Pre-exposure Prophylaxis for Human Immunodeficiency Virus

The Past, Present, and Future

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KEYWORDS

• Pre-exposure prophylaxis • Implementation • Adherence • HIV prevention
• Biomedical intervention

KEY POINTS

- Our knowledge of pre-exposure prophylaxis (PrEP) as a means to prevent human immunodeficiency virus (HIV) acquisition has increased greatly over the decade.
- Evidence from clinical trials conducted among multiple high-risk populations suggests that oral PrEP, if adhered to, can be effective in reducing the risk of HIV acquisition among HIV-uninfected individuals.
- The key issues with PrEP use that have arisen as a result of these trials warranting further research include adherence, risk of drug resistance, and behavioral disinhibition.
- Studies further informing PrEP utilization are ongoing to address issues such as alternate dosing strategies and delivery methods, long-term side effects, and effectiveness in real-world settings.
- PrEP implementation is underway; future studies and activities will need to focus on optimizing PrEP regimens and adherence, increasing education and uptake among high-risk populations and providers, and establishing systems to monitor and evaluate PrEP use.

INTRODUCTION

Human immunodeficiency virus (HIV) prevention research has rapidly advanced over the last decade, with several large-scale research studies demonstrating that antiretrovirals (ARVs) can be used not only for the prevention of mother-to-child transmission, post-exposure prophylaxis, and treatment as prevention (TasP) but also for

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pre-exposure prophylaxis (PrEP). PrEP for HIV prevention involves the use of ARV medications, optimally delivered in concert with risk-reduction counseling and behavioral interventions, such as condom provision and use, to prevent HIV infection among those who are HIV uninfected but at high risk for infection. PrEP entails having an HIV-uninfected individual take ARVs orally or topically (either vaginally or rectally) to prevent sexual or parenteral infection with HIV.[1,2]

The concept of PrEP is not new and has been used as a prevention method for a variety of illnesses, including prevention against rabies[3] and malaria[4] among those traveling to endemic areas. PrEP was considered as a strategy to reduce the number of new HIV infections given the continued high HIV incidence rates both nationally and globally. Globally, an estimated 2.5 million new infections occur every year[5]; in the United States, there are an estimated 50,000 new infections annually.[6] Without an effective HIV vaccine on the horizon, the need for high-impact HIV prevention tools is essential. These tools include interventions such as TasP for HIV-infected individuals; routine HIV testing and linkage to care; and biomedical interventions, such as male circumcision.[7]

Further research into PrEP will add to the toolbox of HIV prevention methods.

This article describes the prior research that informs our current understanding of PrEP, summarizes ongoing research in the area, and highlights key issues that must be addressed in order to optimize the use of this HIV prevention tool.

THE PAST: DEVELOPMENT OF PRE-EXPOSURE PROPHYLAXIS AS AN HIV PREVENTION INTERVENTION

Prior Evidence of Use of Antiretrovirals for Prevention

Proof of concept for the use of PrEP to prevent HIV infection stems from research conducted in both animals and humans. The use of PrEP and postexposure prophylaxis to prevent mother-to-child transmission of HIV has been proven to reduce the risk of transmission by as much as 99%.[8–10] Similarly, the use of postexposure prophylaxis in situations in which a person has had a high-risk sexual or parenteral exposure, or a high-risk occupational exposure, has been shown to be effective with an 81% reduction in transmission.[11] This proof of concept led to the first HIV PrEP trials using animal models.

Animal Trials

The biological plausibility of using ARVs as PrEP for HIV prevention was first examined using animal models as early as 1995. These animal studies also assisted in understanding issues regarding which drugs would be efficacious, drug delivery, and dosing. Among the many ARVs available, tenofovir disoproxil fumarate (TDF), a nucleoside reverse transcriptase inhibitor, has been widely studied for use as both oral and vaginal PrEP. This ARV is generally well-tolerated in HIV-infected persons and has minimal side effects.[12] The combination of tenofovir (TDF) and emtricitabine (FTC) (Truvada) has also been extensively studied for use with PrEP and has been used in many of the animal and clinical trials conducted to date.

The first few nonhuman primate studies assessed the efficacy of injectable TDF for PrEP. In 1995, Tsai and colleagues[13] published data that found that 4 weeks of daily injections of TDF starting 48 hours before, 4 hours after, or 24 hours after intravenous simian immunodeficiency virus (SIV) challenge resulted in 100% protection in macaques. In 1998, Van Rompay and colleagues[14] also concluded that 2 injectable doses of TDF 4 hours before and 20 hours after oral SIV challenge resulted in 100% protection among newborn macaques.

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