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Review Article

PRE-EXPOSURE PROPHYLAXIS (PrEP) AS HIV PREVENTION STRATEGY AND PUBLIC HEALTH IMPLICATIONS

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ABSTRACT

As the rate of AIDS-related mortality continues to decrease due to advanced combination antiretroviral therapies available, many recent efforts have been made to stop new infections. While there are still ongoing research efforts on HIV vaccine development, Truvada® for pre-exposure prophylaxis (PrEP) is available to general public as an HIV prevention strategy. PrEP specifically targets populations at-risk including gay men, men-who-have-sex-with-men(MSM), and heterosexual serodiscordant couples. A recent study of PrEP utilization reported an extraordinary slow uptake of PrEP; it suggests a need to evaluate current PrEP roll-out. This review explores potential causes of the current slow uptake phenomena. These include common concerns among PrEP providers and populations at-risk; long-term side effects, PrEP adherence, fear of drug-resistance, and potential rise of risky sexual behaviors. Previous PrEP randomized clinical trials (RCTs) showed its effectiveness but did not recognize its potential barriers outside clinical settings. Implementation of PrEP in a population-level should therefore include comprehensive counseling programs to support medication-adherence, and future research must carefully monitor current PrEP users and address potential pitfalls to maximize its protective benefits.

Keywords: PrEP, Truvada®- medication-adherence- drug-resistance-risk sexual behavior- long term safety

INTRODUCTION

According to the Human Immunodeficiency Virus (HIV) statistics from Centers for Disease Control and Prevention (CDC), more than 1.2 million people are currently living with HIV infection in the United States with only 14% of whom whose infections have not been diagnosed [1]. The incidence of HIV infection has been stable since 2010, and there has been a significant drop in HIV-related mortality [1]. This is largely due to behavioral changes, such as reduction in the number of sex partners and the use of barrier methods such as condoms, and expanded access to antiretroviral therapy (ART) [2, 3, 4].As antiretroviral drugs and treatment advance infected persons are now living longer than before, HIV has become a chronic disease in our society. In fact, the rate of new infections continues to outpace the rate at which HIV-positive persons start their treatment [5,6]. A study of lifetime cost of HIV in the United States by Schackman et al. in 2006 report suggests that medical costs in person with HIV was more than $300,000 per year [7]. Since HIV treatment is suppression of viral activity rather than complete eradication of HIV-1, continuous medication adherence for rest of a patient's life imposes heavy economic burden and health care utilization in the United States. Hence, reducing number of additional HIV infections has been a national HIV research priority.

PREVIOUS CLINICAL TRIALS & CURRENT PREP UPTAKE

HIV prevention research has focused on various biomedical strategies for preventing new infections such as male circumcision, vaccines, and pre-exposure prophylaxis (PrEP)[8]. Truvada® is an epitome of PrEP: it is a promising HIV prevention method for those who are HIV-1 seronegative with Truvada® being the only U.S. Food and Drugs Administration (FDA) officially approved drug in 2012 for PrEP. Truvada®, a combination regimen with two antiviral ingredients; tenofovir and emtricitabine (FTC) is approved as parts of HIV treatment regimens for newly infected patients in conjunction with three (or more) other HIV antiretroviral medications. There are more than 20 different antiretroviral drugs excluding those that are currently in clinical trials. Most of these drugs are first-line HIV regimens; the aim is to keep viral load in the body at a low level to reduce the risk of HIV transmission and slows down the progression to acquired immunodeficiency syndrome (AIDS). Truvada® for PrEP works the same mechanism of action where it inhibits HIV-1 from replicating as it enters the body. The key difference resides in timing of exposure; Truvada® for PrEP is introduced to uninfected body *before* HIV-1 viral invasion as opposed to after infection for treatment purpose. The rationale for the recent use of Truvada® for seronegative persons with ongoing exposure is based on its efficacy in infants and mucosal simian HIV challenges in primates [9,10]. In both studies of perinatal transmission and animal models, the potential protective benefits of antiretroviral prophylaxis were maximized when Truvada® was administered both before and after HIV exposure [11]. The effectiveness and safety of PrEP use for HIV-1 protection in humans was tested and proven in several placebo-controlled clinical trials [12,13,14]. PrEP has shown a substantial reduction in the risk of HIV-1 infection as high as 92% when used with perfect adherence rate. The highest efficacy has been reported in one of the trials; the Partners-PrEP study started in 2007 whose adherence was reported as nearly perfect in both treatment and placebo groups [13]. Likewise, the first human clinical trial of Truvada® also known as iPrEX study demonstrated the positive correlation between PrEP adherence and its impact on clinical results [12]. Hence, adherence appears to play a critical role in

determining PrEP efficacy. As evident in the meta-analysis by Zolnierek et al. in 2009, and Morgado et al. in 2011, improved health outcomes and medication adherence are dependent upon health care provider-patient communication. A role of pharmacist and physician input will be critical to determine success of PrEP prevention strategy [15,16]. Despite these indications of promise, questions remain in the practical implementation of PrEP and its use as a population-level HIV prevention strategy remains highly controversial in the U.S. [17,18,19]. As a result, PrEP use suffers relatively slow uptake, considering continuous efforts to take the drugs into practice and make them more available and accessible to general public at all-income levels. The number of subjects using Truvada® for PrEP between early 2012 and 2014 were estimated to be approximately 3,000, according to a PrEP utilization study in 2014 [20]. This is significantly smaller number than expected, especially when the annual number of new HIV infections in the United States alone is currently 50,000 [1]. The potential causes of the current extraordinarily low uptake phenomena can be found in different areas in our society; (1) unwillingness of the highest risk population groups for HIV such as homosexual men, men-who-have-sex-with-men (MSM), and (2) reluctance of primary physicians to prescribe PrEP for HIV negative patients. I am going to attempt toreview the potential public health implications with regards to PrEP uptake and suggest solutions to achieve a successful PrEP roll-out.

PUBLIC AWARENESS

According to recent data from CDC, homosexual men and MSM remain disproportionately affected by HIV infection in spite of the fact that new incidence of HIV transmission has been stable since 2010 [1]. Public health campaigns to target these vulnerable population groups to raise the awareness of safe sex practices (i.e. condom usage) as primary prevention strategies do not seem to work. The recent successful demonstration of Truvada® efficacy for PrEP may be a potential solution to prevent additional cases of HIV infections. And yet, PrEP does seem to be catching on yet. According to convenience surveys at gay pride events in several United States cites PrEP awareness was as low as 25% among MSM [21]. A study of awareness and low immediate uptake of PrEP among MSM also suggests that "men who were not familiar with post-exposure prophylaxis (PrEP) and those who only had male partners were less likely to know about PrEP" [22]. In another study of attitudes towards PrEP in a heterosexual population, Khawcharoenporn et al. found that a lack of risk-behavior perception in high-risk participants was correlated with a lack of interest in PrEP [23].Although these findings are based on MSM and heterosexual population, the results are applicable to gay community as well, and therefore, imply that future effective strategies to increase PrEP uptake need to be focused on providing more information and education.

LONG-TERM SAFETY

Another relevant issue related to the low uptake of PrEP in populations at-risk is the safety of long-term use of daily pill. None of the clinical trials including the first iPrEX study in 2010 found significant side effects in the study participants [12,13,24]. Some reported very mild side effects such as GI upset and loss of appetite which were quickly resolved in the first month of therapeutic prevention regimen. Although these studies support the safety of daily use of PrEP, there are not sufficient data supporting its long term usage. The next biggest fear comes from the possibility of HIV virus developing resistance to Truvada®; losing a potential HIV treatment option. Because PrEP is based on anti-retrovirals, there is a considerable concern that it could lead to new infections caused by resistant strains. Interestingly, the fear of drug-resistance in general population overlaps with that of health care providers [25]. Truvada® is not the only available HIV treatment option that creates resistant mutant strain to currently available HIV drug therapies. Emergence of HIV resistance in the context of PrEP use is discussed in several previous PrEP trials. A study of transmitted drug resistance and PrEP use concludes that "if risk compensation occurs, new infections rises and this is most likely be the result of decreasing transmission of wild-type strains and increasing transmission of resistant strains" [26]. This finding indicates that increasing risky sexual behaviors while taking Truvada® may lead to drug-resistance. Likewise, the Partners-PrEP study predicted possible drug resistance when patients acquire HIV infection while receiving PrEP and kept refilling in absence of regular clinical counseling sessionswith PrEP provider and routine HIV screening [13]. The iPrEX study in 2010, however, did not detect any resistance among the study subject who became infected with HIV during the trials [12]. In addition, in the Partners-PrEP study, four participants became infected with HIV resistant to nonnucleoside reverse-transcriptase inhibitors (NNRTIs) which was later found to be secondary to transmitted resistance, as opposed to selection of resistance mutations by the study medication (Truvada®)[13].Regardless of the divergent study results, all of these studies seem to agree on the following two factors in determining resistance: Medication adherence and risk compensation.

ADHERENCE

Treatment/medication adherence in HIV treatment has been a well-recognized factor in successful antiretroviral therapy (ART) for HIV positive individuals since the beginning of the early ART in 1987. Likewise, in all of the PrEP studies discussed in this review demonstrated a strong association between medication adherence and PrEP efficacy. In the Partners-PrEP study of HIV serodiscordant couples, PrEP reduced the risk of HIV infection by up to 90% among the participants with higher adherence [13]. Similar results were reported in the iPrEX study as well as a study of PrEP in injection drug users in Thailand [12,14]. Non-adherence/suboptimal adherence is a crucial stepping stone to success in PrEP efficacy. Despite understanding the impact of adherence from ART and recent PrEP studies, there are no evidence of public health strategies in monitoring, supporting, and improving PrEP adherence in context of PrEP roll-out. Potential barriers and factors to PrEP adherence in the current healthcare setting are still unknown: Is it possible to achieve nearly perfect medication adherence rate? This implies that current on-going efforts to expand public access to the drug must also understand the characteristics of PrEP users and their use patterns for its successful roll-out.

FUTURE DIRECTION

Truvada® PrEP is no longer just an HIV prevention strategy on the horizon. It is now officially approved and available to general public. Although Truvada® PrEP strategyalone cannot be single solution HIV prevention; it is certainly the prominent rising solution to substantially reducing the number of future infections when combined with safe sex practices. In 2004 PrEP utilization analysis showed a depressingly low number of PrEP users. The report indicates that reproducing PrEP use in a wider scale outside experimental study is a current challenge [19]. PrEP certainly can be successful preventive measures but we need a roadmap to successfully implementing evidence-based public health approach. Evidence suggests that the populations at risk who really need preventive measures are either not aware of PrEP or are reluctant to take the medication. Medication adherence is a clinically proven critical factor for success in PrEP efficacy as well as challenge due to fear for drug-resistance. Next steps to PrEP implementation in a population-level approach must include:

- Increasing PrEP awareness and delivering tailored information/education to population at-risk
- Providing comprehensive counseling programs conducted by healthcare providers (i.e. pharmacist's run counseling program) for consistent use and improve medication compliance
- Reinforcing risk reduction strategies including safer-sex practice and traditional barrier methods
- Conducting future research in socio-behavioral approach for monitoring the current PrEP users and measure their risky sexual behaviors to accurately evaluate PrEP effects on the overall HIV epidemic

CONCLUSION

Most current information on PrEP use and its safety has come from double-blinded, randomized controlled trials where participants did not know whether they were having PrEP or a placebo. Since use of PrEP in a "real clinical" setting may be different, it is important to carefully examine the current PrEP roll-out and address possible pitfalls to maximize its protective benefits.

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