HIV Viral Load and Transmissibility of HIV Infection
Undetectable Equals Untransmittable

In 2016, the Prevention Access Campaign, a health equity initiative with the goal of ending the HIV/AIDS pandemic as well as HIV-related stigma, launched the Undetectable = Untransmittable (U = U) initiative. U = U signifies that individuals with HIV who receive antiretroviral therapy (ART) and have achieved and maintained an undetectable viral load cannot sexually transmit the virus to others. This concept, based on strong scientific evidence, has broad implications for treatment of HIV infection from a scientific and public health standpoint, for the self-esteem of individuals by reducing the stigma associated with HIV, and for certain legal aspects of HIV criminalization. In this Viewpoint, we examine the underlying science-based evidence supporting this important concept and the behavioral, social, and legal implications associated with the acceptance of the U = U concept.

A major breakthrough in HIV/AIDS therapeutics came in 1996 with the advent of 3-drug combinations of antiretrovirals, including the newly developed protease inhibitors. These therapeutic regimens resulted in substantial decreases in viral load in a high percentage of patients, usually below the level of detection in plasma and sustained for extended periods. Although not appreciated at the time, the accomplishment of a sustained, undetectable viral load was likely the definitive point when the U = U concept became a reality. Proof of that concept would await further clinical trials and cohort studies. Based on a review of scientific data, a statement from Switzerland in 2008 indicated that individuals with HIV who did not have any other sexually transmitted infection, and achieved and maintained an undetectable viral load for at least 6 months, did not transmit HIV sexually. This was the first declaration of the U = U concept, but it was not universally embraced because it lacked the rigor of randomized clinical trials.

In 2011, the HIV Prevention Trials Network (HPTN) study 052 compared the effect of early with delayed initiation of ART in the partner with HIV among 1763 HIV-discordant couples, of whom 98% were heterosexual. The findings of a 96.4% reduction in HIV transmission in the early-ART group, vs those in the delayed group, provided the first evidence of treatment as prevention in a randomized clinical trial. At that point, the study could not address the durability of the finding or provide a precise correlation of the lack of transmissibility with an undetectable viral load. Importantly, after 5 additional years of follow-up, the durable, protective effect of early ART to maintain viral suppression and prevent HIV transmission was validated. There were no linked transmissions when viral load was durably suppressed by ART.

Subsequent studies confirmed and extended these findings. The PARTNER 1 study determined the risk of HIV transmission via condomless sexual intercourse in 1166 HIV-discordant couples in which the partner with HIV was receiving ART and had achieved and maintained viral suppression (HIV-1 RNA viral load <200 copies/mL). After approximately 58,000 condomless sexual acts, there were no linked HIV transmissions. Since a minority of the HIV-discordant couples in PARTNER 1 were men who have sex with men (MSM), there was insufficient statistical power to determine the effect of an undetectable viral load on the transmission risk for receptive anal sex. In this regard, the Opposites Attract study evaluated transmissions involving 343 HIV-discordant MSM couples in Australia, Brazil, and Thailand. After 16,800 acts of condomless anal intercourse there were no linked HIV transmissions during 588.4 couple-years of follow-up in which the time per HIV partner with an undetectable viral load (<200 copies/mL).

Building on these studies, the PARTNER 2 study conclusively demonstrated that there were no cases of HIV transmission between HIV-discordant MSM partners despite approximately 77,000 condomless sexual acts if the partner with HIV had achieved viral suppression and the uninfected partner was not receiving preexposure prophylaxis or postexposure prophylaxis.

The validity of the U = U concept depends on achieving and maintaining an undetectable viral load in an individual with HIV. Because of the promise of U = U, achieving and maintaining an undetectable viral load becomes an aspirational goal and offers hope for persons with HIV. The principles involved in achieving and maintaining an undetectable viral load are related to (1) taking ART as prescribed and the importance of adherence; (2) time to viral suppression; (3) viral load testing recommendations; and (4) the risk of stopping ART (Box).

Taking ART as prescribed is essential for achieving and maintaining an undetectable viral load. The Centers for Disease Control and Prevention (CDC) reported that of the individuals with HIV in the United States in HIV clinical care in 2015, approximately 20% had not achieved viral suppression (<200 HIV-1 RNA copies/mL) at their last test. CDC also noted that 40% of the individuals in HIV clinical care that same year did not maintain viral suppression for more than 12 months. Lack of adherence with ART is associated with many factors, including the lack of accessibility of quality health care. The stability of health care provided by programs such as the Ryan White HIV/AIDS Program shows that high rates of viral suppression are possible in the context of quality care delivery.
Box. Principles to Achieve and Maintain an Undetectable Viral Load

- In order for antiretroviral therapy (ART) to provide maximum benefit, taking medication as prescribed is essential.
- Achieving an undetectable viral load can take up to 6 months of ART. Once achieved, continued adherence is required.
- According to guidelines from the Department of Health and Human Services, viral load testing should be performed every 3-4 months after the plasma HIV-1 RNA level reaches undetectable (<200 copies/mL). If viral suppression and stable immunologic status are maintained for >2 years, the viral load testing can be extended to every 6 months thereafter.
- Stopping therapy negates the validity of assuming that U = U.

The guidance that viral suppression measured at 6 months after starting therapy is required for U = U has several origins. First, Partners PrEP trial, a prospective cohort study conducted among 4747 heterosexual HIV-discordant couples in Kenya and Uganda, was designed to determine the risk of HIV transmission prior to and following achieving viral suppression (<80 HIV-1 RNA copies/mL). HIV incidence prior to initiation of ART was 2.08 per 100 person-years, 1.79 for 0 to 6 months after initiation of ART, and 0.00 with more than 6 months of ART, indicating that residual HIV transmission risk persists during the first 6 months of ART, during which time there is incomplete suppression of HIV in blood and genital compartments. Second, a case of a linked transmission in Partners PrEP occurred when the treated partner had been taking ART for fewer than 4 months and prior to complete viral suppression. These findings support the requirement for 6 months of ART to achieve virologic suppression.

The recommended schedule for viral load testing for individuals with HIV in the United States, according to the Panel on Antiretroviral Guidelines for Adults and Adolescents, includes testing (1) at entry into care; (2) on initiation of ART or at the time of treatment regimen modification; (3) 2 to 8 weeks after ART initiation or modification and repeated every 4 to 8 weeks until the HIV-1 RNA viral load is suppressed to less than 200 HIV-1 RNA copies/mL; and (4) repeated every 3 to 4 months. For individuals who are adherent to treatment with consistently suppressed viral load and stable immunologic status for more than 2 years, the guidelines panel recommends that monitoring can be extended to 6-month intervals.

Stopping ART represents a significant challenge to successful implementation of U = U. When ART is stopped, viral rebound usually occurs within 2 to 3 weeks. The SPARTAC and SMART clinical trials using stopping ART to determine if the same degree of protection from progression to AIDS could be achieved by ART dosed for defined intervals or continuously delivered. In both studies, stopping ART resulted in viral rebound to levels that would have been associated with increased risk of HIV transmission. A systematic review of 12 recent clinical studies concluded that there is negligible risk (0.00 transmissions/100 person-years, 95% CI, 0.00-0.28) of HIV sexual transmission among HIV-discordant partners when the partner with HIV adheres to ART and maintains a suppressed viral load (<200 HIV-1 RNA copies/mL) measured routinely every 4 to 6 months. To enhance the overall success of the U = U concept, it is important to implement programs that help patients remain in care and address the challenges in their lives that result in their stopping therapy.

In summary, even though the clinical data underpinning the concept of U = U have been accumulating for well over a decade, it is only recently that an overwhelming body of evidence has emerged to provide the firm basis to now accept this concept as scientifically sound. This has important implications in several areas. The U = U concept provides incentives for individuals with HIV to seek, initiate, and adhere to ART. In addition, it adds incentives to efforts to control and ultimately end the HIV/AIDS pandemic because treatment as prevention is a critical tool in preventing the spread of HIV infection. The U = U concept also bridges the best of biomedical science with current concepts in behavioral and social science by removing the sense of fear and guilt that a person may be harming someone else, as well as the feeling of self-imposed and external stigma that many people with HIV experience. Finally, this concept has legal implications related to the criminalization of certain persons with HIV whereby criminal law is used to penalize alleged, perceived, or potential HIV exposure of one person to another.

ARTICLE INFORMATION
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REFERENCES