A Shot in the Arm for HIV Prevention? Recent Successes and Critical Thresholds

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Abstract

Efforts to decrease the spread of HIV worldwide continue at a rapid pace. With the development of new biomedical interventions and findings from pivotal clinical trials, a new framework for short-term and long-term prevention strategies is emerging. It is clear that biomedical-based approaches targeted at the highest risk populations have the greatest potential to have a short-term impact. Unfortunately, challenges with adherence in healthy populations at risk are now well-recognized, and competing health care priorities in the context of fragile delivery infrastructures pose formidable obstacles to implementation. We need better ways to identify high-risk populations, sophisticated understanding of the behavioral parameters that can ensure adherence, and the development of better strategies to provide sustained delivery of preexposure prophylaxis (PrEP). In the long term, we need an effective vaccine—a path that has proven to be rocky. Research facilitating an increased understanding of immune responses and what represents effective responses to prevent HIV acquisition should facilitate progress. While we wait for that time, PrEP offers the best strategy for short-term impact.

IT HAS BEEN AN EVENTFUL YEAR in the world of biomedical HIV prevention science research, characterized by critical failures and amazing success along with a large dose of business as usual. Here we will summarize recent progress in the field and discuss the potential implications moving forward. As we discuss in more detail below, there was keen disappointment in the outcome of the third clinical trial of vaginal tenofovir (TFV) gel, FACTS-001, in which pericoital use did not prevent HIV acquisition.¹ Similar gels had shown to be completely protective in rhesus macaque models and approximately 50% effective in the CAPRISA004 study. Unfortunately, both FACTS-001 and the VOICE Study,² published in 2014, were characterized by a profound lack of adherence to the study products. Clearly, the products were not acceptable to the participants. Hope for microbicides resides in the form of long-acting delivery systems, principally the vaginal ring, which can also deliver contraception.³

The results of the first clinical trials testing a vaginal ring containing dapivirine, the Microbicide Trial Network ASPIRE Study and the International Partnership for Microbicides Ring Study, are expected next year.⁴ The vaccine field continues to advance quickly in its identification and characterization of broadly neutralizing antibodies.⁵ As more and more broadly neutralizing antibodies are identified and characterized, they

are being repurposed as agents to treat and/or prevent HIV acquisition.⁶ Preexposure prophylaxis (PrEP) has proven to be very efficient at preventing acquisition, even with less than daily adherence. In fact, right now, the most effective way to reduce HIV acquisition in sexually active people is to employ oral PrEP in high-risk populations.⁷ Combined with treatment of HIV-infected people,⁸ this intervention has considerable promise to stem the epidemic and ultimately reduce the need for resources to treat HIV infection itself. Of course, the ultimate hope is for a safe and effective vaccine against HIV. In the meantime, “combination prevention”—termed “biobehavioral prevention” by some—offers realistic hope for success. Biobehavioral interventions utilize systemic biomedical approaches designed to target high-risk populations while adjusting for behavioral and social factors that can expedite or hinder ideal outcomes.

Microbicides are antiviral compounds applied topically (vaginally or rectally) that function locally rather than systemically to prevent infection of resident target cells. Having the drug at the right place at the right time without the potential toxicity conferred by systemic administration proved to be very successful in nonhuman primate models under highly controlled conditions.^{9,10} These successes indicated that microbicides might be the first biological intervention allowing

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women to protect themselves from HIV acquisition. The first clinical trial, CAPRISA 004, which utilized vaginal tenofovir (TFV) gel (1%) before and after intercourse, demonstrated a significant reduction in HIV acquisition by 49%.⁹

To advance this concept toward licensure, two subsequent trials—VOICE and FACTS-001—assessed daily and pericoital use of TFV gel, respectively. Unfortunately, product adherence was low in both of these trials.² The reasons for lack of adherence are complex, but the take home message that emerged is that participants did not find the vaginal gels acceptable—a finding that provided a clear directive to the field. The products developed must not only work, but must also be compatible with social and behavioral factors that will facilitate a high level of compliance. It is imperative to design and market products that people will actually use to prevent HIV infection. As a result of these outcomes, the future development of gel-based microbicides is in question, and we might conclude that the idea of using vaginal microbicide gels has failed.

On the other hand, sustained delivery of vaginal microbicides with an intravaginal ring may offer a viable alternative.¹¹ Intravaginal rings are currently utilized by millions of women to deliver contraceptives (NuvaringTM). Qualitative research performed in the VOICE and FEM-PrEP participants posttrial indicated that even in places in which HIV transmission is rampant, women at risk are more interested in obtaining contraception than in obtaining biomedical products aimed solely at HIV prevention.¹² Several concepts concerning the use of an intravaginal ring that delivers combined antiretroviral and contraception agents are being studied.¹³ Results of the first phase 3 clinical trial using a silicone intravaginal ring to deliver dapivirine, the ASPIRE Study, will be essential to inform how this agenda moves forward.

Vaccine research continues to move forward around a handful of concepts that provide immune protection in model systems. There has been great progress in the identification and characterization of broadly neutralizing antibodies (BnAbs) that can potentially inhibit HIV infection in tissue culture models and simian–human immunodeficiency virus (SHIV) transmission in rhesus macaques. We understand quite well the development of these potent and special antibodies during the immune response. They require extensive somatic hypermutations to generate the appropriate binding specificities to broadly neutralize the HIV envelope.^{14,15}

The development of these BnAbs over time in infected individuals reveals that certain weak affinity progenitor antibodies chase the mutating viral envelope over time, ultimately developing binding abilities to the epitopes that cannot change without losing function.¹⁴ These BnAbs have great breadth of neutralization with high affinity. This observation has led to the concept of stimulating BnAbs by vaccination with a series of antigens that initially stimulates expansion of the appropriate germline specificity. The B cell producing this antibody progenitor can then be “trained” with additional antigens selecting for the appropriate somatic hypermutations necessary for the development of broadly neutralizing function.^{16,17} However, this new concept needs to be validated because it was previously shown that vaccination with gp120 can only inefficiently stimulate affinity maturation through somatic hypermutation.¹⁸

Recent advances in vaccine development for respiratory syncytial virus (RSV) and influenza show great promise for better protection. Utilizing highly specialized antigens,

designed to present specific epitopes to the immune system, it was possible to stimulate highly potent antibodies to RSV and influenza.^{19,20} This success supports the potential development of unique HIV antigens that stimulate more potent and protective immune responses. The investment in the study of BnAbs is already beginning to pay dividends. These natural and potent inhibitors of HIV are currently being repurposed for use in both treatment and prevention. This past year a phase 1 clinical trial was reported that hypothesized that the injection of a single broadly neutralizing antibody into HIV-infected individuals could temporarily decrease the viral load.^{6,21} This study revealed that the HIV viral load could decrease more than a log after antibody injection before rebounding. The virus that emerged in the presence of the antibody treatment had clear indications of selection for resistance to the binding activity of the antibody.⁶ Other approaches seek to use gene therapy to stably express the most potent of these human antibodies with the hope that they will provide protection from acquisition.²²

Another exciting area of vaccine research is the utilization of new vectors for antigen delivery. Specifically, the cytomegalovirus (CMV)-based vectors developed by Louis Picker and colleagues are advancing to the first human clinical trials. The CMV vectors elicit potent cytotoxic T lymphocyte (CTL) responses that can apparently clear SIV infection in ~50–60% of vaccinated animals while showing no effect in the remaining animals.²³ These vectors do not elicit any antibody responses, further supporting the concept of a T cell-based vaccine. Atypical CTL responses are generated in all the vaccinated animals, with dominant epitope responses restricted by Class II MHC.²⁴ But these atypical CTL responses do not correlate with protection. Thus, the context of antigen delivery can greatly influence the immune response and subsequent vaccine function, generating great enthusiasm for vector design. There is a significant effort to understand why the CMV vector vaccine protects some animals but not others, and this candidate approach has unique promise to become a human vaccine while providing key insights into the immune response and function.

The field is ramping up for the next round of vaccine trials in South Africa in an attempt to recapitulate the partial protection observed in the RV144 vaccine trial in Thailand.^{25,26} The first step is a clinical trial, HVTN 100, which will determine the safety and immunogenicity of RV144 vaccine components ALVAC and protein boost generated utilizing local Clade C viral sequences.²⁷ This trial will take place over 2 years and include a boost after the first year, which was lacking in RV144. A successful outcome of HVTN 100 will lead to HVTN 702, which will test the efficacy of the Clade C ALVAC and envelope protein boost. A parallel vaccine trial (HTVN 701) will evaluate new vaccine strategies in a discovery-based approach that will advance the products that produce the best immune responses into larger clinical trials. Although these trials will generate much-needed data on what is required for an effective HIV vaccine to eradicate the virus, even with a series of successes this process will take a decade or decades before the general public can be vaccinated.

In contrast to the prevention strategies described above, we have approaches and strategies at our fingertips that we know can effectively slow the epidemic. Essentially these strategies utilize systemic biomedical interventions and education to prevent HIV infection utilizing antiretroviral drugs as PrEP. The use of antiretrovirals has successfully decreased and has

the potential to eliminate mother-to-child transmission.²⁸ Treatment as prevention—that is, treating HIV-infected individuals with the goal of successful suppression of viral replication—can render these people virtually unable to transmit HIV.⁸ In this approach, monitoring people for plasma viral load suppression is an excellent marker of adherence and, ultimately, an exceedingly low likelihood of transmission risk.

In contrast, ensuring and confirming adherence to PrEP present more of a challenge. For example, in the iPrEx trial, PrEP in the form of daily oral tenofovir/emtricitabine (TDF/FTC) led to a 90% reduction in HIV infection with high adherence.²⁹ Importantly, the ANRS Ipergay Trial, performed in men who have sex with men (MSM) in France, revealed that lower rates of adherence to oral TDF/FTC were highly effective when dosing was timed to coincide with the periods before and after anal intercourse—a finding supported by further detailed analysis of the iPrEx Study.³⁰ This is a critical observation because it reveals that perfect compliance is not required to obtain the beneficial effects of PrEP, although it is likely that the timing of dosing relative to HIV exposure is critical. The real-world potential of PrEP is nicely illustrated by a recent study that analyzed data from a large medical care provider in San Francisco (Kaiser Permanente Medical Group); these data suggested that among MSM who used PrEP, no new HIV infections were documented.³¹ Demonstration projects to enhance the delivery and uptake of PrEP are underway globally.

In addition to the vaginal rings discussed above, sustained release approaches in development include injectable formulations that release antiretrovirals with protective levels maintained for up to 3 months.^{32,33} Although this approach has considerable promise, there are drawbacks. First, the release of drugs from the sustained release formulations is asymmetric: initially, too much drug is released and essentially wasted and has the potential for increased adverse effects. On the other end, the drug continues to be released over time, producing a long tail of release at subtherapeutic levels, which has the potential to facilitate the development of drug resistance. Another potential issue is the possibility of adverse reactions to the drugs. Once the formulation is injected, it is impossible to remove; therefore an adverse reaction can be addressed only by systemic countermeasures.^{34,35} However, injectable formulations and other approaches of sustained release PrEP, such as implants, offer great potential to decrease issues of compliance and increase the efficacy of protection.

Another issue that has emerged in the past year in animal studies utilizing injectable sustained release formulations is the possibility of occult infection during PrEP. Occult infections occur when the virus establishes a beachhead at the site of mucosal transmission, but does not become detectable as systemic infection.^{36–38} We know that an infected person or animal with a high viral load can suppress viral replication to undetectable levels after the initiation of antiretroviral therapy. When such drugs are provided as PrEP, for instance in animal models, the lack of detection of systemic virus does not prove that no infection has taken place locally in exposed mucosal tissues.

This is an area of concern because the distribution of different antiretroviral drugs at exposed mucosal sites is highly variable. Two recently published studies highlight this potential problem.^{33,39} In one, rhesus macaques appeared to be protected from multiple vaginal high dose viral challenge by

an injectable nanoformulation of cabotegravir. However, when systemic levels of the drug dipped below therapeutic levels, systemic infection emerged in one of the animals months after the last viral challenge.³⁹

A second study of a sustained released formulation of rilpivirine in humanized mice showed a similar result. In some cases the virus that emerged had remained hidden for up to 4 months before emerging as systemic infection.³³ These occult infections all occurred under conditions of high-dose viral challenge, so the relevance of these observations for physiological transmission in humans is not clear. However, it is imperative that we better understand the frequencies and mechanisms of these types of occult infections.

It may be possible to circumvent this phenomenon by identifying the antiretroviral drugs and therapeutic concentrations that provide the best protection from mucosal transmission. It should also be possible to develop protocols that will be used when PrEP has ceased to be able to rapidly identify emerging occult infection and provide optimal therapy. As we expand the use of PrEP we should be aware of this situation, which could undermine the efforts to utilize PrEP to decrease HIV acquisition worldwide.

Finally, as potential PrEP interventions are developed, there needs to be much greater consideration of how the products will be received by the populations that stand to benefit most from their use.⁴⁰ It is critical that the field utilize state-of-the-art approaches to determine and define consumer interest in various products.⁴¹ This should be supported by programs designed to increase awareness and build public support for product use. These efforts should initially focus on high-risk populations for higher impact.

The path moving forward in the short term is clear. We need to use the effective tools in hand including PrEP with attendant counseling and treatment of HIV-infected persons with ambitious goals to attain maximal community viral load suppression.⁴² From the standpoint of population coverage, it will be critical to better understand the types of interventions that high-risk individuals are willing and eager to utilize to prevent HIV acquisition. Ultimately, to provide protection to everyone on the planet, we need a vaccine. It will be extremely challenging to implement PrEP on the scale needed to prevent all acquisitions, especially those in lower risk populations. However, we have an incredible opportunity to impact the epidemic now through the implementation of the biobehavioral prevention measures at hand.

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