Published in final edited form as:
Lancet. 2010 June 12; 375(9731): 2092–2098. doi:10.1016/S0140-6736(10)60705-2.

Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis

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Abstract

Background—High plasma HIV-1 RNA concentrations are associated with increased risk of HIV-1 transmission. Initiation of antiretroviral therapy (ART) reduces plasma HIV-1 concentrations, but little empiric data are available on the rate of sexual HIV-1 transmission from persons receiving ART.

Methods—3381 African heterosexual HIV-1 serodiscordant couples were followed prospectively for up to 24 months. At enrollment, HIV-1 infected partners had CD4 counts ≥250 cells/mm^3 and

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Contributors

DD, JMB, and CC designed the study, and DD and KT performed the analysis. All investigators contributed to data collection and writing of the manuscript, and all approved the final draft; DD, JMB, and CC wrote the initial manuscript draft and vouch for the data, analysis, interpretation and manuscript submission.

Conflict of Interest:

JM and CC received research grant support from GlaxoSmithKline, which did not include salary support, and JM has received speaker fees from Abbott Laboratories.

did not meet country guidelines for ART initiation; during follow-up, CD4 counts were measured every 6 months and ART initiated following national guidelines. HIV-1 uninfected partners were tested for HIV-1 every 3 months. We compared genetically-linked HIV-1 transmission rates by ART initiation.

Results—349 (10%) HIV-1 infected partners initiated ART, at a median CD4 count of 198 cells/mm^3. Only one of 103 linked HIV-1 transmissions was observed from an HIV-1 infected partner who had initiated ART corresponding to HIV-1 transmission rates of 0.37 versus 2.24 per 100 person-years for those who had initiated versus not initiated ART, respectively (adjusted incidence rate ratio 0.08, 95% confidence interval 0.002–0.57, p=0.004). After ART initiation, plasma HIV-1 RNA concentrations decreased significantly (from median 4.88 to <2.38 $\log_{10}$ copies/mL, p<0.001) as did unprotected sex (6.2% of visits before to 3.7% of visits after ART initiation, p=0.03). Among those not on ART, the highest HIV-1 transmission rate (8.79 per 100 person-years) was from HIV-1 infected persons with CD4 counts <200 cells/mm^3. In couples in which the HIV-1 infected partner had a CD4 ≥200 cells/mm^3, 70% of transmissions occurred when plasma HIV-1 concentrations exceeded 50,000 copies/mL.

Conclusions—Among African heterosexual couples, ART initiation was followed by a 92% reduction in HIV-1 transmission risk, likely due to significantly reduced plasma HIV-1 levels, and was accompanied by increased self-reported condom use. The highest HIV-1 risk and greatest relative prevention benefit from ART was among couples in which the HIV-1 infected partner had CD4 counts <200 cells/mm^3 or plasma HIV-1 RNA concentrations >50,000 copies/mL.

Keywords

HAART; HIV-1 transmission; HIV-1 discordant couples

Introduction

The quantity of HIV-1 in plasma is a primary determinant of the risk of HIV-1 transmission.[1] Antiretroviral therapy (ART) reduces HIV-1 plasma concentrations to undetectable levels within 6 months of initiation in the majority of persons,[2, 3] and seminal and cervicovaginal HIV-1 concentrations are also reduced to undetectable levels in most persons on ART.[4–7] Use of peripartum ART is responsible for the remarkable success in virtually eliminating mother-to-child HIV-1 transmission in resource-rich settings.[8]

It has been hypothesized that the substantial reduction in the quantity of plasma and genital HIV-1 in persons initiating ART should translate into markedly reduced risk of HIV-1 transmission to sexual partners.[9] However, there is a paucity of empiric data on the rate of sexual HIV-1 transmission from persons receiving ART. A recent meta-analysis of data from five studies, some unpublished, found only five cases of HIV-1 transmission in 1098 person-years from HIV-1 infected persons receiving ART to sexual partners, consistent with an infection rate between 0.19 and 1.09 per 100 person-years.[10] Few studies have compared sexual behavior before and after ART initiation, an important behavioral consideration. In addition, it is unknown how evolving HIV-1 treatment guidelines, which currently recommend ART initiation at CD4 counts between 200 and 350 cells/mm^3,[11, 12] relate to HIV-1 transmission risk. Demonstration of HIV-1 transmission benefit for persons initiating ART at CD4 counts at or above current guidelines could provide even greater impetus to provide ART to populations as a prevention strategy for HIV-1 (e.g., the ‘Test and Treat’ concept), in addition to clinical benefits.

We examined ART use and HIV-1 transmission risk in a prospective study among 3381 African, heterosexual HIV-1 serodiscordant couples, as well as sexual risk and plasma

HIV-1 concentrations before and after ART initiation. In those not on ART, we measured HIV-1 transmission rates across a range of CD4 counts and plasma HIV-1 concentrations.

Methods

Population and Procedures

Between November 2004 and April 2007, 3408 HIV-1 seropositive persons who were also seropositive for herpes simplex virus type 2 (HSV-2) were enrolled in a randomized, double-blind, placebo-controlled, clinical trial of acyclovir HSV-2 suppressive therapy, along with their HIV-1 seronegative heterosexual partners.[13] The Partners in Prevention HSV/HIV Transmission Study was conducted at 14 sites in 7 African countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia). Couples were followed for up to 24 months and follow-up was completed in October 2008. As reported previously, acyclovir HSV-2 suppressive therapy failed to reduce HIV-1 transmission within the couples, although HIV-1 infected partners who were randomized to acyclovir experienced a 73% reduction in incident genital ulcer disease due to HSV-2, an average 0.25 $\log_{10}$ copies/mL reduction in HIV-1 plasma concentrations, and a 16% reduction in the risk of HIV-1 disease progression, defined as progression to CD4 count <200 cells/mm^3, ART initiation, or death.[13, 14]

Couples were eligible for the trial if they reported ≥3 episodes of vaginal intercourse during the three months prior to screening. At the time of enrollment, HIV-1 infected partners were ≥18 years of age, HIV-1 and HSV-2 seropositive, had a CD4 count ≥250 cells/mm^3 and no history of AIDS-defining conditions, and were not receiving ART. HIV-1 uninfected partners were ≥18 years of age and HIV-1 seronegative. HIV-1 infected partners were seen monthly for provision of study drug (acyclovir vs. placebo), evaluation of clinical status, and behavioral risk assessment. CD4 counts were assessed every six months, and plasma for HIV-1 RNA quantification was collected at baseline, at months 3, 6 and 12 and at the final study visit. HIV-1 uninfected partners were tested quarterly for HIV-1 seroconversion.

All participants received pre- and post-test HIV-1 counseling, risk reduction counseling (both individual and couple), free condoms, and treatment of sexually transmitted infections (STIs) according to WHO guidelines throughout the study period. The study protocol was approved by the University of Washington Human Subjects Review Committee and ethical review committees at the each of the collaborating organizations. All participants provided written informed consent.

ART initiation among HIV-1 infected partners

Only couples in which the HIV-1 infected partner was not eligible for ART according to national ART initiation guidelines were enrolled. At the time the study was conducted, national guidelines generally recommended ART initiation at CD4 counts less than 200–250 cells/mm^3 or in persons with clinical AIDS. HIV-1 infected persons who met national guidelines for initiation of ART during follow-up, as a result of CD4 decline or change in clinical status, were referred to local HIV-1 care clinics to start ART, and counseling and re-referral was done at subsequent visits for those who failed to initiate ART. HIV-1 infected women who became pregnant were referred to antenatal clinics for prevention of mother-to-child transmission services. At quarterly visits, participants were asked whether they had taken any antiretroviral medication at any time since the last quarterly visit; for those who had received ART, the number of days they had taken ART and the medications received were recorded. Participants who initiated ART continued in follow-up with repeat CD4, viral load and behavioral assessments until the maximum of 24 months of follow-up.

Laboratory analyses

HIV-1 serologic testing was by dual rapid HIV-1 antibody tests, with positive results confirmed by HIV-1 Western blot. For initially HIV-1 uninfected partners who seroconverted to HIV-1, analysis of HIV-1 *env* and *gag* gene sequences from both members of the couple was used to determine whether transmission was genetically linked within the partnership, as previously detailed.13 HSV-2 serostatus was determined by Western blot.[15] CD4 quantification was performed using standard flow cytometry by local laboratories who participated in external quality assurance. Plasma HIV-1 RNA quantity was tested in batch at the end of the study at the University of Washington using the COBAS TaqMan real-time HIV-1 RNA assay, version 1.0 (Roche Diagnostics, Indianapolis, IN), with a lower limit of quantification of 240 copies per mL. Laboratory technicians were blinded to randomization status (acyclovir or placebo) and ART use.

Data analysis

The aim of this post-hoc analysis was to assess the effect of ART use by HIV-1 infected partners on risk of HIV-1 transmission to their initially-HIV-1 seronegative partners. Twenty-seven couples in which the HIV-1 infected partner's baseline serology did not confirm both HIV-1 and HSV-2 infection were excluded.

The primary outcome measure was linked HIV-1 transmission – i.e., HIV-1 seroconversion in which viral sequence analysis determined HIV-1 transmission occurred within the study partnership. Participants who had a genetically unlinked HIV-1 transmission event (i.e., who acquired HIV-1 from someone outside the study partnership) contributed follow-up time until HIV-1 seroconversion and were censored thereafter.

The primary exposure was ART use by HIV-1 infected partners, analyzed as a time-dependent variable. As both HIV-1 serologic testing for HIV-1 seronegative partners and ART assessment for HIV-1 infected partners were performed quarterly, any quarter in which the HIV-1 infected partner reported any combination ART use was conservatively considered an 'ART exposed period' for the HIV-1 uninfected partner, regardless of the number of days in that quarter in which the HIV-1 infected partner received ART. Study quarters in which short-course, mono- or dual-agent ART was used during pregnancy by HIV-1 infected women for prevention of mother-to-child HIV-1 transmission were excluded from the analysis because of the limited duration and potency of the regimen. For HIV-1 infected partners who initiated combination ART during follow-up, ART use was conservatively carried forward (i.e. ongoing ART was assumed) regardless of whether they continued to report ART use at subsequent visits. ART exposure status for HIV-1 uninfected partners was considered unknown if their HIV-1 infected partners were lost to follow-up, and study quarters with unknown ART status were excluded from the analysis.

Exact Poisson regression methods were used to calculate the incidence rate ratio and confidence bounds for HIV-1 transmission among the initially HIV-1 seronegative partners, based on follow-up time in the study and whether or not ART was initiated by their HIV-1 infected partners. ART initiation was more common as the study progressed and more likely to be initiated at lower CD4 counts, and thus estimates of incidence rate ratios were adjusted for time on study and CD4 count (as above or below 200 cells/mm^3). Randomization group in the clinical trial (i.e., acyclovir or placebo) did not confound the relationship between ART and HIV-1 transmission risk and thus the risk estimates were not further adjusted for randomization arm. HIV-1 transmission risk was assessed both overall and in different CD4 count strata, with visits prior to ART initiation classified by the lowest prior CD4 count, and visits after ART initiation classified by the most recent CD4 count prior to ART, to mimic clinical decision-making about ART initiation based on CD4 count. We compared HIV-1

transmission rates from HIV-1 infected partners not on ART, stratified by CD4 count and plasma HIV-1 levels. In this analysis, strata for plasma HIV-1 RNA concentrations were defined by the highest prior concentration.

Sexual behavior was compared before versus after ART initiation for the HIV-1 infected persons who initiated ART during follow-up. Conditional logistic regression was used to model changes in any unprotected sex, and negative binomial regression with generalized estimating equations and robust error estimation to model number of sex acts. Both these models were adjusted for time since enrollment in the cohort, as sexual risk behaviors overall declined during the study period.[13] Plasma HIV-1 concentrations at the most recent visit prior to initiating ART and at the final study visit were compared using a paired t-test for those who initiated ART during follow-up. Plasma concentrations below the limit of quantification were set to 120 copies/mL (half the limit of quantification).

Data were analyzed using SAS version 9.20 and LogXact version 8.0.0.

Role of the Funding Source

The authors designed and executed the study, had full access to the raw data, performed all analyses, wrote the manuscript, and had final responsibility for the decision to submit for publication. The funder had no role in design, data collection, analysis, interpretation, or writing of the report.

Results

Population

A total of 3381 heterosexual HIV-1 serodiscordant couples were eligible for this analysis, 2284 (68%) in which the HIV-1 infected partner was female and 1097 (32%) in which the HIV-1 infected partner was male (Table 1). The duration of partnership was 4.6 years or longer for more than half of the couples. Median sexual frequency was 4 acts per month (IQR 2–8), and 29% of couples reported sex unprotected by condoms during the month prior to enrollment. Among HIV-1 infected participants at enrollment, the median CD4 count was 462 cells/mm^3 (interquartile range [IQR] 347–631) and median plasma HIV-1 RNA concentration was 4.1 $\log_{10}$ copies/mL (IQR 3.4–4.7). CD4 counts were lower (median 424 vs. 483 cells/mm^3, $p<0.0001$) and plasma HIV-1 RNA concentrations were higher (median 4.3 vs. 3.9 $\log_{10}$ copies/mL, $p<0.0001$) for HIV-1 infected men compared with HIV-1 infected women.

Follow-up and ART initiation

Of the 3381 HIV-1 uninfected persons in the study, 3321 (98%) completed at least one follow-up assessment of HIV-1 status, contributing 5016 person years of follow-up. Retention was high: 89% of HIV-1 uninfected partners were retained at 12 months and 84% at 24 months. Loss to follow-up of HIV-1 infected partners and quarters where ART was given for PMTCT resulted in exclusion of 186 (4%) person-years of follow-up.

ART was initiated by 349 (10%) HIV-1 infected participants, including 9% of women and 12% of men (Table 2). The most common ART regimen was stavudine, lamivudine, plus nevirapine (60.7%). Treatment was initiated a median of 13 months after study enrollment. The median CD4 count at ART initiation was 198 cells/mm^3, and was not different for men and women. Over half of those who initiated ART had CD4 counts less than 200 cells/mm^3 at the visit prior to ART initiation, while 33% had CD4 counts between 200 and 350 cells/mm^3, 15% had CD4 counts above 350 cells/mm^3. Eighteen (34%) of the 53 persons initiating ART at CD4 counts ≥350 cells/mm^3 began combination ART while pregnant. Of

the 349 HIV-1 infected persons who initiated ART, 45 (12.9%) later reported no ART use at a subsequent follow-up visit. HIV-1 susceptible partners were followed for a median of 8.2 months (IQR 3.9–12.3) after their HIV-1 infected partners initiated ART.

HIV-1 incidence and effect of ART on HIV-1 transmission risk

A total of 103 linked HIV-1 transmission events occurred during study follow-up where ART use was known (incidence 2.15 per 100 person-years). An additional 39 unlinked transmissions (HIV-1 transmissions from non-study partners) occurred during study follow-up (incidence 0.81 per 100 person-years). Of the 103 linked HIV-1 transmissions, 102 occurred in couples in which the HIV-1 infected partner had not yet initiated ART (incidence 2.24 per 100 person-years, Table 2). Only 1 HIV-1 transmission event was observed in 349 couples after the HIV-1 infected partners had initiated ART (incidence 0.37 per 100 person-years). In analysis adjusting for time since study enrollment and CD4 count strata, ART use by the HIV-1 infected partner was associated with a 92% reduction in risk of HIV-1 transmission, an effect that was statistically significant (adjusted incidence rate ratio [IRR] 0.08, 95% confidence interval [CI] 0.002–0.57, p=0.004).

The sole ART-exposed HIV-1 transmission event was a female-to-male transmission in which the HIV-1 infected female's CD4 count was 302 cells/mm^3 at enrollment and 201 cells/mm^3 at the 6 month study visit. At the 9 month study visit, she reported initiating ART 18 days earlier, and her male partner tested seronegative for HIV-1 (later testing of his archived plasma confirmed that he was HIV-1 RNA PCR negative at that time). Ninety days later, at the 12 month study visit, the male partner tested seropositive for HIV-1. The female partner's HIV-1 plasma viral load was 4.72 $\log_{10}$ copies/mL at the 6 month study visit (prior to ART initiation); at the 12 month study visit plasma viral load was undetectable (<240 copies/mL) and CD count was 637 cells/mm^3.

The rate of HIV-1 transmission from HIV-1 infected partners not receiving ART was highest for those with CD4 counts <200 cells/mm^3 (8.79 per 100 person-years), and was relatively similar across higher CD4 count strata: 2.79, 1.70, and 1.82 per 100 person-years for CD4 counts 200–349, 350–499, and ≥500 cells/mm^3, respectively, and there was no statistically significant difference in these rates (p=0.09). No HIV-1 transmissions were seen among couples in which the HIV-1 infected partner initiated ART at a CD4 count <200 cells/ mm^3; this lack of any transmissions in the CD4 <200 cells/mm^3 stratum on vs. not on ART was statistically significant (adjusted IRR 0, 95% CI 0–0.38, p=0.001). Combining CD4 strata ≥200 cells/mm^3, ART use was associated with reduced HIV-1 transmission risk, although the person-years of follow-up was limited in this strata and this effect was not statistically significant (adjusted IRR 0.55, 95% CI 0.01–3.24, p=0.93).

Plasma HIV-1 concentrations and sexual behavior after ART initiation

For HIV-1 infected participants who initiated ART, the median plasma HIV-1 concentration prior to ART initiation reduced from 4.88 to <2.38 $\log_{10}$ copies/mL (the limit of quantification) at the final study visit (p<0.001, n=344 participants who had both measurements), with 70% achieving virologic suppression at the final study visit. The median time from ART initiation to the final study visit at which plasma HIV-1 was measured was 7.3 months (IQR 3.4–12.1).

As previously detailed,[13] reports of high-risk sexual behavior in this cohort decreased substantially after study enrollment, with unprotected sex reported by HIV-1 infected partners at only 7% of all follow-up visits. Among those HIV-1 infected partners who initiated ART, the proportion of visits at which sex was unprotected by condoms decreased further after ART initiation, from 6.2% before ART to 3.7% of visits after ART (adjusted

OR=0.63, 95% CI 0.41–0.96, p=0.03), an effect that was similar for HIV-1 infected female and male participants. Notably, the mean number of sexual acts per month did not change significantly after compared to before ART initiation (p=0.6). Further adjustment for sexual activity unprotected by condoms did not appreciably change the estimate for the effect of ART on reducing HIV-1 transmission risk (IRR 0.088, 95% CI 0.002–0.61, p=0.005).

Increased HIV-1 transmission risk at high plasma HIV-1 concentrations with CD4 counts above 200 cells/mm^3

For HIV-1 infected partners with CD4 counts above 200 cells/mm^3, HIV-1 transmission risk was highest for those with plasma HIV-1 concentrations >50,000 copies/mL, regardless of whether their CD4 count was between 200 and 350 cells/mm^3 or was >350 cells/mm^3 (Table 3). In the 94 HIV-1 transmissions from HIV-1 infected partners who had CD4 counts >200 cells/mm^3 and who had not initiated ART, 66 (70.2%) occurred from those with plasma HIV-1 concentrations above 50,000 copies/mL, although they accounted for only 33.4% of person-time in follow-up.

Discussion

In this prospective study of almost 3400 heterosexual HIV-1 serodiscordant couples from 7 African countries, ART use by the HIV-1 infected partner was accompanied by a 92% reduction in the risk of HIV-1 transmission. An important strength of our study was phylogenetic linkage of HIV-1 transmissions within the study partnerships, which likely reduced misclassification of the source of HIV-1 transmission and improved the precision in the measurement of the effect of ART on HIV-1 risk. These observational data strongly support the hypothesis that ART substantially reduces HIV-1 infectiousness and transmission risk. We found that plasma HIV-1 RNA concentrations decreased significantly after ART initiation, likely serving as the mechanism by which ART reduced HIV-1 transmission risk, and we found a modest but statistically significant increase in condom use after ART was initiated. The magnitude of ART effect on HIV-1 transmission risk was greatest for persons with CD4 counts <200 cells/mm^3, emphasizing the potential synergy of ART for clinical and prevention benefits in persons whose CD4 counts have fallen to 200 cells/ mm^3.

Our results are highly consistent with the findings of a recent meta-analysis that estimated a 92% reduction in HIV-1 transmission risk as a result of ART, from 5.64 to 0.46 HIV-1 transmissions per 100 person-years.[10] Recent mathematical modeling studies have predicted that universal testing of HIV-1 serostatus and immediate initiation of ART (a strategy called “Test and Treat”) could dramatically reduce new HIV-1 transmissions on a population level. [16] To date, little empiric data have been available on the rate of HIV-1 transmission from persons receiving ART, and our findings provide valuable information for anticipating the degree of HIV-1 prevention benefit that might be achieved with ART over a two year time period.17

In our cohort, the highest rate of HIV-1 transmission occurred from persons with CD4 counts <200 cells/mm^3, and ART had the greatest absolute benefit in reducing HIV-1 transmission risk in this stratum. Less than 50% of persons worldwide with CD4 counts <200 cells/mm^3 are currently receiving ART.[18, 19] Our data emphasize that an HIV-1 transmission benefit would be achieved if coverage of ART was maximized for persons with CD4 counts <200 cells/mm^3. Moreover, HIV-1 transmissions were seen in our study across all strata of CD4 counts, including a relatively consistent rate of HIV-1 transmission (~2% per year) at CD4 counts >200 cells/mm^3. To our knowledge, this is the first study to suggest reduced HIV-1 transmission risk as a result of ART across different ranges of CD4 counts, which indicates that use of ART to dramatically reduce HIV-1 transmission will require

coverage of those with higher CD4 counts as well as those with CD4 counts <200 cells/mm^3. WHO recently recommended raising the threshold for ART initiation for HIV-1 treatment from CD4 counts of 200 cell/mm^3 to 350 cell/mm^3. [12] Our finding that 70% of the transmissions from HIV-1 infected partners who had CD4 counts >200 cells/mm^3 occurred from those who also had plasma HIV-1 concentrations >50,000 copies/mL suggests targeting HIV-1 infected individuals with high plasma HIV-1 concentrations could maximize the HIV-1 prevention benefits of ART. Development of inexpensive point of care tests for plasma HIV-1 concentrations could permit real-time plasma HIV-1 testing that might allow targeted ART provision to those who have higher CD4 counts and high plasma HIV-1 concentrations,[1, 20] given our and others' findings about the relationship of plasma HIV-1 levels to HIV-1 transmission risk.[21]

As with the recent meta-analysis of the effect of ART on HIV-1 transmission risk,[10] we found a low rate of HIV-1 transmission (<0.5% per year) after ART initiation. In the single HIV-1 transmission event we observed, HIV-1 transmission happened less than four months after ART was begun, and thus it is probable that transmission occurred prior to complete HIV-1 suppression as a result of ART. A 2008 statement from the Swiss Federal Commission for HIV/AIDS argued that HIV-1 infected persons with undetectable plasma and genital HIV-1 levels as a result of ART can be considered sexually non-infectious.[22, 23] Little is known about the time course of infectiousness for those who initiate ART, and durable suppression of both semen and blood HIV-1 levels is not achieved in a fraction of treated patients.[2, 6, 7] Mathematical modeling studies have found that if HIV-1 risk is low but non-zero in persons with suppressed HIV-1 levels, population-level increases in HIV-1 incidence could result if condom use declined among persons starting ART.[22] Our data reinforce the findings of others that ART initiation does not lead to increased sexual activity or decreased condom used in heterosexual couples.[17, 24–27] However, the follow-up time on ART in this study was short relative to the lifetime duration of ART that will be required of persons who start ART. It is essential to obtain reliable information about the comparative long-term transmission benefits and behavioral risks associated with ART, particularly ART initiated at higher CD4 levels. The US National Institutes of Health, through the HIV Prevention Trials Network, has an ongoing five-year clinical trial of ART initiation at CD4 counts between 350 and 550 cells/mm^2 (versus at <250 cells/mm^3), which will be invaluable for understanding the balance of long-term risks and benefits of ART for treatment and prevention.[28]

In this study, information on ART treatment initiation was obtained by self report, thus there is potential for misclassification of ART-exposed time, although the one case of HIV-1 transmission after ART initiation appeared to be truly in the context of ART use, given the change in plasma HIV-1 levels observed in the HIV-1 infected partner. Some study participants were unwilling to initiate ART in spite of repeated site staff efforts to link participants to treatment clinics, and thus we observed some follow-up time for participants with CD4 counts <200 cells/mm^3. We did not collect data on the reasons for ART initiation for those who started ART at CD4 counts >250 cells/mm^3, but approximately one-third occurred among pregnant women, potentially reflecting earlier ART initiation for prevention of mother-to-child HIV-1 transmission. We had limited numbers and follow-up for partners of those initiating ART at CD4 counts >250 cells/mm^3 so cannot reliably estimate the impact of ART on HIV-1 transmission in higher CD4 strata. We also did not have information on ART adherence, although we did see substantial declines in plasma HIV-1 RNA levels with 70% of persons with undetectable levels at a median of 7 months after ART initiation. All HIV-1 infected partners in this study were HSV-2 seropositive; however, HSV-2 is common among persons with HIV-1 worldwide (seroprevalence 50–90%), and thus this study entry requirement is unlikely to limit the generalizability of our findings.

We demonstrated a 92% reduction in HIV-1 transmission risk after initiation of ART in heterosexual African HIV-1 discordant couples. While this population level reduction in HIV-1 transmission is highly encouraging, on an individual basis, counseling needs to reinforce that a potential for HIV-1 transmission to partners remains after ART initiation. This cohort received frequent counseling during quarterly follow-up, and we observed no evidence of behavioral risk disinhibition after ART initiation. We found HIV-1 transmissions across the range of CD4 count strata, with most transmissions occurring from those who had low CD4 counts or high plasma HIV-1 concentrations. The greatest priority for ART provision for both HIV-1 treatment and prevention coincides in those with CD4 counts below 200 cells/mm^3. As countries strategize how to optimize resources to expand ART provision beyond individuals with low CD4 counts, targeting ART to those with high plasma HIV-1 concentrations could become a cost-effective strategy to maximize population-level reductions in HIV-1 transmission, as a step toward universal ART provision to all HIV-1 infected persons.

Acknowledgments

We gratefully acknowledge the invaluable contributions of the HIV-1 serodiscordant couples who participated in this study. We thank the teams at the study sites and at the University of Washington for work on data and sample collection and management. We acknowledge Dr. Renee Ridzon from the Bill & Melinda Gates Foundation for study oversight.

Funding: The Partners in Prevention HSV/HIV Transmission Study was funded by the Bill and Melinda Gates Foundation (grant ID #26469). HIV-1 RNA testing was also supported by a grant through the University of Washington Center for AIDS Research (UW CFAR, AI-27757) Clinical Retrovirology Core. Roche HIV-1 RNA quality assessment panels were obtained under the auspices of the UW AIDS Clinical Trials Group Virology Support Laboratory (ACTG VSL, AI-38858). Additional support provided by the US National Institutes of Health (National Institute of Allergy and Infectious Diseases grant R01 083034).

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Data management was provided by DF/Net Research, Inc. (Seattle, USA) and site laboratory oversight was provided by Contract Lab Services (University of the Witwatersrand, Johannesburg, South Africa).

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Table 1

Demographic, behavioral, and clinical characteristics at study enrollment

	Median (IQR) or number (%)	
	HIV-1 serodiscordant couples N=3381	
	HIV-1 infected partner	HIV-1 susceptible partner
Demographic characteristics		
Age, years	32 (26–38)	33 (28–40)
Education, years	8 (6–11)	8 (7–12)
Any monthly income	1218 (36.0%)	1652 (48.9%)
Female	2284 (67.6%)	1097 (32.4%)
Couple characteristics[1]		
East Africa (vs. southern Africa)	2230 (66.0%)	
Duration of partnership, years	4.6 (1.9–9.6)	
Number of sex acts, prior month	4 (2–8)	
Any unprotected sex acts, prior month	992 (29.3%)	
Clinical characteristics, HIV-1 infected partners		
CD4 count, cells/mm^3	462 (347–631)	--
Plasma HIV-1 viral load, log_{10} copies/mL	4.1 (3.4–4.7)	--
Randomized to acyclovir (vs. placebo)	1688 (49.9%)	--
Circumcised (men only)	371/1096 (33.9%)	--
Clinical characteristics, HIV-1 susceptible partners		
HSV-2 seropositive	3381 (100%)	2294 (67.9%)
Circumcised (men only)	--	1248/2284 (54.7%)

HSV-2, herpes simplex virus type 2; IQR, interquartile range

[1] Couple characteristics were from data collected from the HIV-1 infected partner

Table 2

Characteristics of ART initiation by the HIV-1 infected partners.

	Median (IQR) or number (%)	
Initiated ART	349/3381	(10%)
Female	215/2284	(9%)
Male	134/1097	(12%)
Medical characteristics at ART initiation, HIV-1 infected partners who initiated ART (N = 349)		
CD4 count, visit prior, cells/mm^3		
<200	103	(48%)
200–349	72	(33%)
350–500	17	(8%)
≥500	23	(11%)
Median CD4 count, visit prior, cells/mm^3	191	(161–265)
Study duration at ART initiation, months		
<6	23	(11%)
7–12	69	(32%)
13–18	78	(36%)
19–24	45	(21%)
Median study duration at ART initiation, months	13	(8–17)
Initial ART Regimen		
stavudine, lamivudine, nevirapine	212	(61%)
zidovidine, lamivudine, nevirapine	47	(14%)
protease inhibitor-containing regimen	11	(3%)
other	55	(16%)
insufficient information to determine full regimen	24	(7%)

Table 3

Antiretroviral therapy use and risk of HIV-1 transmission

	Follow-up time during which HIV-1 infected partner had not initiated antiretroviral therapy			Follow-up time after HIV-1 infected partner initiated antiretroviral therapy			Unadjusted Incidence Rate Ratio (95% CI)[1] *p-value*	Adjusted Incidence Rate Ratio (95% CI)[1] *p-value*
	HIV-1 transmissions	Person-Years of Follow-up	HIV-1 Incidence (95% CI)	HIV-1 transmissions	Person-Years of Follow-up	HIV-1 Incidence (95% CI)		
Overall	102	4558	2.24 (1.84–2.71)	1	273	0.37 (0.09–2.04)	0.17 (0.004, 0.94) *p=0.04*	0.08 (0.002, 0.57) *p=0.004*
By CD4 count[2]								
CD4 <200	8	91	8.79 (4.40–17.58)	0	132	0.00 (0.00–2.80)	0.0 (0.0, 0.40) *p=0.001*	0.0 (0.0, 0.38) *p=0.001*
CD4 200–349	41	1467	2.79 (2.06–3.80)	1	90	1.11 (0.27–6.19)	0.40 (0.01, 2.34) *p=0.58*	0.65 (0.02, 4.0)[3] *p=1.0*
CD4 350–499	24	1408	1.70 (1.14–2.54)	0	30	0.00 (0.00–12.30)	0.0 (0.0, 8.16) *p=1.0*	0.0 (0.0, 15)[3] *p=1.0*
CD4 ≥500	29	1592	1.82 (1.27–2.62)	0	21	0.00 (0.00–17.57)	0.0 (0.0, 10.29) *p=1.0*	0.0 (0.0, 15)[3] *p=1.0*

[1] All analyses adjusted for time since study enrollment and, for the overall analysis, CD4 count (as ≥ vs. <200 cells/mm^3).

[2] For follow-up prior to ART initiation, CD4 count was lowest prior value, for follow-up after ART initiation, CD4 count at the time of ART initiation was used.

[3] Combining CD4 strata ≥200 cells/mm^3, adjusted IRR 0.55, 95% CI 0.01–3.24, p=0.9.

Table 4

HIV-1 transmission rates by CD4 counts and plasma HIV-1 concentrations in couples in which the HIV-1 infected partner has not initiated antiretroviral therapy, those with CD4 counts >200 cells/mm^3

CD4 count (cells/mm^3)	Plasma HIV-1 concentrations (copies/mL)	HIV-1 transmissions	Person-years of follow-up	HIV-1 incidence (95% CI)	Proportion of HIV-1 transmissions[1]	Proportion of person-years[1]
200–349	>50,000	32	687	4.66 (3.19–6.58)	34%	15%
	10,000–50,000	8	413	1.94 (0.84,3.82)	9%	9%
	≤10,000	1	367	0.27 (0.01, 1.52)	1%	8%
≥350	>50,000	34	805	4.23 (2.93–5.90)	36%	18%
	10,000–50,000	9	887	1.02 (0.46, 1.93)	10%	20%
	≤10,000	10	1309	0.76 (0.37, 1.41)	11%	29%

[1] Proportion of HIV-1 transmissions occurring from HIV-1 infected partners who had CD4 counts >200 cells/mm^3 and who were not on ART (total N=94)