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The Role of ARVs in HIV Prevention: Microbicides and PrEP

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Introduction

The evolving list of HIV prevention interventions that currently rely on antiretrovirals (ARVs) include prevention of mother-to-child transmission (PMTCT), Post Exposure Prophylaxis (PEP), and highly active antiretroviral therapy (HAART) as prevention.[1] Current research is underway to expand this list of interventions to include ARV-based microbicides, and Pre-Exposure Prophylaxis (PrEP); both of which recently demonstrated promising results in clinical trials.

Twenty years ago, these interventions were merely a wish list based on the logic that if a drug can lower the viral load of HIV in the body, then it should be able to reduce transmission of the virus. Further, if a drug can limit the replication of HIV, it can help abort HIV infection before it takes root in the body.[2] Slowly, these wishes are becoming realities and some have been translated into standards of care.[3] In this article, we discuss recent breakthroughs in ARV-based microbicides and PrEP, what the likely policy and programmatic implications and drawbacks may be, and how they can be addressed.

ARV-based Microbicides

In July 2010, microbicides researchers received a long awaited 'proof of concept' with the results of the CAPRISA 004 trial. The double-blind, randomized, controlled trial was conducted to assess the effectiveness and safety of a vaginal gel formulation of 1% tenofovir gel, a nucleotide reverse transcriptase inhibitor (NRTI), for prevention of HIV in women.[4] The study was conducted among 889 women, aged 18–40, in urban and rural KwaZulu-Natal, South Africa between May 2007 and March 2010. Results from the study found that tenofovir gel reduced HIV acquisition by an estimated 39% among participants. Further, the trial demonstrated no change in tenofovir resistance in HIV seroconverters. The only adverse event found more frequently in the tenofovir gel arm was diarrhea and gastrointestinal infections (16.9% vs. 11.0%, p=0.015), however the reported cases of diarrhea were mild and rarely required medication.

Though this is not the first microbicide trial to be conducted, it is the first to show efficacy. One hypothesis for the lack of effectiveness in past microbicide trials is that adherence had not been high enough

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to demonstrate effectiveness.[5,6,7] The CAPRISA 004 trial showed that in high adherers, defined as women who had greater than 80% gel adherence, HIV incidence was 54% lower in the tenofovir arm. HIV incidence was reduced by 38% and 28% in intermediate and low gel adherers, respectively. It is important to note that women in the CAPRISA 004 trial followed a coitally dependent dosing strategy, known as 'BAT24.' Modeled on the proven strategy of dosing for preventing mother-to-child HIV transmission, women were instructed to use one dose of gel within 12 hours before sex and another dose as soon as possible

within 12 hours after sex, and no more than two doses in a 24-hour time period. Due to the dosing strategy, no conclusions can be drawn about the effectiveness of the gel in relation to the timing of application.

The CAPRISA 004 trial results are only the first step towards an effective ARV-based microbicide. The trial was conducted on a specific population and the relatively small sample size limits the generalizability of the results. Additional studies are necessary to support and confirm the CAPRISA 004 findings, as well as provide further information on the use of daily versus coitally dependent gels, oral versus gel formulations, and the safety and effectiveness of the use of tenofovir gel rectally.

Pre-Exposure Prophylaxis

In addition to the positive safety findings for tenofovir in a vaginal gel formulation, preliminary analysis suggests no safety concerns from the first study examining the safety of daily oral tenofovir for HIV prevention among gay and bisexual men. The Phase II study, conducted among 400 HIV-negative men who have sex with men (MSM) in San Francisco, Atlanta, and Boston, randomized men to one of four study arms: two arms of the study received either a daily 300 mg tablet of tenofovir or placebo immediately upon enrollment, and the two remaining arms received either tenofovir or placebo after nine months of enrollment.[8] This study design allowed researchers to compare risk behaviors among those men taking a daily pill and those who are not.

Prior studies have found the daily tenofovir regimen safe among high-risk heterosexual women in Ghana, Nigeria, and Cameroon, but this is the first PrEP study to focus solely on safety among gay and bisexual men, as well as the first to assess the potential impact of a daily preventative drug on HIV risk behaviors. Preliminary analysis suggest there was no increased risk, or "behavioral dis-inhibition," in men taking a study pill compared to those not yet taking study pills.[8]

It is important to note that this study was not designed to provide conclusions about the potential efficacy of PrEP in preventing HIV infection. As analysis continues, this study will provide useful information on the relationship among adherence, perception of treatment arm, perception of efficacy and individual risk behavior, as well as acceptability and feasibility of daily PrEP for the study population.

Policy and Programmatic Implications

An over-arching programmatic implication for potential ARV-based microbicides and PrEP is the cost and provision of supply. Pharmaceutical industry partners have been generous in supplying certain drugs for the ongoing and planned clinical trials. Conversations surrounding the manufacturing, distribution, and pricing for these potential prevention options need to be ongoing throughout their development so as to establish a firm and sustainable process should trial results continue to be positive.

Further, the general consensus among leaders in HIV prevention is that both ARV-based microbicides and PrEP will be offered through prescription, not as an over-the-counter prevention method, such as condoms. There needs to be careful planning and development related to the infrastructure of how these prevention methods would be distributed, regulated, and overseen in the markets for which they are most needed.

ARV-based microbicides will only be partially effective, thus it will be vital that it is promoted as part of a package of preventive interventions, rather than as a single magic bullet.

Microbicides should be promoted as part of a prevention package: The target population for a vaginal ARV-based microbicide gel will be women in sub-Saharan African and other regions where women are having unprotected sex with multiple partners (such as sex workers), are unable to practice mutual monogamy, and/or are unable to negotiate condom use with their sexual partners. Further, should ARV-based microbicides prove effective in protecting HIV transmission through anal sex, receptive partners in MSM relations would also be a target population.

This suggests that both target populations will be largely self-identifying. Hence, the successful implementation of an ARV-based microbicide will depend on extensive community education and accessible and confidential counseling services, coupled with provision of condoms. Further, ARV-based microbicides will only be partially effective. Thus, it will be vital that it is promoted as part of a package of preventive interventions, rather than as a single magic bullet.

PrEP will require regular HIV testing and partner disclosure: The current regimens being explored for PrEP use a single ARV, tenofovir. If taken by a person who is HIV-positive, there is danger of the development of resistance. Logically, PrEP would only be considered for people proven to be HIV-negative, which would require initial HIV testing and consistent re-testing. This will require infrastructure and accountability.

If proven effective, PrEP will likely be targeted at individuals who are most at risk, such as HIV-negative partners in discordant couples. Theoretically, these partners may be easy to reach through their HIV-positive partners who are attending HIV care and treatment services. However, there are reports of people living with HIV/AIDS (PLHAs) who do not disclose their HIV status to their partners and continue to have unprotected sex.[9] Thus, a key pre-requisite for PrEP among discordant couples is going to be increased counseling of PLHA about disclosure, provision of couples communication and counseling, and access to couples voluntary testing and counseling (CVCT).

PrEP may also be recommended for individuals, especially women, who are in a sexual relationship with an individual who is at high-risk, including sex workers and their clients, certain men who have sex with men (MSM), intravenous drug users (IDU), and polygamous men. If PrEP is proven effective, it will require extensive community education as well as the availability of confidential counseling and testing to enable such individuals at risk to seek services, and to receive HIV testing and counseling followed by PrEP.

General drawbacks of using ARVs as a preventive technology

Potential for ARV resistant strains of HIV: If ARVs are used as prevention interventions there is a potential for widespread or indiscriminate use of ARVs beyond the currently controlled use in HAART or PMTCT. Even if provided through prescription, potential exists for pill sharing and non-compliance to recommended adherence and dosing. Use of PrEP without strict HIV testing to restrict it to HIV-negative individuals could also result in HIV-positive people receiving mono- or dual-ARV therapy, which could lead to development of resistance.

Behavior Dis-Inhibition: While behavior dis-inhibition in the advent of ARV therapy has been reported among MSM in San Francisco,[10] this was before observation studies showed that highly active antiretroviral therapy (HAART) has a preventive effect.[4] Further, the more recent data from the PrEP safety trial described above suggest there was no increased risk-behavior in men taking the study pill versus those not yet taking the pills. However, this was in a controlled setting where extensive steps were taken to ensure participants understood they were testing a drug not proven to prevent HIV. If PrEP is proven effective, additional research and interventions will be necessary to prevent the increase of risk behaviors in real world settings. An increase in risk-taking behavior resulting from a false sense of protection could easily outweigh the benefits of any ARV-based prevention method.

Recent data from the PrEP safety trial described above suggest there was no increased risk-behavior in men taking the study pill versus those not yet taking the pills.

Overcoming these drawbacks and the way forward

Overall strengthening of health services: Programming and distribution of these two potential ARV-based prevention methods would inevitably be centered on health care facilities. It should not be assumed that health facilities and systems are optimally functional and have enough personnel, infrastructure, and supplies to provide high quality services that are available to the most vulnerable people.

Further, as the HIV prevention toolkit expands, the HIV response needs to consider the integrated health systems strengthening approach. It would be prudent to begin conducting cost and systems analysis of this integrated approach compared to the currently accepted vertical approach of specialized HIV projects, such as PMTCT, HAART and male circumcision.

This is an area which requires critical review if ARV-based prevention methods are going to play an increased role in HIV/AIDS programming in developing countries.[11]

Comprehensive education to PLHA about ARVs and HIV prevention: Now is the time, in anticipation of the expanding list of HIV-prevention methods that rely on ARV, to take the bull by the horns and revise education and counseling messages to PLHAs and the general community about issues regarding the role of ARVs in HIV prevention. Education needs to be accurate and available to properly inform PLHAs that ARVs lower their viral loads and make them less infectious,[1] and that taking ARVs before or immediately after exposure to HIV can abort the infection.[12]

Further, correct and timely information about newly emerging prevention methods, such as ARV-based microbicides and PrEP, needs to be continually updated and available for public consumption. Both prevention methods are still in the clinical development phase, and each new result will bring new information and inevitable new questions.

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Setting aside some ARVs for prevention: In order to reduce the risk of developing or transmitting ARV resistant strains, it may be reasonable to propose that certain ARVs be set aside for preventive strategies. The criteria for selecting such ARVs will require much thought.

First, they must be proven effective through clinical trials. Second, they should have the least side effects, as they are going to be taken by persons who have no illness, and thus may easily give them up if they are toxic. Third, they should not be the platform for first or second-line HAART regimens in the developing world since the withdrawal of these agents, due to widespread resistance, could spell disaster if there are no cheap alternatives.

Conclusion

The recent safety and efficacy data surrounding ARV-based microbicides and PrEP has breathed new life and hope into the field of ARV-based HIV prevention interventions. As the clinical science moves forward, there are policy and programmatic implications for expanding the ARV-based HIV prevention toolkit. Now is the time to address policy, programmatic, and ethical drawbacks so we can forge a clear path forward.

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