Antiretroviral Therapy for Prevention of HIV and Tuberculosis: A Promising Intervention but Not a Panacea

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**Abstract:** The demonstration of the efficacy of antiretroviral therapy (ART) in preventing HIV transmission offers promise for controlling the HIV epidemic.1–4 The HIV Prevention Trials Network (HPTN) 052 study demonstrated the efficacy of ART when used by HIV-infected persons for the prevention of HIV transmission in serodiscordant heterosexual couples.1 This clinical trial, in conjunction with a number of ecological, observational, and mathematical modeling studies, provides support for the concept of “Treatment as Prevention” (TasP). Other evidence from ecological and observational studies provides support for the potential role of ART for prevention of tuberculosis (TB).5–6 The potential for ART to prevent HIV transmission has resulted in advocacy for widespread implementation of TasP and has inspired discussions about a future AIDS-free generation.2 Mathematical modeling studies have also assessed the impact of TasP in conjunction with other prevention interventions on the HIV epidemic8 and its impact on the incidence of HIV-associated TB.9 In this article, we present the evidence regarding the use of ART for prevention of both HIV and TB and summarize key issues that need to be addressed to appropriately situate this intervention within the context of other available prevention interventions. We also highlight the need for further research to provide empiric data on the effect of ART for individual health and its effects on the trajectory of the HIV and TB epidemics at population level.

**EFFECT OF ART ON HIV INCIDENCE**

The HPTN 052 study was a randomized-controlled trial that compared early versus delayed initiation of ART in 1763 serodiscordant heterosexual couples in 9 countries.1 HIV-infected partners with CD4+ counts between 350 and 550 cells/µL were randomized to receive early therapy (ie, immediate ART) or delayed therapy at CD4+ count of 200–250 cells/µL or onset of HIV-related symptoms. A total of 39 HIV-1 transmissions were observed, of which 28 were virologically linked to the infected partner. Of the linked transmissions, only 1 occurred in the early therapy group (hazard ratio [HR]: 0.04, 95% confidence interval [CI]: 0.01 to 0.27) with evidence of 96% protection. In terms of overall transmission, ART had a protective effect of 89%.

There have been a series of ecological, observational, and mathematical modeling studies supporting TasP. Ecological studies from San Francisco, South Africa, Taiwan, and Canada suggested that expansion of ART use was associated with a reduction in the number of new HIV infections or expected HIV cases.10–14 In the study from San Francisco, an association between expansion of ART use and decreases in community viral load was reported, measured as the sum of the most recent viral loads in HIV-infected individuals, over the period between 2004 and 2008 in conjunction with a decrease in number of new infections.13 Data from the British Columbia, Canada, revealed a significant inverse association between the number of individuals on ART and the number of individuals newly testing HIV positive per year.12 Similarly, a recent study from South Africa demonstrated that increase in coverage of ART use in 1 region was associated with a decrease in HIV incidence.14 In the latter study, an HIV-uninfected individual living in a community with high ART coverage, defined as 30%–40% of persons with HIV infection on ART, was 38% less likely to acquire HIV than an individual living in a community with ART coverage of less than 10%.

Observational studies supporting an association between ART use and decrease in HIV transmissibility have largely been derived from studies that included HIV serodiscordant couples. The earliest study reporting such an association was with use of zidovudine monotherapy.15 Followed by further studies that included the use of combination ART in HIV-discordant couples.16–20 Only 1 study failed to demonstrate association between use of ART and decrease in transmission,
the latter including a limited number of discordant couples from China.\textsuperscript{21} A 2011 review of 7 observational studies and 1 randomized-controlled trial collectively identified 464 episodes of HIV transmission among serodiscordant couples, of which 72 episodes occurred among couples in which the HIV-infected partner was on ART and 392 occurred in couples in the absence of ART.\textsuperscript{22} The rate ratio of HIV transmission for these studies was 0.34 (95% CI: 0.13 to 0.92)—ie, there was an estimated 66% decrease in risk of HIV transmission with ART use by the HIV-infected partner.

In a more recent study from China, the effect of ART on HIV transmission among 38,862 heterosexual serodiscordant couples was reported from national HIV epidemiology and treatment databases between 2003 and 2011.\textsuperscript{15} A total of 1,613 HIV transmissions were identified, with an overall transmission rate of 1.6/100 person-years (95% CI: 1.5 to 1.7). The rate of transmission for the treated couples was 1.3/100 person-years (95% CI: 1.2 to 1.3), which was significantly lower than the rate in the ART-naive cohort (2.6/100 person-years [95% CI: 2.4 to 2.8]; adjusted HR: 0.74 [95% CI: 0.65 to 0.84]). This study’s findings are particularly important as they demonstrate the efficacy of this intervention outside of the context of a research study. A key limitation of both the ecological and observational studies is that they cannot support causal association between use of ART and decrease in HIV infections, as the latter effect may have been caused by other factors.

Evidence supporting ART for prevention is also derived from mathematical modeling studies. In a study by Granich et al,\textsuperscript{23} which was based on optimistic assumptions of ART coverage and adherence and used data from the South African epidemic, expansion of use of ART for all individuals identified with HIV infection was shown to have the potential to lead to HIV elimination, defined as HIV incidence less than 0.1%, in 50 years. A meta-analysis of 12 modeling studies regarding the HIV epidemic in South Africa found that TSP could substantially reduce new infections under similarly optimistic assumptions of annual voluntary testing, followed by greater than 90% linkage to care with immediate ART initiation and 85% of patients remaining on treatment over 3 years.\textsuperscript{24} The HIV Modeling Consortium raised several priority issues for future modeling studies of ART for prevention including the need to report on the impact of decisions over both the short and long term, to estimate the impact of current programs rather than radically different future programs, and to use real-life assumptions about testing, linkage to and retention in care, and medication adherence.\textsuperscript{25–27}

The authors also encouraged future models to examine negative outcomes of expanded treatment programs, including their potential influence on risk behaviors by individuals living with HIV.

**EFFECT OF ART ON TB INCIDENCE**

HIV-infected individuals have 20–37 times the risk of developing TB compared with HIV-uninfected individuals.\textsuperscript{28} The case-fatality rates among HIV-infected persons are several-fold higher than those without HIV infection and are strongly associated with the degree of immunodeficiency.\textsuperscript{29,30} Data from clinical trials and observational studies have shown that initiation of ART in patients with TB is associated with a reduction in mortality.\textsuperscript{31–34} In addition, data from clinical trials, cohort studies, ecological studies, and mathematical modeling suggest that use of ART has the potential to reduce the risk of TB in patients with HIV infection.\textsuperscript{13,35–41}

A recent meta-analysis of 3 randomized-controlled trials and 8 cohort studies from resource-limited countries that compared TB incidence by ART use in HIV-infected adults demonstrated that ART was strongly associated with a reduction in TB incidence (HR: 0.35, 95% CI: 0.28 to 0.44).\textsuperscript{3} This association was significant across all baseline CD4\textsuperscript{+} cell count strata: less than 200 cells/µL (HR: 0.16, 95% CI: 0.07 to 0.36), 200–350 cells/µL (HR: 0.34, 95% CI: 0.19 to 0.60), and greater than 350 cells/µL (HR: 0.43, 95% CI: 0.30 to 0.63), without evidence of HR modification with respect to baseline CD4\textsuperscript{+} count. Clinical trial data demonstrated nearly identical reductions in TB incidence when initiating ART at CD4\textsuperscript{+} count 200–350 cells/µL (HR: 0.50, 95% CI: 0.28 to 0.83) compared with <200 cells/µL\textsuperscript{22} and at greater than 350 cells/µL (incidence rate ratio: 0.51, 95% CI: 0.28 to 0.91) when compared with CD4\textsuperscript{+} count of 200–250 cells/µL.\textsuperscript{1} A reduction in TB incidence was also demonstrated in high-income countries following ART initiation in adults with CD4\textsuperscript{+} counts greater than 350 cells/µL.\textsuperscript{5} However, it is important to note that the absolute reduction in TB rates is greatest at lower CD4\textsuperscript{+} strata, and no evidence is available for the effect of use of ART at CD4\textsuperscript{+} count >500 cells/µL on the incidence of TB. Surprisingly, findings from HPTN 052 did not show a decrease in pulmonary TB incidence in individuals who initiated ART at CD4\textsuperscript{+} count between 350 and 550 cells/µL versus those who initiated ART at CD4\textsuperscript{+} 200–250 cells/µL, whereas there were fewer episodes of extrapulmonary TB, largely presumptive in nature, with early use of ART.\textsuperscript{1} Of note, a trial conducted in Botswana found that reductions in TB incidence with ART use at CD4\textsuperscript{+} counts <200 cells/µL were similar among HIV-infected adults receiving 6 months of isoniazid preventive therapy (IPT) with either positive or negative tuberculin skin tests,\textsuperscript{40} suggesting that ART impacts risk of TB following either endogenous reactivation or exogenous exposure.\textsuperscript{43}

Studies evaluating the impact of ART on TB incidence at a population level are more limited. An ecological study from a high HIV and TB burden community of approximately 15,000 persons in South Africa demonstrated an association between implementation of an ART program using criteria based on prevailing national guidelines and TB notification rates. Between 2002 and 2008, as ART coverage increased from 0% to 21% of the HIV-infected population, adult TB notification rates increased to a maximum of 2,500 cases per 100,000 population between 2002 and 2005, then decreased by an average of 202 cases/100,000/yr, reaching 2,000 cases per 100,000 population in 2008.\textsuperscript{44} Notably, the decline in new TB notifications was observed exclusively among the HIV-infected population receiving ART. Furthermore, 2 cross-sectional surveys performed in the same community showed a significant reduction in TB prevalence among a randomly selected HIV-infected population sample, from 9.2% in 2005 to 3.6% in 2008 (adjusted P = 0.013), whereas the prevalence among HIV-negative individuals remained unchanged.\textsuperscript{45} Similar findings were reported in a retrospective descriptive study in which ART scale-up between 2005 and 2009 in a rural district in Malawi was associated with a 33% (95% CI: 27 to 39%) reduction in new TB cases and
a 25% (95% CI: 9 to 49%) reduction in recurrent cases. It is also important to note that, in these 2 studies, ART was initiated at advanced stages of HIV disease, largely at CD4+ count of <200 cells/µL. Given the observational nature of these studies, they are unable to demonstrate a causal relationship between use of ART and reduction in TB incidence/prevalence. The observed trends may have been confounded by high mortality before case diagnosis, provision of IPT (in Malawi), or changes in TB case detection efficiency. It is likely that TB case finding was increased in the ART programs, which may have led to a reduction in TB transmission because of undiagnosed, untreated TB.

Mathematical modeling using data from 9 countries in sub-Saharan Africa suggested that widespread implementation of annual HIV testing and ART initiation early in the course of HIV infection regardless of CD4+ count would lead to rapid reduction in HIV-associated TB at the population level. Assuming that coverage increases to 95% by 2015, initiating ART within 5 years of HIV seroconversion would reduce the incidence of HIV-related TB in 2015 by 48% (range: 37%–55%). The reduction would be greater if ART is started within 2 years of HIV seroconversion (63%; range: 52%–72%). More substantial reductions would be anticipated if the intervention is sustained until 2050: if ART is started 5 or 2 years after HIV seroconversion, the incidence in 2050 will be reduced by 66% (range: 57%–80%) and 95% (range: 93%–96%), respectively.

**TasP: WHO SHOULD BE PRIORITIZED?**

Much of the ongoing discussion regarding TasP has centered on initiation of ART for individuals with higher CD4+ count who would otherwise not be eligible for ART for their own health. Expansion of ART to individuals with higher CD4+ counts has been noted to be associated with certain challenges. Studies have shown that HIV-infected individuals with higher CD4+ counts are at higher risk for loss to follow-up both during the pre-ART phase and when they receive ART. In addition, there remains uncertainty with regard to the balance of benefits versus risks of ART for the health of HIV-infected individuals at higher CD4+ counts.

It is also ironic that, although substantial attention has been given to initiation of ART at a higher CD4+ count, largely for the purpose of prevention of HIV transmission, there remains a gap in coverage for individuals who are in urgent need of ART for their own health and where use of ART will also have substantial prevention effects. In most resource-rich and resource-limited countries, ART initiation is occurring at advanced stages of HIV disease, significantly below the recommended CD4+ count thresholds. A recent study of 36,411 adult patients who started ART between 2005 and 2009 in Mozambique reported that the proportion of patients with late ART initiation, defined as initiation at a CD4+ count < 100 cells/µL or WHO clinical stage IV, decreased from 46% to 27% during 2005–2007 but remained constant at more than 33% during the period between 2007 and 2009. Globally, it is estimated that only 47% (range: 44%–50%) of adults and children in low- and middle-income countries who were eligible for ART for their own health have access to such treatment. Thus, there is a huge need for the expansion of ART access to those who need ART for their own health (at CD4+ count < 350 cells/µL) and for prevention of transmission to others, the latter a benefit of treatment not appreciated in this population. Importantly, data from 1 discordant couples study demonstrated that the risk of HIV transmission follows a gradient with HIV-infected individuals with lower CD4+ counts at higher risk of transmission to their sexual partner. Indeed, it is important to note that the weight of evidence in support of TasP from ecological and observational studies is based largely on the effect of ART initiation at lower CD4+ counts, ie, when the HIV-infected partner was eligible for ART based on their own health needs, as indicated earlier (Table 1). In only 2 discordant couples studies, an observational study and HPTN 052, was ART initiated in HIV-infected individuals for the purpose of HIV prevention, ie, when the HIV-infected partners were not yet eligible for ART for their own health. Similarly, the evidence in support of the effect of ART use on HIV incidence is derived from use of ART in HIV-infected individuals with low CD4+ count.

**TasP: AN UNLIKELY PANACEA**

Enthusiasm for TasP must be tempered by acknowledging that it is not a panacea but rather its success is dependent on a multiplicity of other complementary and necessary interventions. Behavioral, biomedical, and structural interventions are required to ensure that various components of the HIV care cascade are optimized to achieve the ultimate goal of TasP. Achieving higher coverage with ART for those in need will require expansion of HIV testing, using innovative approaches such as provider-initiated testing and counseling, household testing, and community-focused approaches. It will also require attention to maximize every step of the HIV care cascade from linkage of those found to be HIV positive to retention in care, prompt determination of ART eligibility, and initiation of ART with provision of adherence support. Without attention to the HIV care cascade, the promise of TasP as an intervention for both HIV treatment and HIV prevention will fail to be realized (Figure 1). Two meta-analyses from sub-Saharan Africa demonstrated that less than a third of persons testing HIV positive remain in care until ART initiation. Results are similar in the United States, where 19%–29% of persons with HIV infection are estimated to achieve viral load suppression.

In reality, it may be difficult to achieve the magnitude of coverage with ART for all individuals with HIV in a community as presumed in many of the modeling studies, supporting the need for other HIV and TB prevention interventions. As noted in Figure 1, HIV testing is the foundation of all prevention interventions. Although, for those individuals found to be HIV infected, TasP is an important prevention intervention when combined with supportive interventions, those found
### TABLE 1. Summary of Cited Studies of ART for Prevention of HIV Transmission

<table>
<thead>
<tr>
<th>Author of Study</th>
<th>Type of Study</th>
<th>Population</th>
<th>Location</th>
<th>Criteria for ART Use</th>
<th>Effect of ART</th>
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<tbody>
<tr>
<td>Porco et al</td>
<td>Ecological</td>
<td>Largely MSM</td>
<td>San Francisco, United States</td>
<td>Prevailing guidelines&lt;sup&gt;80&lt;/sup&gt; Study period: 1994–1999 -1994–1998: Provider opinion -1998–1989: CD4 &lt; 500, symptomatic disease</td>
<td>Estimated 60% decline in HIV infectivity from 0.120 before widespread use of ART to 0.048 after widespread use of ART (&lt;i&gt;P&lt;/i&gt; = 0.028)</td>
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<tr>
<td>Lu et al</td>
<td>Observational</td>
<td>Discordant couples (N = 1,927)</td>
<td>China</td>
<td>Prevailing guidelines&lt;sup&gt;86&lt;/sup&gt; Study period: 2006–2008 2006–2008: CD4 &lt; 200, symptomatic disease</td>
<td>No statistically significant difference in seroconversion rates between couples in whom the index partner was on ART (4.8%) and couples in whom index partner was not on ART (&lt;i&gt;3.2%; P&lt;/i&gt; = 0.12)</td>
</tr>
<tr>
<td>Sullivan et al</td>
<td>Observational</td>
<td>Discordant couples (N = 2,993)</td>
<td>Rwanda, Zambia</td>
<td>Prevailing guidelines&lt;sup&gt;86&lt;/sup&gt; Study period: 2002–2008 CD4 &lt; 200 or WHO Stage III/IV</td>
<td>Eight linked seroconversions among 647 couples where index partner was taking ART as compared with 171 seroconversions in 6062 couples where index partner was not taking ART (RR 0.32, 95% CI: 0.14 to 0.73)</td>
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to be HIV-uninfected should also be candidates for HIV prevention interventions. They need to be linked to appropriate prevention interventions such as voluntary medical male circumcision (VMMC) and preexposure prophylaxis (PrEP), with ongoing counseling and adherence support, as needed, and repeat HIV testing. Despite substantial evidence in support of the efficacy of VMMC for prevention of HIV transmission,63–65 its implementation and scale-up has been suboptimal in some

### TABLE 1. (Continued) Summary of Cited Studies of ART for Prevention of HIV Transmission

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| Del Romero et al17  | Observational | Discordant couples (N = 424) | Spain    | Prevailing guidelines41,63-65  
-1998–1999: CD4 < 500, symptomatic disease  
-2008–2009: CD4 < 350, symptomatic disease | No HIV conversions in 144 couples where the index partner was taking combination ART as compared with 5 seroconversions in 341 couples where the index partner was not taking ART |
| Melo et al18        | Observational | Discordant couples (N = 93) | Brazil   | Study period: 2000–2006  
33 cases where index partner on ART for pregnancy  
8 cases where index partner on ART for CD4 < 350 cells/μL | No seroconversions among couples in whom index partner was on ART as compared with 6 seroconversions in 52 couples where index partner was not on ART (incidence 6.45; 95% CI: 2.65 to 12.93) |
Chinese national treatment criteria  
-2003–2008: CD4 < 200 or WHO Stage III/IV  
-2008–2011: CD4 < 350 | 26% relative risk reduction in HIV transmission (adjusted HR 0.74, 95% CI: 0.65 to 0.84) in couples with the index partner on ART |
CD4 > 250 and at the time of study did not meet national guidelines for ART | 92% reduction in HIV transmission in couples in whom the index partner was on ART (adjusted incidence rate ratio 0.08, 95% CI: 0.00 to 0.57, P = 0.004). |
| Cohen et al, HTPN 0521 | Randomized controlled trial | Discordant couples (N = 1,763) | African countries, Brazil, India, Thailand, United States | Study Period: 2007–2010  
-Early initiation: CD4 350–550  
-Delayed initiation: CD4 200–250 | 96% reduction in linked transmissions 89% reduction in all transmissions |

### FIGURE 1. Cascade for comprehensive prevention strategies for individuals with and without HIV infection.
settings. Availability of new nonoperative methods for male circumcision that do not require anesthesia and can be performed by nurses holds great promise. A recent study demonstrated that expansion of VMMC is cost effective and may have a substantial effect on decreasing the number of new HIV infections in the short term, with TasP demonstrating substantial effect in the long term. PrEP using antiretroviral drugs in HIV-uninfected individuals is also a promising intervention shown to be efficacious in several studies, whereas conflicting results have been noted in other studies where adherence with PrEP was compromised. That a significant proportion of transmissions in couples in HPTN 052 and other discordant couple studies were unlinked highlights the potential importance of PrEP if monogamy among couples is not assured. PrEP may also be appropriate for individuals at high risk who are unaware of their partner’s HIV status or in settings where an HIV-infected partner is unwilling or unable to take ART for prevention.

Enthusiasm for the potential effect of ART on TB incidence should not divert resources from other TB control strategies, including the “three I’s,” ie, intensified case finding, IPT, and infection control, in addition assuring provision of directly observed therapy for those diagnosed with TB. A comprehensive public health approach that includes these strategies is needed to control the TB epidemic, particularly among HIV-infected individuals. HIV-infected individuals on ART remain at an increased risk for TB when compared with HIV-uninfected individuals, even when their CD4+ counts are high. With the increase in survival associated with ART, the lifetime risk of TB in HIV-infected persons in the absence of other interventions is likely to remain high. IPT and ART prevent TB via complementary mechanisms, and evidence supports an additive protective benefit from concomitant IPT use among individuals on ART. To provide IPT safely, it must be implemented in the context of intensified case finding, to prevent the development of drug resistance from inadvertently prescribing monotherapy to individuals with undiagnosed TB. Implementation of infection control measures is also essential to prevent nosocomial transmission of TB in health care settings where ART is provided.

**RESEARCH GAPS**

There is an urgent need for empiric data to evaluate the effectiveness of TasP at a population level. Two studies are planned to address this question, the HPTN 071 (PopART) Study in South Africa and Zambia and the Mochudi Study in Botswana. In addition, there is a paucity of data regarding whether ART use will be an efficacious intervention for prevention of HIV transmission in key populations, particularly among men who have sex with men and injection drug users.

There is also an urgent need to obtain empiric data to assess the potential benefits and risks associated with use of ART for individuals at higher CD4+ counts, who are largely the target group of current considerations for TasP. Few data exist with regard to this issue in patients with CD4+ count >350 cell/μL from resource-limited settings, supporting the need for clinical trials to inform this question. The ongoing START study is aiming to address this question largely in developed countries, whereas the TEMPRANO study in Cote d’Ivoire (ANRS12136) may provide some insights on this question. However, neither study will provide definitive answers to the question of the benefits and risks of early versus deferred ART in terms of key outcomes including mortality, TB incidence, and hospitalizations in resource-limited countries.

There is the need for implementation research that aims at examining the “how” with regard to implementation of TasP and its scale-up, if found to be effective at population level.

**CONCLUSIONS**

Expanded use of ART holds great promise for saving lives and enhancing the health and well being of persons living with HIV and for the prevention of HIV and TB. The evidence for TasP should serve to further energize efforts to reach all those who need ART for their own health as an important priority. Aspiration for TasP should not distract attention from the quality of HIV programming, the effectiveness of the HIV care cascade, and the need for inclusion of other HIV prevention interventions and other TB prevention measures.

Important questions that remain to be answered include which population to prioritize, what other interventions to use, how to integrate TasP in the health system, how best to use ART for the benefit of individuals and society, and how to measure its effectiveness and impact at population level.

**REFERENCES**


67. Mutabazi V, Kaplan SA, Rwamasirabo E, et al. One arm, open label, prospective, cohort field study to assess the safety and efficacy of the PrePex device for scale up of non-surgical circumcision when performed by nurses in resource limited settings for HIV prevention. J Acquir Immune Defic Syndr. 2013 [Epub ahead of print].
69. Marrazzo J, Ramjee G, Nair G, et al.; and the VOICE Study Team. Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine, or vaginal tenofovir gel in the VOICE Study (MTN 003), Abstract 26LB. Paper presented at; Conference on Retroviruses and Opportunistic Infections; 2013; Atlanta, GA.