AIDSVAX (promotes antibody production to HIV) and ALVAX (designed to stimulate a cellular response to the virus) had proven effective (20). Following specific modification of the AIDSVAX/ALVAC molecule in terms of region specific clade and changing the adjuvant to canarypox, the vaccine has entered Phase I trials in South Africa, the seat of the HIV pandemic.

These results are eagerly anticipated as the evidence pointing to the licensure track starts to evolve. If this vaccine reaches fruition, questions of distribution and accessibility would arise. Would vaccine implementation compare favourably with massive expansion of the ARV programme? Would it prove cost-effective and could we actually afford it? How would the vaccine impact on existing HIV prevention strategies?

Going forward

Eradicating HIV with the tools we have currently seems improbable. Unless we somehow invoke a massive, sustained drive to change behaviours amongst those at risk, it seems likely that the numbers of people eventually requiring ARV therapy will outstrip the resources available to provide it. Contemplating this scenario, it is understandable why the search for the HIV vaccine presents one of the greatest quests in scientific research.

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