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VIEWPOINTS

Ending the Human Immunodeficiency Virus Pandemic: Optimizing the Prevention and Treatment Toolkits

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Unprecedented basic and clinical biomedical research advances over the past 4 decades have led to the development of "toolkits" of highly effective interventions for preventing and treating human immunodeficiency virus (HIV). Despite many successes in decreasing the incidence and mortality of HIV, major challenges remain in the goal of ending the HIV pandemic in the United States and globally. Overcoming these challenges will require optimization of the implementation of existing interventions for HIV prevention and treatment together with the continued development of new and innovative approaches that can be readily utilized by individuals with HIV and those at risk of infection.

Keywords. HIV; prevention; treatment.

Extraordinary scientific advances over the past 4 decades have yielded robust "toolkits" of interventions for treating and preventing human immunodeficiency virus (HIV) that have transformed the lives of persons with HIV and at risk of HIV [1] (Figure 1).

Today, more than 30 antiretroviral drugs are approved by the US Food and Drug Administration for treating HIV infection, including 13 single-tablet drug combinations of 2 or more antiretroviral drugs. These antiretrovirals are usually administered in simplified dosage regimens—sometimes, only 1 pill per day—and demonstrate high potency with minimal toxicity. The use of antiretroviral therapy (ART) has resulted in near-normal life expectancies for people in their 20s newly diagnosed with HIV, compared with the 1- to 2-year life expectancy in the early 1980s when ART was not yet available and patients often presented to the healthcare system with advanced disease [2]. From 1995 to 2015, ART averted approximately 9.5 million acquired immune deficiency syndrome (AIDS) deaths and 7.9 million new HIV infections worldwide, resulting in economic benefits of more than $1 trillion, according to a recent analysis. In that period, a return of $3.50 was realized for every dollar spent on ART [3]. AIDS-related deaths among patients of all ages declined 55% globally between 2005 and 2018, a reduction largely due to the use of ART [4].

In addition to the significant benefits of ART for the individual with HIV, several large, prospective clinical trials have demonstrated clearly that ART also has an important role in HIV prevention in the context of treatment as prevention (TasP) and pre-exposure prophylaxis (PrEP). A clinical trial known as HPTN 052 [5] demonstrated that individuals with HIV who received ART early during the course of infection and achieved and maintained an undetectable viral load had a markedly diminished likelihood of transmitting the virus to their sexual partner. Subsequent corroborative studies, including the Opposites Attract [6] and Partners of People on ART - A New Evaluation of the Risks 1 [7] and 2 [8], found no linked transmissions in a cumulative total of more than 150 000 condomless sex acts when the partner with HIV was on suppressive ART and viral load was below detectable levels. These findings provided the scientific basis to validate the principle that, with regard to viral load, "undetectable equals untransmittable," a concept commonly referred to as "U = U" [9].

The second transformative concept in preventing HIV infection with ART is PrEP. Accumulated data indicate that high adherence to a PrEP regimen of emtricitabine + tenofovir disoproxil fumarate, taken as 1 pill per day or on demand (immediately before and following a sexual encounter), is 99% effective in preventing HIV acquisition by an at-risk uninfected individual. The findings from 29 clinical studies involving 55 000 individuals resulted in the recent grade A recommendation by the US Preventive Services Task Force (USPSTF) that PrEP be offered to persons at high risk of HIV acquisition. The USPSTF emphasized that adherence to PrEP is important for, and highly associated with, its efficacy in preventing HIV acquisition [10].

OPTIMIZING IMPLEMENTATION OF EXISTING TOOLKITS

With the demonstrated success of TasP and PrEP, it is theoretically possible to rapidly end the HIV pandemic as an

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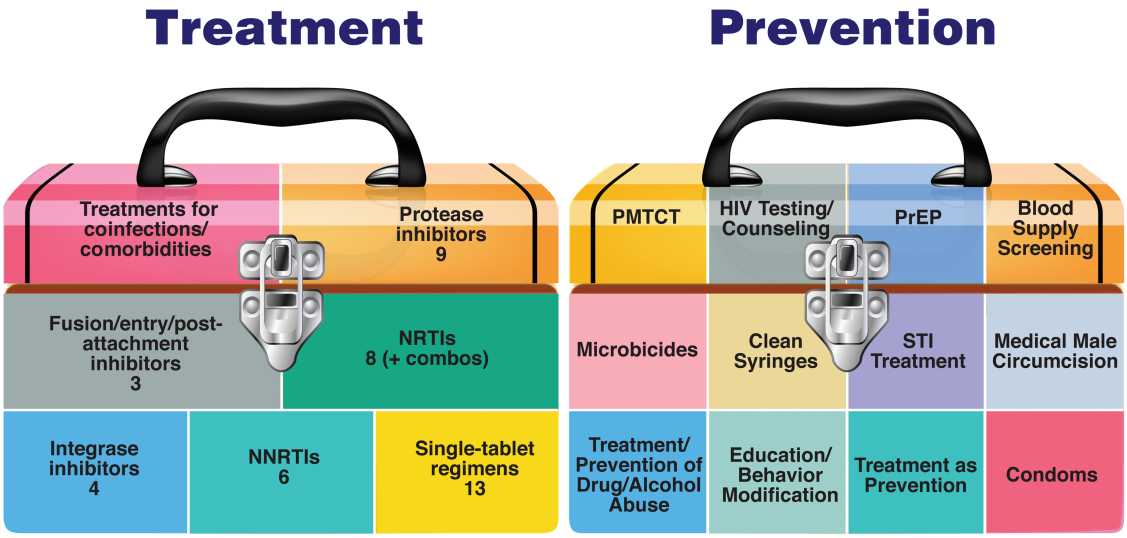

Figure 1. Current HIV treatment and prevention toolkits. The HIV treatment toolkit includes several classes of antiretroviral drugs approved for use by the US Food and Drug Administration to treat HIV and single-tablet formulations of antiretrovirals. This toolkit also includes treatments for HIV-associated coinfections and comorbidities. The HIV prevention toolkit includes HIV testing and counseling, treatment of STIs, PrEP, medical male circumcision, condoms, and blood supply screening. Abbreviations: HIV, human immunodeficiency virus; NNRTI, non-nucleoside transcriptase inhibitor; NRTI, nucleoside transcriptase inhibitor; PMTCT, prevention of mother-to-child transmission; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

epidemiological phenomenon by providing ART to all or most individuals with HIV and making PrEP widely available to individuals at high risk of HIV. However, as is usually the case, a gap exists between theory and reality, and much needs to be done before an end to the pandemic is at hand. Despite the availability of proven modalities of treatment and prevention, there were 1.7 million new HIV infections and 770 000 deaths from AIDS-related illnesses globally in 2018; an estimated 37.9 million people were living with HIV at the end of the year [4]. Global HIV incidence has declined less than 2% per year since 2010 [4]. Implementation gaps are evident in all stages of the treatment and prevention cascades, including HIV testing, treatment, retention in care, achieving viral suppression, uptake of prevention/harm-reduction services, addressing food and housing insecurities, and fighting stigma and discrimination [1, 11]. Of the 37.9 million people living with HIV at the end of 2018, 14.6 million were not receiving ART—a significant treatment gap [4]. Retention in HIV treatment remains suboptimal: only about 60% of people who start ART in low- and middle-income countries are still receiving therapy 4 years later [12]. Additionally, PrEP is vastly underutilized, with only 475 000 PrEP users globally as of April 2019, well below the United Nations' target for 2020 of 3 000 000 [13].

The implementation gaps in treatment, PrEP uptake, and other areas must be bridged if an end to the global HIV pandemic is to be achieved. The current HIV treatment and prevention toolkits can be optimized with improved implementation strategies. For example, in San Francisco, a city that was an early adopter of "treat all" recommendations to provide HIV-infected persons with ART irrespective of $CD4^+$ T-cell count, the Rapid ART Program for Individuals with an HIV Diagnosis (RAPID) program at San Francisco General Hospital has had great success in accessing hard-to-reach, at-risk individuals, providing them HIV testing and initiating ART almost immediately following diagnosis. Patients with HIV are provided 5-day ART starter packs and followed up with ongoing counseling and psychosocial support. After 1 year of ART uptake at a San Francisco clinic, 96% of the patients enrolled in the RAPID program between 2013 and 2017 achieved viral suppression despite high rates of substance use, housing instability, and mental illness [14]. From 2006 to 2018, new HIV diagnoses in San Francisco declined by 63%, concomitant with an increase in individuals accessing HIV prevention (including PrEP) services, testing, treatment, and care [15]. Modeling studies suggest that bringing the San Francisco experience to scale globally could avert an estimated 35 million deaths and 40 million HIV infections between 1995 and 2030 [3].

Despite the demonstrated life-saving benefits of ART for treatment and prevention and even with the availability of simplified drug treatment regimens, uptake remains suboptimal because of adherence challenges, including those related to substance abuse, housing deficits, pill fatigue, drug toxicity, stigma, and discrimination. Therefore, in addition to maximizing the implementation of the existing treatment and prevention toolkits, it is equally important to improve and optimize the treatment and prevention tools themselves.

OPTIMIZING THE THERAPEUTICS TOOLKIT

Developing new and improved HIV treatment and prevention tools requires the translation of basic and clinical biomedical

research findings into strategies and modalities that are user-friendly and can be effectively and efficiently taken up in real-world settings by diverse communities. The need to take a medication for any disease, even just a single pill per day is for some people a considerable burden, and adherence to both HIV treatment and prevention regimens remains suboptimal. The underlying reasons for poor adherence are multifaceted and include the inclination to avoid a pill that may be a daily reminder that one is living with HIV. Stigma, sometimes leading to violence that is associated with taking daily ART, also is an important stumbling block. One way to optimize the treatment of HIV infection would be to achieve durable control of the virus without the need for daily ART. There are several approaches aimed at achieving this goal including the following: eradication of HIV from the body (ie, achieving a "cure"), long-acting ART that could be taken only intermittently, and broadly neutralizing antibodies (bNAbs) administered at intervals of several months.

Many potential strategies are being pursued to eradicate the virus from a person with HIV. Stem cell transplantation from donors with a genetic defect conferring resistance to HIV infection, together with the necessary immunosuppressive conditioning, has been successful in achieving eradication of HIV and hence a cure in 2 individuals: the "Berlin" [16] and "London" [17] patients. Both of these individuals had a neoplastic process that required stem cell transplantation independent of their HIV status. Although this approach is a proof-of-concept, it is neither feasible nor scalable for the more than 37 million individuals with HIV worldwide. Another approach to HIV eradication is gene editing targeted to the *CCR5-Δ32* mutation. However, previous reports have suggested that individuals homozygous for the *Δ32* allele have reduced protection against influenza [18] and certain other infectious diseases, such as West Nile virus [19], instilling a note of caution in decisions to manipulate the *CCR5* gene. The recently developed cluster regularly interspaced short palindromic repeats-CRISPR-associated protein 9 (CRISPR-Cas9) gene-editing method has successfully been used to excise, both ex vivo and in vivo, integrated Simian immunodeficiency virus (SIV) proviral long-terminal repeat and Gag regions in rhesus macaques [20]. Similarly, CRISPR-Cas9 has been combined with long-acting, slow-effective-release antiviral therapy (LASER ART) to eliminate replication-competent HIV-1 DNA from various tissues in HIV-infected humanized mice [21]. Although this approach is promising, it is still in its earliest stage of development, and potentially detrimental off-target effects of the CRISPR-Cas9 approach in HIV infection must be considered as this strategy is pursued in humans.

Another approach toward optimizing treatment of HIV infection is long-acting ART, including once-monthly, injectable cabotegravir plus rilpivirine [22]. Ultimately, it may be possible to greatly expand the interval between injections. Another alternative to controlling HIV without daily ART is using bNAbs to clear the virus and directly kill HIV-infected cells [23]. Several anti-HIV bNAbs are currently in clinical development. In 1 study, passive infusion of bNAbs has been shown to delay plasma HIV rebound following cessation of ART; however, viral suppression was not maintained in study participants beyond week 8 [24]. A combination of 2 potent bNAbs, 3BNC117 and 10–1074, administered to viremic patients resulted in HIV suppression for 3 months following the first of up to 3 infusions [25]. This same combination of bNAbs resulted in HIV suppression for more than 5 months during analytical treatment interruption of ART in individuals whose viremia had been successfully suppressed below detectable levels with ART [26]. A phase 1 clinical trial (NCT03705169) is evaluating trispecific bNAbs that interact with the CD4 binding site, the membrane proximal external region, and the V1V2 glycan site of the HIV envelope. These trispecific bNAbs were previously shown to confer complete protection against several simian-human immunodeficiency virus (SHIVs) in a nonhuman primate (NHP) model [27]. In addition, humanized antibodies targeting the CD4 binding site have been assessed. In 1 clinical trial, monotherapy with UB-421 maintained viral suppression for 8 to 16 weeks in the absence of ART [28]. In addition, ibalizumab combined with an optimized background ART regimen had significant anti-HIV activity as "salvage" therapy for 25 weeks in patients with multidrug-resistant HIV [29]. The ultimate goal of these approaches is to replace daily ART with a regimen of passive transfer of combinations of bNAbs up to every 6 months or longer. In this regard, mutations in the Fc portion of the immunoglobulin molecule, referred to as the LS mutation, confer a considerably longer plasma half-life than the bNAbs currently used in clinical trials [30].

OPTIMIZING THE PREVENTION TOOLKIT

The optimization of HIV prevention will require innovative approaches in 2 key areas: PrEP and vaccines. Recent studies have demonstrated that TasP alone, even with aggressive implementation, did not significantly reduce community HIV incidence [31], suggesting that both PrEP and TasP will be needed to decrease overall HIV incidence. It is therefore critical to increase the acceptability, utilization, and adherence to PrEP regimens. Novel strategies are currently being investigated to optimize PrEP, including short- and long-acting oral pills, long-acting injectables and implants, monoclonal antibodies, topically applied products for rectal and vaginal use, and multipurpose tools for HIV prevention and contraception [32, 33].

Antiretroviral therapy and bNAbs are both being studied as long-acting PrEP. With regard to ART, 2 randomized controlled trials are investigating long-acting injectable cabotegravir compared with oral Truvada (Gilead Sciences, Inc.) as PrEP. These clinical studies include HPTN083 (NCT02720094), enrolling

4500 men who have sex with men (MSM) and transgender women in multiple countries, and HPTN084 (NCT03164564), enrolling up to 3200 women not infected with HIV in sub-Saharan Africa. A once-weekly oral dosing of a novel reverse transcriptase–translocation inhibitor, MK-8591 (Islatravir, Merck Corp.), has been shown to provide protection in rhesus macaques against multiple intrarectal challenges with SHIV [32]. An implant of MK-8591 in NHPs led to HIV-suppressive plasma levels for more than 1 year [34]. If translatable to humans, such a long-acting implant could have an enormous positive impact in HIV prevention.

The second approach for achieving long-acting PrEP involves optimization of bNAbs to prevent HIV acquisition. This can be accomplished by developing long-acting bNAbs. A single injection of a combination of 2 long-acting bNAbs, 3BNC117-LS plus 10-1074-LS, protected macaques against repeated mucosal challenges of $SHIV_{AD8\text{-}EO}$ for a median of 4–6 months. These findings suggest that this combination of bNAbs as a PrEP regimen could be administered on a 6-month or yearly interval to at-risk individuals [35]. Currently, 2 clinical studies, HVTN704/HPTN085 (NCT02716675) and HVTN703/HPTN081 (NCT02568215), are evaluating passive transfer of VRC01 monoclonal antibody in high-risk men and women, respectively, in clinical sites around the world. The successful outcome of these clinical trials would prove the concept that the bNAb could be a safe and effective intervention to prevent HIV acquisition among high-risk individuals.

The second strategy to optimizing HIV prevention is a safe and effective HIV vaccine. The development of a moderately effective HIV vaccine together with the optimal implementation of existing treatment and prevention modalities could end the HIV epidemic [36]. Multiple approaches to an HIV vaccine are in various stages of preclinical and early clinical development [37]. Two key strategies have progressed to advanced clinical trials: (1) the empiric or inductive approach to testing vaccine candidates in order to identify and optimize the correlate(s) of immunity and (2) the deductive approach of assuming a correlate of immunity and then designing vaccine candidates that can induce that specific correlate [38] (Figure 2).

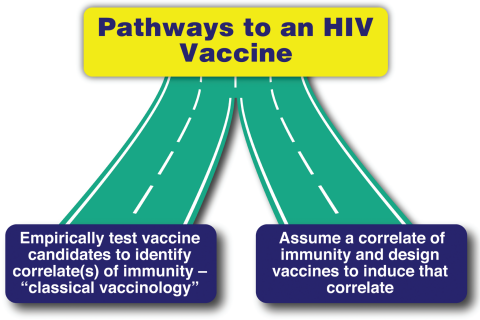

Figure 2. Pathways to an HIV vaccine. There are 2 pathways for the development of an HIV vaccine. The empiric pathway, known as "classical vaccinology," tests vaccine candidates to identify correlates of immunity. The second pathway assumes a correlate of immunity and involves designing vaccines to induce that correlate. Abbreviation: HIV, human immunodeficiency virus.

Using the empiric approach, only a single vaccine candidate has produced a modestly effective response. The RV144 clinical trial of a prime boost regimen showed a 31.2% efficacy among 16 000 participants in Thailand [39]. While the RV144 vaccine regimen was not deployed, it led to the identification of immune correlates of protection against HIV. Subsequent analysis of the RV144 clinical trial specimens has indicated that nonneutralizing antibodies targeting the V2 epitope of the HIV gp120 envelope glycoprotein correlated with reduced risk of HIV infection [40].

Several strategies are currently being pursued to amplify the strength, breadth, and durability of the RV144 response. These potential strategies include use of multiple boosts, modified vectors, adjuvants, and mosaic antigens. Currently, 3 large-scale clinical trials are underway to address these approaches, including HVTN702 (Uhambo), HVTN705/HPX2008 (Imbokodo), and HVTN706/HPX3002 (Mosaico). Uhambo (NCT03964415) is evaluating a modified RV144 pox virus prime with a boost using clade C gp120 with MF59 adjuvant and has enrolled 5407 men and women in South Africa. Imbokodo (NCT03060629) is designed to test a quadrivalent Ad26-vectored mosaic vaccine plus an HIV clade C gp140 among 2637 women in sub-Saharan Africa and represents a vaccine for use against multiple HIV strains. The latest vaccine clinical trial to optimize this approach is the Mosaico study (NCT02968849), which will evaluate the quadrivalent Ad26-vectored mosaic vaccine plus bivalent HIV clade C and mosaic gp140 among 3800 MSM and transgender individuals in the Americas and Europe.

The second or deductive pathway to the development of an HIV vaccine assumes a correlate of immunity and then designs vaccine candidates to induce that correlate. This pathway assumes that bNAbs induced by a vaccine will afford protection against the acquisition of HIV. An approach being pursued is based on the recognition by bNAbs of neutralizing epitopes on the HIV envelope trimer. Ongoing studies are using 1 or more of these epitopes as immunogens that could be used as a vaccine to induce bNAbs [41]. Three general strategies to design immunogens include the following: (1) lineage-based vaccines (germline targeting), (2) epitope-based vaccines, and (3) native trimer vaccines. Several recent studies have reported the feasibility of successfully utilizing germline targeting in the mouse model by using B-cell lineage-based immunogens that are designed to induce the germline precursor B cells to produce HIV bNAbs [41]. The germline targeting strategy has progressed to phase 1 clinical testing (NCT03547245) using the eOD-GT8 60mer immunogen.

The development of an epitope-based design uses structure-based analysis to characterize the binding sites of known bNAbs, identification of precise epitopes critical to binding of

bNAbs, and utilization of these epitopes as immunogens to induce bNAbs [41]. An epitope-designed vaccine targeting the N-terminal residues of the fusion peptide on the HIV envelope elicited monoclonal antibodies from immunized mice capable of neutralizing 31% of a cross-clade panel of 208 HIV-1 strains. These findings suggest that the N-terminal 8 residues of the HIV fusion peptide may be a potential target for vaccines designed to elicit bNAbs [42]. The native trimer vaccine strategy is based on the use of the full stabilized native HIV-1 envelope glycoprotein trimer as a boost to the epitope fusion peptide as the prime [41].

Finally, an approach that has produced promising results in the NHP model is the use of a live-attenuated cytomegalovirus-vectored vaccine candidate. Findings showed that the ΔRh11068-1 RhCMV/SIV vaccine candidate expressing homologous or heterologous SIV antigens controlled and eliminated SIV infection in 59% of vaccinated rhesus macaques. Among the 12 vaccinated macaques that controlled and eliminated the initial SIV challenge, 9 macaques were able to control a second SIV challenge approximately 3 years after last vaccination [43].

While these various approaches and strategies to develop an HIV vaccine are being actively pursued and optimized, the question remains how effective an HIV vaccine should be to have a major impact on the HIV epidemic. Recent modeling analyses project that by maintaining the status quo of treatment and prevention, there will be approximately 49 million new HIV cases between 2015 and 2035. The availability and deployment of an HIV vaccine with 50% efficacy could significantly impact this projection and potentially avert approximately 17 million new HIV infections [44].

CONCLUSIONS

In 2019, robust toolkits for treating and preventing HIV infection are available. It is essential that we maximally implement these existing interventions while continuing to pursue the discovery and development of innovative approaches, novel technologies, and experimental interventions. These new tools potentially will have improved efficacy but also could help achieve greater coverage because of better acceptability/usability by people with HIV or at risk of infection.

Notes

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