MILESTONE 20

Antiretrovirals for prevention

Since the first reports identifying patients with AIDS in 1981 (MILESTONE 1) and the discovery of HIV-1 as the etiological agent in 1983 (MILESTONE 2), a major goal has been to find and develop effective anti-HIV therapeutic options. This yielded results in 1987 with the approval of the first antiretroviral therapy, azidothymidine (AZT), only a year after it was first administered and shown to reduce HIV viral load in patients. Further antiretroviral drugs targeting other aspects of the retroviral lifecycle were discovered and resulted in combinations of drug classes associated with successful and sustained prevention of AIDS progression (MILESTONE 14).

The advent and widespread use of combinatorial antiretroviral therapy resulted in successful virological control in HIV-infected patients. However, this did not address another key tenet of HIV medicine: the prevention of viral transmission. For most viruses, lower viral loads are known to minimize the chance of transmission, and it is on the basis of this that the initial premise of antiretrovirals for prevention came to fruition. Proof of concept for antiretrovirals as prevention was first shown in 1994, where administration of AZT reduced mother-to-child transmission of HIV. Since this first clinical demonstration, antiretrovirals as prevention have gathered momentum, which has resulted in pivotal strides forward.

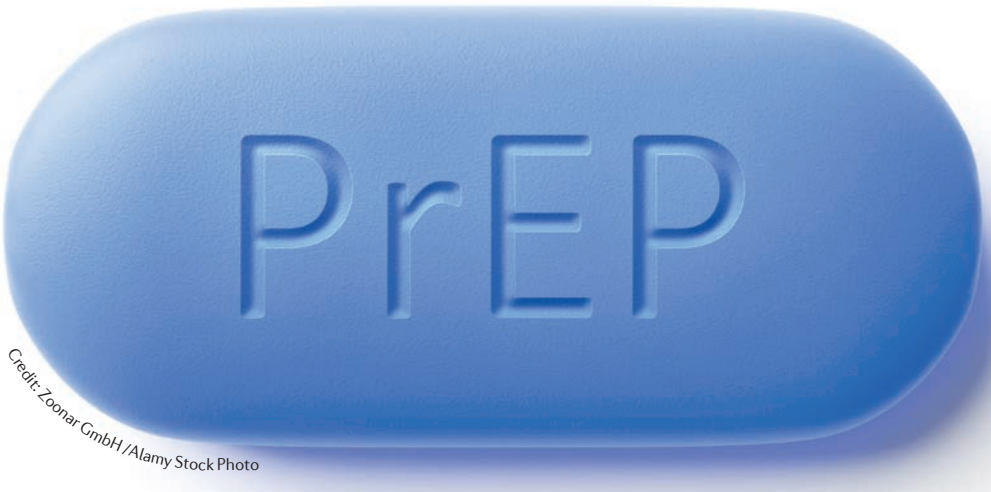
On the basis of these initial findings showing reduced rates of transmission by minimizing viral loads in HIV-seropositive patients, two key studies demonstrated a crucial role for such applications of early antiretroviral intervention. Initiation of early antiretroviral therapy and reduction in viral load in confirmed HIV-positive patients was shown to successfully reduce sexual transmission in serodiscordant couples, establishing the potential benefits of early commencement of therapy and the associated reduction in HIV transmission.

Complementary approaches utilizing antiretroviral therapy in HIV-seronegative persons have also shown efficacy in terms of preventing infection in at-risk populations. Two large-scale, randomized, double-blind, placebo-controlled studies paved the way toward the advent of pre-exposure prophylaxis (PrEP). The iPrEx trial assessed the administration of the anti-retrovirals emtricitabine plus tenofovir disoproxil fumarate (Truvada) in 2,499 high-risk HIV-negative men or transgender women who have sex with men. The Partners PrEP trial evaluated administration of Truvada or tenofovir disoproxil fumarate monotherapy among 4,758 HIV-serodiscordant heterosexual couples. PrEP administration to seronegative individuals in both settings was estimated as conferring greater than 90% protection from HIV infection in persons with good adherence to the PrEP regimen.

> “these pivotal studies… firmly establish the importance of antiretrovirals for preventing HIV transmission”

Consequently, in 2012, the US Food and Drug Administration approved the use of Truvada as PrEP for HIV on the basis of the initial data from these studies, which established that its use was well tolerated, safe and effective in reducing HIV transmission in high-risk individuals. Although the implementation of antiretrovirals for prevention in both HIV-positive and HIV-negative persons is still in its relative infancy and the further impact of such interventions remains to be fully determined, collectively these pivotal studies transform the risk of HIV transmission and firmly establish the importance of antiretrovirals for prevention as a potential game changer in preventing HIV transmission and turning the tides of the HIV epidemic.

Gavin Mason,
Nature Communications



Credit: Zoonar GmbH / Alamy Stock Photo

ORIGINAL ARTICLES Yarchoan, R. et al. Administration of 3′-azido-3′-deoxythymidine, an inhibitor of HTLV-III/LAV replication, to patients with AIDS or AIDS-related complex. *Lancet* **327**, 575–580 (1986) | Connor, E. M. et al. Reduction of maternal–infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N. Engl. J. Med.* **331**, 1173–1180 (1994) | Donnell, D. et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet* **375**, 2092–2098 (2010) | Cohen, M. S. et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N. Engl. J. Med.* **365**, 493–505 (2011) | Grant, R. M. et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N. Engl. J. Med.* **363**, 2587–2599 (2010) | Baeten, J. M. et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N. Engl. J. Med.* **367**, 399–410 (2012)