Prevention of HIV Transmission and the HPTN 052 Study

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Abstract

The HIV Prevention Trials Network 052 study (HPTN 052) was a clinical trial designed to determine whether early treatment for HIV infection prevented transmission of the virus in couples where one partner was infected with HIV and the other was not, referred to as HIV serodiscordant or serodifferent couples. The study enrolled 1,763 couples at 13 sites in 9 countries in Asia, Africa, and the Americas. HPTN 052 demonstrated a minimum of 96% reduction of HIV in heterosexual couples ascribed to antiretroviral treatment; early treatment of HIV significantly reduced other infections in the HIV-infected subjects. This study, in conjunction with similar research, led to significant changes in international HIV treatment guidelines and the concept of treatment as prevention (TasP). This article provides the scientific background and history of how HPTN 052 came into being, the challenges it faced, and the ultimate impact it had on the fields of HIV treatment and prevention.

INTRODUCTION

In December 2011, the HIV Prevention Trials Network 052 study (HPTN 052) was named by *Science Magazine* as the Breakthrough of the Year (1). HPTN 052 was a multinational randomized controlled clinical trial designed to determine whether early treatment for HIV infection prevented transmission in HIV serodiscordant couples (2, 3). Why were the results of this study deemed of such global importance? The purpose of this article is to provide the history, results, and implications of the HPTN 052 study.

A Brief History of the HIV Pandemic

In 1981, the report (4) of a cluster of cases of pneumocystis pneumonia in men who have sex with men (MSM) served as the harbinger of a new, fatal, and sexually transmitted infection (STI), which ultimately became known as acquired immunodeficiency syndrome (AIDS). People with hemophilia suffered from the same illness (5, 6), demonstrating contamination of blood and blood products with an infectious agent that was ultimately proven to be human immunodeficiency virus (HIV). The spread of HIV caused great fear, and it was only gradually recognized that the virus was transmitted only by sex, through blood and blood products, and from mother to child. Transmission of HIV was found to be highly variable and generally inefficient (7–9). Infection with HIV proved to be rapidly fatal until the discovery that the antiviral agent azidothymidine (AZT) could stop viral replication and reduce mortality (10, 11). The discovery that AZT could treat HIV infection launched decades of development of ever better treatment (12). Today, HIV-infected patients have a manageable chronic disease and a near normal lifespan (13).

Evidence That Treatment of Infection Might Reduce HIV Transmission

What might be the effects of treatment of HIV on transmission? This idea was first examined in a study where HIV-infected women were treated with AZT to prevent mother-to-child transmission of HIV (14). In this placebo-controlled trial, AZT was shown to reduce HIV transmission by 67.5% compared to a placebo.

The effects of antiviral treatment on sexual transmission were more complex. HIV can be readily detected in genital secretions, but the virus is not eliminated by treatment (15). Different antiviral agents concentrate in male and female genital secretions with considerable variability (16). In addition, since the genital tract is susceptible to other STIs, which amplify transmission of HIV (17), the breakthrough shedding of HIV in semen during antiretroviral therapy (ART) with a secondary STI attracted attention (18).

These concerns notwithstanding, we and others explored the effects of ART on HIV transmission, and thus the idea of treatment for prevention of HIV was launched (19). This idea was galvanized by better and safer ART and several critical observational studies. In 2000, Quinn et al. (20) reported a direct relationship between the concentration of HIV in blood and sexual transmission. Later, Baeten et al. (21) were able to link the concentration of HIV in genital secretions with the probability of HIV transmission. These results suggested that reduced replication of HIV with ART could limit HIV transmission. Using observational data, Musicco et al. (22) reported that AZT treatment reduced HIV transmission to a sexual partner by 50%, and a series of other observational studies supported this result (23).

In aggregate, these early results suggested that treatment of HIV could be expected to reduce transmission, but surprisingly this strategy received virtually no attention. By 1996, highly active antiretroviral therapy (HAART), also called triple-drug ART (24, 25), was developed to reduce resistance observed when AZT was used alone. ART was generally withheld until some depletion

of CD4 cell count (but before irreparable damage to the immune system) because of the belief that earlier treatment of infection had limited benefit relative to toxicity-related side effects and greater risk of resistance (26). It should be noted, however, that Ho argued for earlier treatment in an editorial entitled "Time to Hit HIV, Early and Hard" (27).

Further complicating progress, it was widely believed that ART could not be delivered to people in resource-limited countries, particularly in Africa (28, 29), although sub-Saharan Africa was (and remains) the epicenter of the epidemic. In response, the XIIIth International AIDS Conference, held in 2000 in Durban, South Africa, was themed "Break the Silence" and called for the urgent need for equal access to treatment and care for HIV/AIDS. Still, there was a long road ahead, and the route to an ethical and practical clinical trial to determine the magnitude and benefits of "treatment as prevention" was not apparent.

THE HPTN 052 STUDY

The HPTN 052 study was designed to determine the effects of ART on HIV transmission and to measure the magnitude and durability of any observed transmission reduction. HPTN 052 faced several study design issues. First, the design had to consider the timing of the initiation of treatment (26); de facto, the potential public health benefit of earlier ART might be at odds with earlier treatment believed to be unnecessary and perhaps even harmful to the health of the infected person. In addition, although numerous antiretroviral agents were becoming available (at least in the United States and Western Europe), the best combination for initial treatment might not be the best combination for prevention, since clinically effective antiretroviral drugs demonstrated differential penetration into the male and female genital tract (16). Perhaps most important, how could the study of HIV transmission be conducted in an ethical manner?

In order to study the prevention of HIV transmission, we perceived the need to recruit sexually active serodiscordant couples, in which only one partner was HIV infected. But it was widely believed that a person infected with HIV had likely already transmitted the virus to their partner at the time of detection of infection, such that identification of serodiscordant couples would be difficult. Only later was it demonstrated that detection of serodiscordant couples is common (30) and, accordingly, that the prevention of HIV transmission within such couples is a critical goal (31). It was also suspected that an exposed partner who remained uninfected might have special defenses against infection (32), limiting HIV transmission events in a clinical trial. Another difficulty was that every HIV transmission event within a clinical study of serodiscordant couples represented failure to prevent infection through the standard of care, suggesting a potential conflict of interest, since transmission events in a placebo or control group were required to show benefit of a new intervention.

Meeting HPTN 052 Challenges

Ultimately, it was decided that the best way to approach the problems in study design was to include prospective consideration of all potential challenges. While the study would focus on prevention of HIV transmission, it would also measure the effects of ART on the health of the HIV-infected sexual partner (the index participant) as a coprimary endpoint. The study was designed to assess the possibility that the earlier ART required for prevention of HIV transmission would improve treatment outcomes by reducing opportunistic infections and other clinical complications. The availability of HIV-serodiscordant couples meeting the required eligibility criteria in a study would be determined through the recruitment process itself. The required provision of extensive prospective couples counseling (31) was expected to reduce HIV transmission events irrespective of any benefit of ART, a benefit that was carefully considered in the statistical analysis plan.

In light of all these challenges, the HPTN 052 study required a pilot component. In the pilot, HIV-serodiscordant couples were recruited in six countries (the United States, Brazil, South Africa, Malawi, India, and Thailand). In the original study design, the index participant was recruited with a blood CD4 cell count (as a surrogate for the need for treatment) of 300–500 cells/mm^3. One group of participants—the early treatment group—was to be treated at CD4 cell counts higher than what was then the standard of care, allowing for assessment of the effect of earlier ART both on the index participant's health and on transmission of the virus to his or her HIV-uninfected sexual partner. Participants in the control or delayed group would receive ART before their CD4 cell count fell below 200 cells/mm^3, when opportunistic infections would become a greater risk. In addition, couples were counseled together using an HPTN 052–specific script that emphasized the importance of relationship fidelity and condom use. We expected to reduce HIV transmission to a level about half that anticipated from an earlier observational study (20).

Initially, ART included Combivir® (lamivudine/zidovudine), atazanavir, efavirenz, nevirapine, tenofovir, lamivudine, didanosine, and stavudine. Enrollment of 82 HIV-serodiscordant couples into the pilot component took place between April 2005 and October 2006. But in order to proceed beyond the pilot and into a full study, we had to secure the donation of additional drugs approved by the US Food and Drug Administration (FDA), including Kaletra®/Aluvia® (lopinavir/ritonavir) and Truvada® (emtricitabine/tenofovir), in order to provide more options for secondary and tertiary regimens. Based on the success of the pilot, enrollment into the full study began in June 2007 and was completed in May 2010 (2).

HPTN 052 and Equipoise

Any clinical trial may only continue if the questions raised remain worth addressing and are not compromised by new knowledge related to benefit or risk (33). Under these conditions, the study is said to be in equipoise. In addition, the clinical management of study participants infected with HIV had to follow dynamic guidelines issued by major organizations [e.g., the World Health Organization (WHO)] or participating country guidelines. For HPTN 052, one of the challenges was the need for a change in thinking about when to start ART (34). When the study started, local investigational review boards and ethics committees questioned the dangers of providing ART to people with higher CD4 cell counts (before CD4 cell count fell below 200 cells/mm^3). As the study progressed, the WHO and some countries where the study was taking place changed their guidelines to recommend ART at higher CD4 cell counts, which led to a critical change in study enrollment criteria (34). In November 2006, after the pilot component was complete, but before enrollment into the full study began, the CD4 cell count inclusion criterion was increased by 50 cells/mm^3 in each arm, where the early treatment arm was revised to 350–550 cells/mm^3 (**Figure 1**), and the delayed treatment arm to 200–250 cells/mm^3. When an index participant's CD4 cell count fell below 250 cells/mm^3, a second measurement was made. Ultimately, the median CD4 cell count for ART initiation in the delay arm was 230 cells/mm^3 (35).

The most serious challenge to the integrity of HPTN 052 surfaced in July 2010, when researchers working in Haiti indicated that they had proven the benefit of early ART (36). Such a report might have breached the equipoise that allowed HPTN 052 to continue because it might no longer have been ethical to delay ART in the control group. A special meeting of the study's data and safety monitoring board (DSMB) was arranged to review the Haitian study results. Ultimately, the DSMB overseeing HPTN 052 recommended that the study continue with no modifications, as it was recognized that the majority of participants in the Haiti study experienced serious opportunistic infections at a CD4 cell count lower than the level being explored in HPTN 052 and that the results did not address the benefits of starting ART at much higher CD4 cell

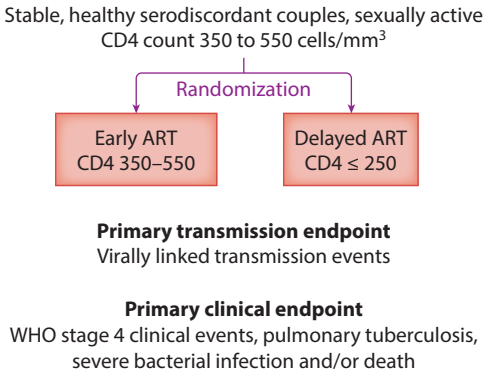

Figure 1

HPTN 052 study design. The study randomized people with HIV infection to an "early" group where ART was initiated at higher CD4 counts and a "delayed" group where ART was initiated at a CD4 count and clinical status consistent with the country standard of care. The primary endpoints of the study included evaluation of potential reduction of transmission of HIV and opportunistic infections resulting from ART. Abbreviations: ART, antiretroviral therapy; HPTN, HIV Prevention Trials Network; WHO, World Health Organization.

counts, a primary goal of HPTN 052. This outcome emphasizes the critical importance of the DSMB in clinical trials (34).

The Critical Role of Molecular Virology

Proving that ART prevented HIV transmission within a serodiscordant couple would be impossible without the ability to reliably identify the source of infection, as the sexual partner in a couple could acquire HIV from a steady partner or from another partner. To determine the source of infection, a sensitive assay linking viral isolates from each member of a serodiscordant couple was required. Eshleman et al. (37) used conventional pol gene sequences and deep sequencing to evaluate the relationship between the HIV variants. In addition, sequence results were submitted to an independent committee of virologists as well as a statistician to confirm the interpretation of the results. Ultimately, HIV transmission results and viral linkage results were concomitantly presented as part of the closed report submitted to the study's DSMB. Parenthetically, it should be noted that methods to understand linkage of HIV in couples and the direction of HIV transmission have continued to improve (38, 39).

HPTN 052 Interim and Final Results

The blinded safety and primary endpoint results of the HPTN 052 study were reviewed by the DSMB every six months. On April 28, 2011, after a routine closed meeting, the DSMB recommended that the interim results of the study be made public. What had the data shown that led to this recommendation?

Ultimately, 1,763 subjects were enrolled at 13 sites in nine countries (**Figure 2**). At the time of the interim analysis in 2011, 39 partners had acquired HIV. Among 28 virally linked transmissions (i.e., the virus was verified to have been transmitted within the couple), only one was found in the early treatment arm, and 27 were found in the delayed arm. This demonstrated that ART plus the couples counseling and STI treatment prevention package provided to couples led to 96% reduction in HIV transmission (2), an overwhelming benefit found in the early treatment arm.

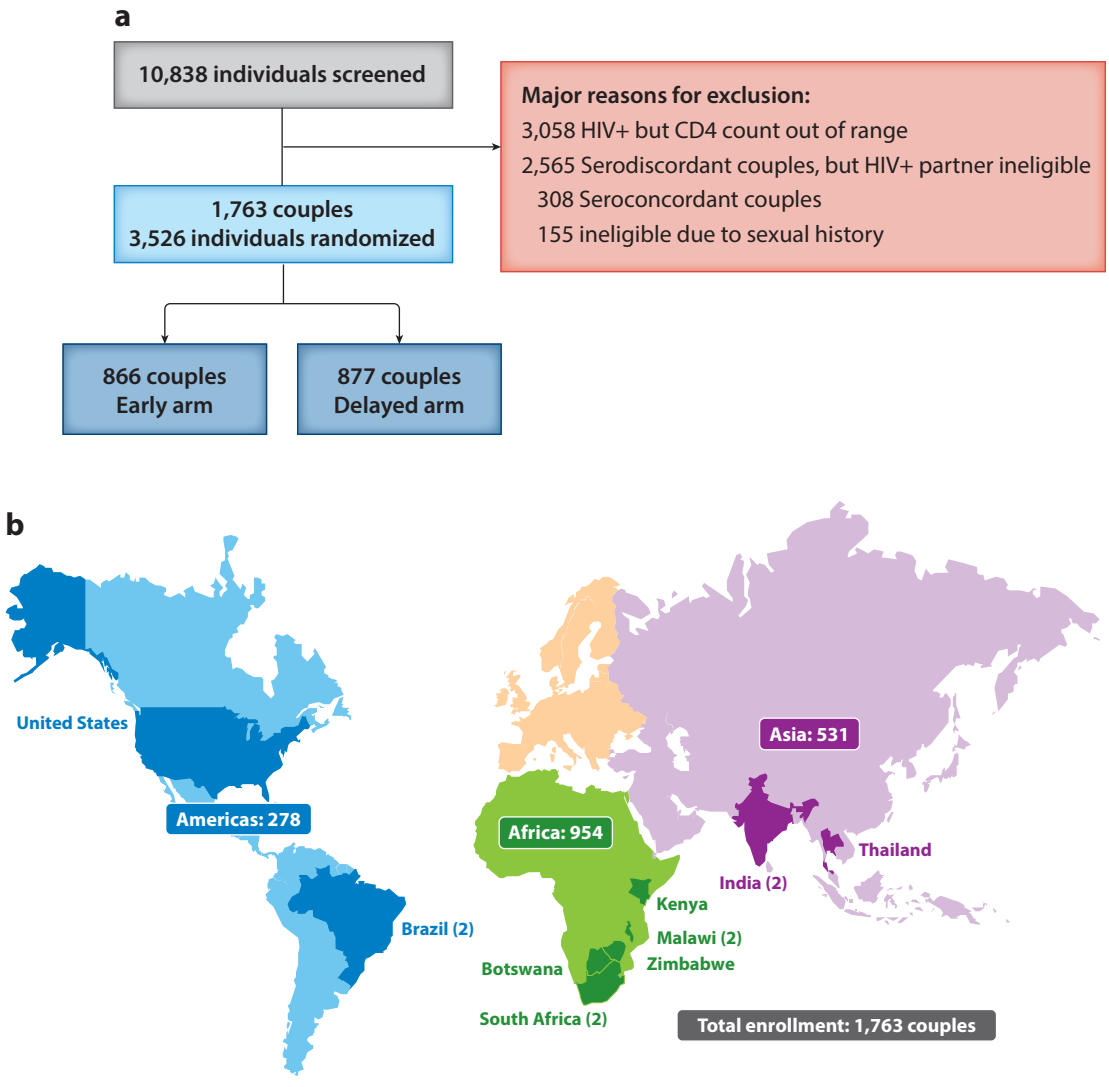

Figure 2

(*a*) HPTN 052 screening and enrollment. We screened more than 10,000 people with HIV infection and identified 1,763 people whose clinical status made them eligible for the HIV Prevention Trials Network (HPTN) 052 trial, and who had an HIV-negative sexual partner who was also willing to participate as part of a serodiscordant/serodifferent couple. (*b*) Geographic location of HPTN 052 participants. The couples were recruited from 13 sites in 9 countries in Asia, Africa, and South America.

Through further analysis, we determined that the single transmission event in the early treatment arm likely occurred shortly after enrollment in the trial, before viral suppression could be achieved (40). The seven unlinked transmission events indicated that condomless sex was taking place outside of the primary relationship, despite the couples risk reduction counseling provided by the study. However, the overall HIV incidence rate at the time of the interim results in the delayed ART arm was 2.2 per 100 person-years of follow-up, far below the anticipated incidence rate of approximately 12 per 100 person-years (20), emphasizing the impact of couples counseling in this study.

There were also substantial improvements in the health of those who received earlier HIV treatment (35). Primary clinical events (WHO stage 4 HIV disease, tuberculosis, severe bacterial infections, serious cardiovascular or vascular disease, serious liver disease, end-stage renal disease, new-onset diabetes mellitus, and non-AIDS malignant disease) occurred in 57 participants in the early treatment arm compared to 77 participants in the delayed treatment arm [hazard ratio (HR) = 0.73, 95% confidence interval (CI) 0.52–1.03, $p = 0.074$], demonstrating the protective effect of early ART initiation. Significantly more primary and secondary clinical events occurred in the delayed treatment arm than in the early treatment arm (29.2 versus 24.9 per 100 person-years, $p = 0.02$). Following ART initiation, the median CD4 cell count increased by 225 cells/mm^3 in the early treatment arm and by 246 cells/mm^3 in the delayed treatment arm (in response to initiation of ART after 2011). In addition, the absolute CD4 counts in the early treatment arm remained consistently higher than those in the delayed treatment arm (35), emphasizing the personal benefit of earlier ART.

The interim results were made public in a press conference held on May 11, 2011, approximately two weeks after the DSMB made their recommendation, demonstrating the urgency of public awareness of these important results. The interim results were presented at the sixth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention in Rome, Italy, in July 2011, and simultaneously published in the *New England Journal of Medicine* (2). Because the statistical plan assumed all participants would ultimately be treated, the study continued, and all those not already on ART were invited to initiate treatment. Within a year of the public release of the interim results, 83% of index participants in the delayed arm were receiving ART, and by the end of the study (May 2015), this percentage had increased to 96% (3).

Over the entire study, a total of 78 HIV transmission events took place (46 linked, 26 unlinked, and 6 with unknown linkage status). Of the linked HIV transmissions, three occurred in the early treatment arm and 43 in the delayed treatment arm, indicating a final 93% transmission reduction overall due to early ART initiation (HR = 0.07; 95% CI, 0.02–0.22). There were eight linked transmission events diagnosed after the index participant started ART (three in the early treatment arm and five in the delayed treatment arm). In four cases, the partner was diagnosed with HIV infection shortly after the index participant started ART; in these cases, partner infection most likely occurred before the index participant was virally suppressed. In the other four cases, partner infection occurred after the index participant failed ART. No linked infections were observed when the index participant was stably suppressed on ART (3).

Twenty-six unlinked transmission events (cases where the partner acquired HIV outside of the primary relationship) were documented, representing approximately 30% of the partner infections, a percentage similar to that found in another study of HIV-serodiscordant couples (41). The observed risk of unlinked infection was one for every 300 person-years of follow-up (3). The final results are shown in **Figures 3** and **4**.

FURTHER EVIDENCE OF THE BENEFITS ON HEALTH OF EARLY ANTIRETROVIRAL THERAPY

Treatment as prevention (TasP) allows the HIV-infected person an important chance for reduced stigma and personal health. The HPTN 052 study reported significant health benefit to the infected partner from earlier ART (35). The START (42) and Temperano (43) studies demonstrated health benefits from treatment of HIV at even higher CD4 counts (i.e., >500 CD4 cells/mm^3). In considering both personal and public health benefits observed in HPTN 052, Walensky et al. reported that earlier ART was "very cost-effective" (44). In aggregate, these studies led to the universal test and treat (UTT) strategy (45–47).

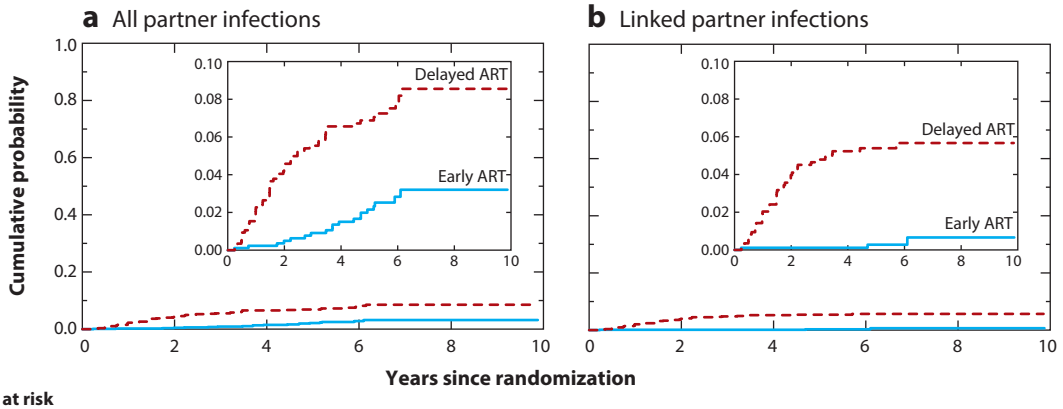

Figure 3

Cumulative probabilities (Kaplan-Meier estimates) of all partner infections (*a*) and virally linked partner infections (*b*). The insets show the same data on an expanded y axis. Results represent 10,131 person-years of index case follow-up and 8,509 person-years of partner follow-up (3). Abbreviation: ART, antiretroviral therapy.

COMPLEMENTARY RESULTS FOR TREATMENT AS PREVENTION

While the HPTN 052 study demonstrated remarkable prevention benefit of ART, it focused on heterosexual couples. The PARTNER and PARTNER2 studies (48, 49) and the Opposites Attract study (50) demonstrated that ART also prevents HIV transmission in MSM couples, where

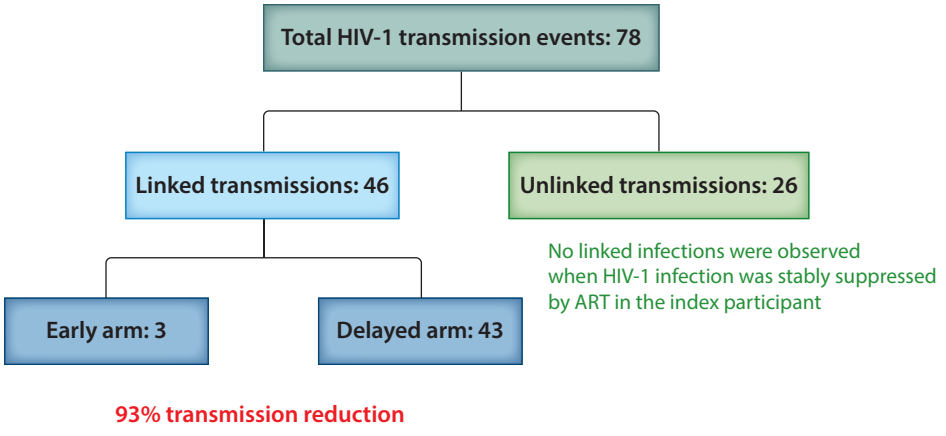

Figure 4

Final results of HPTN 052 with regard to HIV transmission events. A total of 78 HIV incident infections in HIV-negative partners were detected, but only 46 infections were linked by analysis of the virus to the HIV-infected partner. ART in combination with condoms, counseling, and treatment of sexually transmitted infections reduced the probability of HIV transmission (by intention-to-treat analysis) by 93% in the early arm of the study. Three HIV transmission events from people provided ART in the early arm of the study reflected failure of the drugs to suppress viral replication. No HIV transmissions were observed when viral replication was successfully prevented by ART. Abbreviations: ART, antiretroviral therapy; HPTN, HIV Prevention Trials Network.

condomless anal intercourse is the primary transmission risk factor. In the PARTNER study (48), Rodger et al. enrolled 1,166 serodiscordant couples at 75 sites in 14 European countries; 340 MSM couples were included. The authors observed no HIV transmission from ART-treated MSM index cases to their sexual partners, but the upper confidence limit of calculated risk from unprotected receptive anal intercourse with ejaculation was 2.70/100 couple-years of follow-up.

To further address this issue, Rodger and colleagues launched the PARTNER2 Study (49). From 2014 through 2017, the investigators continued recruitment of an additional 495 MSM couples. In the PARTNER2 study, 782 couples provided evaluable results over 1,593 couple-years of follow-up, including 76,088 self-reported episodes of condomless intercourse. The authors observed no episodes of HIV transmission from the infected person to their sexual partner. They concluded that the risk of HIV transmission from an HIV-infected man receiving ART with <200 copies/mm^3 of HIV in blood plasma over the preceding year was zero.

Bavinton et al. (50) studied HIV transmission in 358 serodiscordant MSM couples living in Brazil, Thailand, and Australia. The study accumulated data for 588.4 couple-years of follow-up. Durable suppression of HIV to <200 copies/mm^3 in blood plasma was achieved in $>75\%$ of the study subjects. The investigators detected no virally linked HIV transmission events in 16,800 episodes of reported anal intercourse.

TREATMENT AS PREVENTION COMPARED TO PRE-EXPOSURE PROPHYLAXIS

At approximately the same time the HPTN 052 interim results were presented, several studies exploring ART for pre-exposure prophylaxis (PrEP) for HIV-uninfected persons were completed (51–54). These studies, and others more recently (55, 56), demonstrated that the combination of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC, or Truvada) can prevent HIV acquisition when used reliably. The use of PrEP in serodiscordant couples is now primarily directed toward HIV-uninfected partners at higher risk of acquiring HIV (who are not in a monogamous relationship) or HIV-infected partners shortly after initiation of treatment, when viral suppression has not yet been accomplished (57). PrEP and TasP are often confused as they both involve ART, but they are complementary HIV prevention tools offering ART to people regardless of their HIV status; this is referred to as a status-neutral approach to HIV prevention.

THE LEGACY OF HPTN 052

The results of HPTN 052 led to almost immediate changes in global public policy and guidelines geared toward earlier and, in many countries, immediate treatment (58). These programs became known as test and treat, TasP, and UTT. The Joint United Nations Programme on HIV and AIDS launched the 90–90–90 campaign (59), which allowed a focus on the cascade of care (60) to maximize the treatment and prevention benefits of ART. More recently, activists have successfully launched the global U = U (undetectable = uninfectious) campaign to communicate the benefit of ART directly to the public (47). This campaign is designed to inspire HIV testing and the earliest possible treatment, as well as to reduce stigma.

Observational and interventional studies have focused on the benefits of TasP. Results from South Africa demonstrated a close relationship between increased access to ART and reduced incidence of HIV (61). However, community-based trials have had more difficulty in showing the benefits of ART (62–68), in part because of limits of study design and improving standards of care that made intervention benefits more difficult to observe. More recently, population-based public

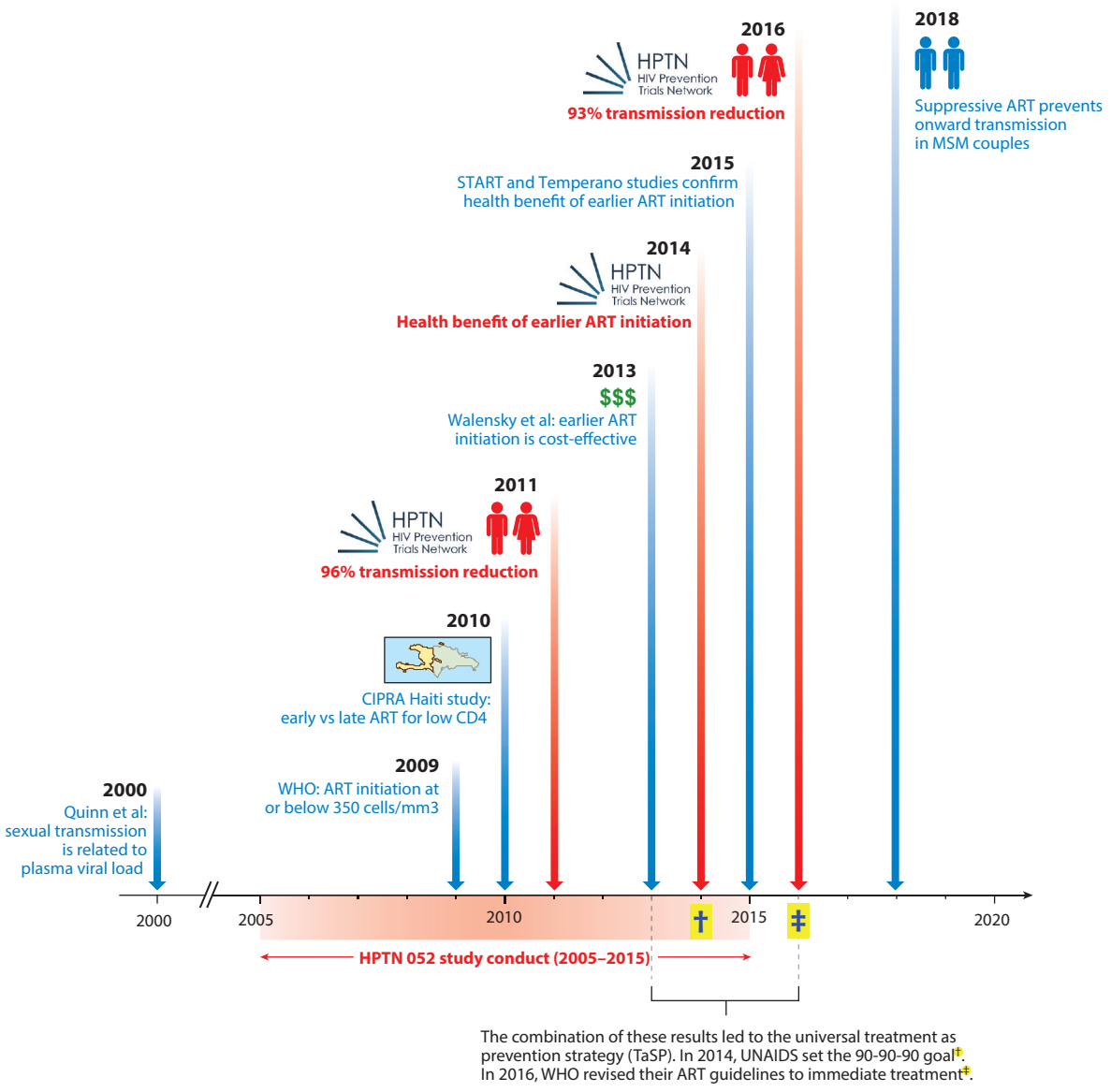

Figure 5

Timeline of HPTN 052 conduct and results, looking back at the past 20 years, when treatment as prevention has been the focus. After the relationship between blood viral load and transmission probability was established (20), it was logical to better understand the magnitude and durability of benefit from ART. HPTN 052 (2) and other studies provided unequivocal evidence for the treatment and prevention benefits of the earliest possible ART. Abbreviations: ART, antiretroviral therapy; CIPRA, Comprehensive International Program of Research on AIDS; HPTN, HIV Prevention Trials Network; MSM, men who have sex with men; UNAIDS, United Nations Programme on HIV and AIDS.

health studies have drawn a link between ART and reduced incidence of HIV (69). Denmark has reported the success in the 90–90–90 campaign (70). Mathematical modelers have highlighted strategies to better understand the results of observational and ecological studies and to maximize the benefits of TasP (70–72).

THE WAY FORWARD

Despite remarkable achievements over the last 30 years, HIV remains one of the biggest pandemics of the twenty-first century. While the infection inspires far less fear than it did 30 years ago, stigma (73, 74) and health disparities (75, 76) compromise the benefits of ART. Efforts toward HIV vaccine development (77), better and longer-lasting ART for treatment and prevention (78), broad neutralizing antibodies for treatment and prevention (79), and the cure of HIV (80) demonstrate sustained focus on dealing with HIV. The HPTN 052 study and its results represent a critical contribution toward the goal of ending AIDS and the HIV pandemic (**Figure 5**).

DISCLOSURE STATEMENT

M.S.C. acts in an advisory role for Merck and Gilead.

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