ORIGINAL ARTICLE

Pre-Exposure Prophylaxis (PrEP): Current Concerns and Future Considerations

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The release of the first anti-retroviral (ARV) drugs in 1986 for the treatment of HIV-1 infection signaled an important point in the fight against the HIV/AIDS pandemic. More recently, mounting evidence has suggested that the use of ARV drugs as prophylactics could prove effective in preventing HIV infection in high-risk populations. Results from two recent studies, the iPrEx and CAPRISA trials, provided evidence for the effectiveness of pre-exposure prophylaxis (PrEP), although a number of questions and concerns remain that must be addressed before the scientific community considers PrEP as a preventative strategy at the population level.

INTRODUCTION

According to the Joint United Nations Program on HIV/AIDS (UNAIDS) 2010 HIV/AIDS Progress Report, an estimated 33.4 million people worldwide are infected with HIV; the current incidence rate stands at 2.5 million infections per year.[12] Although the advent of generic pharmaceutical companies in the beginning of the new millennium led to a significant decrease in ARV prices and an increase in access to treatment, 14.6 million infected individuals worldwide continue to live without antiretroviral treatment (ART) [12], exacerbating the disease burden through continuing transmission and premature morbidity/mortality of patients. Motivation to test the effectiveness of ARV drugs for PrEP in humans arose over a decade ago, stemming from data from several animal trials, as well as efficacy trials that tested ARVs for preventing mother to child transmission (PMTCT). Preliminary results from the iPrEx and CAPRISA studies are encouraging, although evidence from successive studies must be attained before PrEP will be recommended for use in clinical settings.[1] Issues in both adult and adolescent populations concerning drug safety, feasibility, acceptability, patient adherence, and resistance development must also be addressed adequately if PrEP is to become available for use in occupational settings as a biomedical prevention for HIV infection.[10]

The iPrEx Study

The iPrEx study, sponsored by the US National Institutes of Health (NIH), the Bill & Melinda Gates Foundation, and J. David Gladstone Institutes, looked to determine the safety and efficacy of once-daily oral co-formulated TDF/FTC (or Truvada) as an HIV prevention intervention in 2,499 men who have sex with men (MSM) and transgendered women who have sex with men.[1,3] Each participant was randomly assigned to one of two treatment arms, active or placebo. Participants received risk-reduction counseling, monthly HIV-tests, condoms, and treatment for simultaneously occurring sexually transmitted infections (STIs).[3,11] Participants who seroconverted during the course of the treatment discontinued treatment and were referred immediately to appropriate medical care.[11] Upon completion of the study, investigators reported a statistically significant 42% reduction rate in HIV seroconversions in the active drug arm compared to the placebo arm.[9]

CAPRISA 004

While evidence for the efficacy of oral ARV-based prevention has existed for over ten years, evidence of the effects of ARV microbicide gels on HIV transmission did not materialize until the release of the CAPRISA study results in July 2010. Considering the persistent economic, social, and political inequities among men and women in most developing countries, investigators recognized the need for a "woman-controlled substance" for HIV prevention.[4] A total of 889 HIV-negative, at-risk women in KwaZulu-Natal, South Africa were enrolled in the study to determine the effectiveness of a microbicide gel containing 1% Tenofovir (TDF) as a prevention strategy against HIV-infection.[4] Findings indicated a 54% protection rate in woman who applied the gel as prescribed, twelve hours before and after the coital act, 80% of the time [4]. The projected implication of this trial is that the use in South Africa alone could prevent 1,323,000 new HIV infections and 800,000 deaths over the course of the next 20 years [4]. Although results from both the iPrEx and CAPRISA studies are promising, they mark only a preliminary step in the emerging field of HIV/AIDS research. Furthermore, several recently published studies and reviews call attention to a set of questions, concerns, and gaps in research pertaining to both adult and adolescent populations that must be addressed systematically before the initiation of a global PrEP rollout can even be considered.[9]

RESULTS

Preparatory Behavioral & Safety Studies: Feasibility, Acceptability and Adherence

Recognizing that adherence patterns depend heavily on the mode of delivery and are influenced considerably by users' attitudes towards the product, investigators report a need for comprehensive studies looking at drug acceptability and feasibility patterns across MSM, heterosexuals, and adolescents populations.

According to the AIDS Vaccine Advocacy Coalition's "PrEP at CROI" review, there is a lack of data on social and behavioral trends in MSM, such as frequency of sexual activity and "consistent" condom use in these high-risk populations.

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Table 1. Summary of Prophylaxis Studies

Study	Methods	Primary Findings
Saftey and Side Effects		
First Safety Study of Daily Tenofovir for HIV Prevention Among MSM; the Centers for Disease Control and Prevention[8]	Phase II safety study enrolled 400 HIV-negative MSM in three cities across the US. Each participant to one of four study arms either immediately after enrollment or nine months following enrollment in order to contrast any risk behaviors between those receiving pills, whether placebo or active drug, and those not[8]	No significant adverse effects.[8] Besides reports of rare events with kidney function and bone mineral density (BMD) declination, study investigators reported minor side effects of nausea and loss of appetite.[8] Investigators also reported no significant evidence of increases in risk behaviors among participants in the active arm, although they noted the experimental setting in which the study was conducted. Participants received counseling throughout the study, something to which patients in a clinical setting receiving the drug may not necessarily have access.[8]
SubStudy of the First Safety Study of Daily Tenofovir for HIV Prevention Among MSM[9]	184 MSM randomly assigned to oral TDF or placebo	A small but statistically significant reduction in BMD in participants taking the active drug compared to those receiving the placebo was reported [9]. Investigators describe the need for further examination of this phenomenon before a final assessment of its implications can be provided. A sub-study of the VOICE trial, an ongoing study involving close to 2,000 heterosexual women in South Africa, also addresses the issue concerning BMD and will provide additional insight as to its significance upon the release of the study results.[9]
Preparatory and Behavioral Studies: Feasibility, Acceptability and Adherence		
MTN 001; Craig Hendrix (John's Hopkins University[9]	Enrolled 144 South African, Ugandan, and American women who had received PrEP in both gel and oral forms	Results showed a 93% pill adherence rate and an 83% gel adherence rate. In terms of preference, investigators found that while American women favored the oral form, African women showed no partiality, although they reported satisfaction from the "added sexual pleasure" from the gel microbicide.[9] Chief investigator Craig Hendrix reported gel concentrations in the vaginal tissues that were 100-times greater than oral concentrations in vaginal tissues. In addition, he observed that oral concentrations in the blood were 20-times greater than gel concentrations in the blood. Investigators also note the possibility for gel forms of PrEP to hold more "tolerance" for missed doses.[9]
ATN (Adolescents Medicine Trials Network for HIV/ADIS Interventions) 082 (ENROLLING)[10]	99 young American men between the ages 18-22 who have sex with men (YMSM) [10]. Each young man was administered either once-daily TDF/FTC, daily placebo, or no pill at all.	Upon study completion, investigators hope to identify any contrasting adherence patterns in the three study arms, as well as the presence of behavioral disinhibition or other observable behavioral trends. They expect to gain valuable information on both the acceptability and feasibility of oral TDF/FTC among this population, as well as potential aspects of "PrEP protocol" to be include in the future PrEP efficacy studies designs.[10]
MTN (Microbicide Trials Network) 004 (completed 2009, results pending)[10]	Looked at the safety, tolerability, and "systemic absorption" of 3% Viva gel in young, sexually active female participants.[10] Participants received either 3% wt/wt VivaGel, VivaGel placebo, or the hydroxyethyl cellulose placebo gel, all of which they applied vaginally twice a day for 14 straight days	
Microbicide Safety and Acceptability in Young Men (ONGOING)[10]	Examined acceptability and safety trends of a rectal microbicide in young, ethnic MSM [10]. This is an ongoing 2-stage longitudinal study with a clinical and behavioral evaluation, along with an acceptability and adherence trial. These are followed by a randomized control trial in which participants are receiving either an active microbicide or a placebo [10].	

Authors argue that this "knowledge gap" slows dramatically the development of "effective new prevention programmes," making it difficult to identify possible "PrEP users" for inclusion in future studies.[9] The review also draws attention to the grave need for programmes focused on reducing stigma. The authors noted the difficulty in estimating demand quantities for PrEP due to the sensitivity associated with conversations between health care providers and at-risk individuals concerning sexual history.[9]

The ongoing VOICE trial (MTN 003), a combined behavioral and efficacy study involving close to 2,000 participants, compares two topical PrEP interventions (TDF gel vs. placebo) to three oral groups (TDF, TDF/FTC, and placebo). Investigators hope that these results will not only support the findings from the CAPRISA study, but will provide significant insight on oral vs. topical preference patterns. These trends in adherence, drug concentration levels, and missed-dose tolerance will influence considerably PrEP delivery strategies.[5]

One review published in the 2010 edition of Journal of AIDS addresses the substantial importance of the development of preparatory behavioral studies focusing specifically on at-risk adolescent populations.[10] According to these authors, trials designed to collect data on feasibility, acceptability, and adherence trends of at-risks adolescents are truly lacking despite the degree to which they could affect future HIV transmission rates and the burden of the epidemic. The authors address the need for the development of behavioral trials using coitally independent vs. coitally dependent PrEP that look specifically for potential effects that this difference might have on adherence patterns.[10] Identifying coital independence and dependence will be essential in guaranteeing PrEP efficacy in adolescent populations because of the tendency for regimen neglect. The release of the results from both studies will provide necessary information for the designing of future adolescent-focused PrEP behavioral and efficacy trials.

Adherence to PrEP regimens among all at-risk populations will have a tremendous impact on the effectiveness of pre-exposure prophylactics and its overall contribution to reducing the burden of HIV. The ways by which individuals on treatment view the drug in terms of ease of administration, comfort or discomfort, efficiency, and status among family and community members will determine their observance patterns to the prescribed regimen. Therefore, distinguishing the feasibility and acceptability trends characteristic of each specific at-risk population of HIV negative individuals is essential. Experts must develop strategies that cater to the attitudes and opinions specific to each population in order to ensure maximum adherence rates. Extensive studies that examine these distinctive characteristics must be conducted.

Resistance Development

Although evidence from the iPrEx and CAPRISA studies suggests significant efficacy rates for preventative mono and co-formulated therapies, the development of drug-resistance remains a clinically important complication. Authors from several commentaries and reviews address this issue as it applies to PrEP, as well as the current debate regarding a simultaneous rollout of ART and PrEP in high-burden regions.

Authors of one commentary published in the Journal of AIDS in 2010 discuss one small study in which no signs of TDF resistance appeared in individuals who received two weeks of TDF monotherapy.[7] They note several recently designed mathematical models for predicting HIV resistance incidences that predict that less than 1% of expected seroconversions during TDF regimens would develop strains resistant to TDF.[7]

One review published after the release of the CAPRISA trial results calls attention to the role that dosing strategies play in the development of drug resistant strains of HIV. Questions regarding the effects of intermittent vs. daily dosing strategies on drug-resistance development remain unanswered. Although the designs of three ongoing studies, the IAVI E001, IAVI E002, and HPTN 067, address this issue by looking at the pharmacokinetics of intermittent oral therapies, authors note the need for the development of large-scale trials comparing drug-resistance incidences in both dosing strategies.[5]

At the recent Conference on Retrovirals and other Opportunistic Infections (CROI), one young researcher presented the results of her study. She and colleagues designed three mathematical models to identify potential effects of a simultaneous rollout of PrEP and ART.[9] The models, which looked at ART alone, PrEP alone, and ART with PrEP, calculated the number of new infections and resistance incidences in each scenario.[9] Results of the study showed that a joint rollout of ART and PrEP would have the biggest "prevention impact" out of all three scenarios.[9]

Strict adherence patterns, efficient drug regimens, and stringent prescription regulations remain important in averting the growth of drug-resistant strains.[7] Monotherapy TDF and co-formulated TDF/FTC are two of the most desirable ARVs for PrEP, mainly because of several pharmacodynamic properties of TDF, including its long half-life and ability to achieve high concentrations in genital tissues.[10] Because TDF is used as the predominant drug in antiretroviral treatment, experts fear the continued surfacing of drug-resistant strains with additional use of TDF for PrEP. [7,9] Exposing the virus to the same drug with such frequency presents ample opportunity to develop resistance. Therefore, experts need to continue to address the production of new ARVs and the development of clinical efficacy trials for these ARVs as a top priority, looking to stay ahead of the growth and transmission of drug-resistance strains of HIV. Frequent diagnostic testing in those receiving PrEP will monitor HIV resistance, ensuring that high-risk HIV-negative individuals involved in efficacy trials remain negative. Identifying seroconversions as early as possible will lessen the chances for the development and transmission of drug resistant strains.[7]

Treatment vs. Prevention

With recent reports of data demonstrating efficacy rates of PrEP, a lively debate regarding the relative importance of ART vs. PrEP has surfaced. Willard Cates, author of "After CAPRISA 004: time to re-evaluate the HIV lexicon," addresses

the "compartmentalized terminology" that has come to define the ART-PrEP discussion today.[5] Elly Katabira, President of the International AIDS Society, discusses the compelling need for the AIDS community to recognize "treatment" and "prevention" as one concerted effort.[6] In his presentation at CROI 2011, Bob Grant, chief investigator of the iPrEX study, stressed the significance of "messages" that portray PrEP as the "bridge to universal access to treatment".[9] All three experts maintain the stance that without this necessary cohesion between the two concepts, universal access will not be achieved, and the HIV burden will remain as it stands today. Several reports also highlight the need for an accurate cost-effectiveness assessment of the relative benefits of working towards large-scale PrEP implementation programs.[2]

Establishing a more "integrated" approach for discussing PrEP is a necessity if it is to become the primary method for fighting HIV transmission. As argued by Cates, existing terminology used to define PrEP leads to the compartmentalization of the prevention strategy based on modes of delivery with microbicides referring to topical delivery, and PrEP to oral.[5] This classification method leads to divided "scientific" discussions and meetings, resulting in further segregation between the terms. Both topical and oral PrEP methods work towards the same goal, and the integration of both terms with one another will be important in allowing the scientific community to continue to progress towards commercial release and use of the drugs.

ART generally results in what Mr. Katabira describes as "undetectable viral loads" in patients that maintain strict adherence to their prescribed regimens.[6] This depletion in viral load diminishes significantly the risk of HIV transmission during the coital act, and has the effect of serving as both a treatment and a prevention mechanism.[6] Katabira's take home message on the importance of the concept of ART as prevention correlates directly with Bob Grant's vision of PrEP as the bridge to universal access to ARVs. PrEP will ensure HIV-prevention in myriad populations of at-risk individuals while simultaneously reducing the number of individuals in need of ART, while ongoing ART will continue to deplete viral loads in even the most acute cases around the world, reducing the risk of transmission.[6] This scenario will not happen without universal dedication to the development and implementation of PrEP behavioral and efficacy trials. The creation of even a rudimentary cost-effectiveness model will allow experts to assess the potential economic benefits of a large-scale PrEP rollout. The investment in PrEP regimens for at-risk populations, particularly adolescents, could lead to fewer ART expenses to be paid in the future.[7]

CONCLUSIONS

The preliminary evidence on the potential effectiveness of chemoprophylaxis against HIV has brought the HIV/AIDS field one step further in its efforts against the HIV pandemic. Nonetheless, this new data has raised important questions and concerns relevant to the safety, efficacy, and rationale for using ARV drugs to prevent HIV transmission. The number of unanswered questions that have emerged and the diversity of at-risk groups to which they apply further complicates this issue. Understanding the attitudes and economic and social trends of the targeted populations will be critical in ensuring optimal adherence rates in all PrEP users, particularly adolescents. Biological, psychosocial, and cognitive aspects of each population must be considered, requiring the development of extensive pharmacokinetic drug profiles to ensure appropriate dosing and use in each at-risk population.[10] Monitoring and tracking closely all PrEP users will be crucial in preventing drug-resistant strains from developing. Avoiding drug resistant strains during the experimental phase is also critical in order to then implement large-scale PrEP use, as the development of HIV-resistant strains early on during efficacy trials will compromise drug effectiveness.

In order to continue to make significant progress in the field of ARV based prevention, experts must establish a more integrated approach to defining PrEP drugs and forms of delivery, as well as accept the position of PrEP as the link to universal access. Experts in the field must continue to communicate and collaborate as they work towards universal access through ART and PrEP delivery.

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