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

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Summary

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. We aimed to assess the effect of ART use by patients infected with HIV-1 on risk of transmission to their uninfected partners.**

Methods **Participants in our prospective cohort analysis were from a randomised placebo-controlled trial that enrolled heterosexual African adults who were seropositive for both HIV-1 and herpes simplex virus type 2, and their HIV-1 seronegative partners. At enrolment, HIV-1 infected participants had CD4 counts of 250 cells per μL or greater and did not meet national guidelines for ART initiation; during 24 months of follow-up, CD4 counts were measured every 6 months and ART was initiated in accordance with national guidelines. Uninfected partners were tested for HIV-1 every 3 months. The primary outcome was genetically-linked HIV-1 transmission within the study partnership. We assessed rates of HIV-1 transmission by ART status of infected participants.**

Findings **3381 couples were eligible for analysis. 349 (10%) participants with HIV-1 initiated ART during the study, at a median CD4 cell count of 198 (IQR 161–265) cells per μL. Only one of 103 genetically-linked HIV-1 transmissions was from an infected participant who had started ART, corresponding to transmission rates of 0·37 (95% CI 0·09–2·04) per 100 person-years in those who had initiated treatment and 2·24 (1·84–2·72) per 100 person-years in those who had not—a 92% reduction (adjusted incidence rate ratio 0·08, 95% CI 0·00–0·57, p=0·004). In participants not on ART, the highest HIV-1 transmission rate (8·79 per 100 person-years) was from those with CD4 cell counts lower than 200 cells per μL. In couples in whom the untreated HIV-1 infected partner had a CD4 cell count greater than 200 cells per μL, 66 (70%) of 94 transmissions occurred when plasma HIV-1 concentrations exceeded 50 000 copies per mL.**

Interpretation **Low CD4 cell counts and high plasma HIV-1 concentrations might guide use of ART to achieve an HIV-1 prevention benefit. Provision of ART to HIV-1 infected patients could be an effective strategy to achieve population-level reductions in HIV-1 transmission.**

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Introduction

The quantity of HIV-1 in plasma is a primary determinant of the risk of HIV-1 transmission.[1] Antiretroviral therapy (ART) reduces plasma HIV-1 to undetectable concentrations within 6 months of initiation in most patients,[2,3] and seminal and cervicovaginal HIV-1 concentrations are also reduced to undetectable levels in most people on ART.[4–7] Use of peripartum ART has led to almost complete elimination of mother-to-child HIV-1 transmission in resource-rich settings.[8] Substantial reduction in plasma and genital HIV-1 concentrations in patients initiating ART could greatly reduce risk of HIV-1 transmission to sexual partners.[9] However, empirical data for the rate of sexual HIV-1 transmission from patients receiving ART are scarce. In a meta-analysis of data from five studies, some of which were unpublished, investigators reported only five cases of HIV-1 transmission from patients receiving ART to sexual partners during 1098 person-years of follow-up, which is consistent with an infection rate of 0·19–1·09 per 100 person-years.[10] Few studies have compared sexual behaviour before and after ART initiation, which is an important behavioural consideration. Additionally, the relation between evolving HIV-1 treatment guidelines,[11,12] which recommend ART initiation at CD4 cell counts between 200 cells per μL and 350 cells per μL, and HIV-1 transmission risk is unknown. Demonstration of an HIV-1 transmission benefit for patients initiating ART at CD4 cell counts at or above present guidelines could provide impetus to provide ART to populations as a prevention strategy for HIV-1 (eg, the test and treat approach), in addition to clinical benefits.

The Partners in Prevention HSV/HIV Transmission Study enrolled participants co-infected with HIV-1 and herpes simplex virus type 2 (HSV-2), along with their HIV-1 seronegative heterosexual partners, in a randomised, double-blind, placebo-controlled, clinical trial[13] of aciclovir HSV-2 suppressive therapy. As reported previously, aciclovir did not reduce HIV-1 transmission within the couples, although infected participants who were randomly allocated to aciclovir had a 73% reduction in incident genital ulcer disease due to HSV-2, an average 0·25 $\log_{10}$ copies per mL reduction in HIV-1 plasma concentration, and a 16% reduction in risk of HIV-1

disease progression.[13,14] We undertook a post-hoc analysis of data from this study, with the aim of assessing effect of ART use by HIV-1 infected participants on risk of HIV-1 transmission to their initially uninfected partners.

Methods

Study design and participants

Participants in our prospective cohort analysis were from the Partners in Prevention HSV/HIV Transmission Study[13] of aciclovir HSV-2 suppressive therapy versus placebo. Between November, 2004, and April, 2007, 3408 participants seropositive for HIV-1 and HSV-2 were enrolled, along with their HIV-1 seronegative heterosexual partners, from 14 sites in seven African countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia). Couples were followed-up for up to 24 months, and follow-up was completed in October, 2008. Couples were eligible for the trial if they reported three or more episodes of vaginal intercourse during the 3 months before screening. At the time of enrolment, HIV-1 infected participants were aged 18 years or older, were seropositive for HIV-1 and HSV-2, had a CD4 count of 250 cells per μL or higher, had no history of AIDS-defining conditions, and in accordance with national guidelines were not receiving ART. Uninfected partners were aged 18 years or older and were HIV-1 seronegative. The study protocol was approved by the University of Washington human subjects review committee and ethics review committees at the each of the collaborating organisations. All participants provided written informed consent.

Procedures

HIV-1 infected participants were seen once a month for provision of study drugs (aciclovir or placebo), assessment of clinical status, and behavioural risk assessment. CD4 cell counts were assessed every 6 months, and plasma for HIV-1 RNA quantification was obtained at baseline, at months 3, 6, and 12, and at the final study visit. Uninfected partners were tested every 3 months for HIV-1 seroconversion. All participants received pretest and post-test HIV-1 counselling, risk-reduction counselling (both individual and couple), free condoms, and treatment of sexually transmitted infections according to WHO guidelines throughout the study.

At the time the study was undertaken, national guidelines generally recommended ART initiation at CD4 cell counts less than 200–250 cells per μL or in patients with clinical AIDS. Participants who met national guidelines for initiation of ART during follow-up, as a result of a fall in CD4 cell count or change in clinical status, were referred to local HIV-1 care clinics to start ART, and counselling and re-referral was done at subsequent visits for those who did not start treatment. Women infected with HIV-1 who became pregnant during the study were referred to antenatal clinics for prevention of mother-to-child transmission services.

At visits taking place once every 3 months, participants were asked whether they had taken any antiretroviral drug at any time since the last quarterly visit; for those who had received ART, the number of days of treatment and the drugs received were recorded. Participants who initiated ART continued in follow-up with repeat CD4 cell count, viral load, and behavioural assessments until a maximum 24 months of follow-up.

HIV-1 serological testing was by dual rapid antibody tests, with positive results confirmed by western blot. For initially uninfected partners who seroconverted to HIV-1, analysis of HIV-1 *env* and *gag* gene sequences from both partners was used to establish whether transmission was genetically linked within the partnership.[13] HSV-2 serostatus was established by western blot.[15] CD4 quantification was done with 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 with the COBAS TaqMan real-time HIV-1 RNA assay, version 1.0 (Roche Diagnostics, Indianapolis, IN, USA), with a lower limit of quantification of 240 copies per mL. Laboratory technicians were masked to randomisation status (aciclovir or placebo) and ART use.

The aim of this post-hoc analysis was to assess the effect of ART use by HIV-1 infected participants on risk of HIV-1 transmission to their initially seronegative partners. The primary outcome measure was genetically linked HIV-1 transmission—ie, HIV-1 seroconversion in which viral sequence analysis showed that transmission occurred within the study partnership. Partners who had a genetically unlinked HIV-1 transmission event (ie, who acquired HIV-1 from someone outside the study partnership) contributed to follow-up until HIV-1 seroconversion, and were censored thereafter.

Statistical analysis

The primary exposure was ART use by HIV-1 infected participants, which we analysed as a time-dependent variable. Since both HIV-1 serological testing for partners and ART assessment for HIV-1 infected participants were done once every 3 months, any 3-month period during which the infected participant reported any combination ART use was conservatively regarded as an ART-exposed period for the uninfected partner, irrespective of the number of days in that period on which the infected participant received ART. Study periods in which short-course, mono-agent or dual-agent ART was used during pregnancy by women infected with HIV-1 for prevention of mother-to-child transmission were excluded from the analysis because of the restricted duration and potency of the regimen. For participants infected with HIV-1 who initiated combination ART during follow-up, ART use was conservatively carried forward (ie, continuing treatment was assumed), irrespective of whether they continued to report ART use at subsequent visits. We regarded ART exposure status for uninfected partners as

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unknown if their HIV-1 infected partners were lost to follow-up, and study periods with unknown ART status were excluded from analysis.

We used exact Poisson regression methods to calculate the incidence rate ratio and confidence bounds for HIV-1 transmission in the initially seronegative partners, on the basis of follow-up time and whether or not ART was initiated by their HIV-1 infected partners. ART initiation became more common as the study progressed and was most likely to be initiated at low CD4 cell counts, and thus estimates of incidence rate ratios were adjusted for time on study and CD4 cell count (as higher or lower than 200 cells per μL). Randomisation group in the clinical trial (ie, aciclovir or placebo) did not confound the association between ART and HIV-1 transmission risk, and thus we made no additional adjustments for risk estimates for the randomisation group. HIV-1 transmission risk was assessed both overall and by CD4 cell count strata, with visits before ART initiation classified by lowest previous CD4 cell count, and visits after initiation classified by the most recent CD4 cell count before ART, to mimic clinical decision making about ART initiation on the basis of CD4 cell count. We compared HIV-1 transmission rates from HIV-1 infected participants not on ART, stratified by CD4 cell count and plasma HIV-1 concentrations. In this analysis, strata for plasma HIV-1 RNA concentrations were defined by the highest previous concentration.

Sexual behaviour was compared before and after ART initiation for participants infected with HIV-1 who initiated treatment during follow-up. Conditional logistic regression was used to model changes in any unprotected sex, and negative binomial regression with generalised estimating equations and robust error estimation to model number of sex acts. Both these models were adjusted for time since enrolment in the cohort, because sexual risk behaviours overall decreased during the study.[13] We compared plasma HIV-1 concentrations at the most recent visit before ART initiation and at the final study visit using a paired *t* test for participants who initiated ART during follow-up. Plasma concentrations lower than the limit of quantification were set to 120 copies per mL (half the limit of quantification). Data were analysed with SAS (version 9.20) and LogXact (version 8.0.0).

Role of the funding source

The authors designed and undertook the study, had full access to the raw data, did all analyses, wrote the report, 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

3408 heterosexual HIV-1 serodiscordant couples were enrolled in the Partners in Prevention HSV/HIV Transmission Study. 27 couples for whom baseline serology did not confirm both HIV-1 and HSV-2 infection in the participants infected with HIV-1 were excluded. Table 1 shows baseline characteristics of the 3381 couples eligible for analysis. CD4 cell counts were lower (median 424 [334–571] *vs* 483 [355–664] cells per μL, p<0·0001) and

	HIV-1 infected partner (n=3381)	HIV-1 susceptible partner (n=3381)
Demographic characteristics		
Age (years)	32 (26–38)	33 (28–40)
Education (years)	8 (6–11)	8 (7–12)
Any monthly income	1218 (36%)	1652 (49%)
Women	2284 (68%)	1097 (32%)
Couple characteristics*		
East Africa, versus southern Africa	2230 (66%)	..
Duration of partnership (years)	4·6 (1·9–9·6)	..
Number of sex acts during past month	4 (2–8)	..
Any unprotected sex acts during past month	992 (29%)	..
Clinical characteristics		
CD4 cell count (cells per μL)	462 (347–631)	..
Plasma HIV-1 viral load (log_{10} copies per mL)	4·1 (3·4–4·7)	..
Assigned to receive aciclovir, versus placebo	1688 (50%)	..
Circumcised, men only	371 (34%)	1248 (55%)
HSV-2 seropositive	3381 (100%)	2294 (68%)

Data are n (%) or median (IQR). HSV-2=herpes simplex virus type 2. *Couple characteristics are from data for HIV-1 infected partners.

Table 1: **Demographic, behavioural, and clinical characteristics of HIV-1 serodiscordant couples at study enrolment**

	Median (IQR) or n/N (%)
Initiated ART	
Women	215/2284 (9%)
Men	134/1097 (12%)
Total	349/3381 (10%)
CD4 cell count at visit before initiation	
<200 cells per μL	182 (52%)
200–349 cells per μL	114 (33%)
350–500 cells per μL	29 (8%)
≥500 cells per μL	24 (7%)
Median CD4 cell count at visit before initiation (cells per μL)	198 (161–265)
Study duration at ART initiation	
<6 months	33 (9%)
7–12 months	119 (34%)
13–18 months	117 (34%)
19–24 months	80 (23%)
Median study duration at ART initiation (months)	13 (8–17)
Initial ART regimen	
Stavudine, lamivudine, nevirapine	212 (61%)
Zidovidine, lamivudine, nevirapine	47 (13%)
Protease inhibitor-containing regimen	11 (3%)
Other	55 (16%)
Insufficient information to establish full regimen	24 (7%)

Table 2: **Characteristics of HIV-1 infected partners who initiated antiretroviral therapy (ART)**

	Follow-up during which HIV-1 infected partner had not initiated ART			Follow-up after HIV-1 infected partner initiated ART			Unadjusted incidence rate ratio (95% CI; p value)*	Adjusted incidence rate ratio (95% CI; p value)*
	Number of HIV-1 transmissions	Length of follow-up (person-years)	HIV-1 incidence per 100 person-years (95% CI)	Number of HIV-1 transmissions	Length of follow-up (person-years)	HIV-1 incidence per 100 person-years (95% CI)		
Overall	102	4558	2·24 (1·84–2·72)	1	273	0·37 (0·09–2·04)	0·17 (0·00–0·94; p=0·04)	0·08 (0·00–0·57; p=0·004)
By CD4 cell count†								
<200 cells per μL	8	91	8·79 (4·40–17·58)	0	132	0·00 (0·00–2·80)	0·00 (0·00–0·40; p=0·002)	0·00 (0·00–0·38; p=0·001)
200–349 cells per μL	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 (0·02–4·00; p=1·0)‡
350–499 cells per μL	24	1408	1·70 (1·14–2·54)	0	30	0·00 (0·00–12·30)	0·00 (0·00–8·16; p=1·0)	0·0 (0·0–15·3; p=1·0)‡
≥500 cells per μL	29	1592	1·82 (1·27–2·62)	0	21	0·00 (0·00–17·57)	0·00 (0·00–10·29; p=1·0)	0·0 (0·0–15·0; p=1·0)‡

*All analyses adjusted for time since study enrolment and, for the overall analysis, CD4 cell count (as ≥200 cells per μL *vs* <200 cells per μL). †For follow-up before ART initiation, CD4 cell count was lowest previous value; for follow-up after ART initiation, CD4 cell count at the time of ART initiation was used. ‡Adjusted incidence rate ratio for combined CD4 cell count strata of 200 cells per μL or more was 0·55 (95% CI 0·01–3·24; p=0·9).

Table 3: **Antiretroviral therapy (ART) use and risk of HIV-1 transmission**

plasma HIV-1 RNA concentrations were higher (median 4·3 [3·7–4·9] *vs* 3·9 [3·2–4·5] $\log_{10}$ copies per mL, p<0·0001) in HIV-1 infected men than in infected women. Of the 3381 uninfected partners not infected with HIV-1, 3321 (98%) completed at least one follow-up assessment of HIV-1 status, contributing 5017 person-years of follow-up. Retention was high; 2920 (89%) of 3170 HIV-1 uninfected partners were retained at 12 months and 1235 (84%) of 1470 at 24 months. Loss to follow-up of HIV-1 infected participants and exclusion of periods in which ART was given for prevention of mother-to-child transmission resulted in loss of 186 (4%) person-years of follow-up.

349 (10%) participants infected with HIV-1 initiated ART (table 2). Median CD4 cell counts at ART initiation were 192 (162–241) cells per μL in men and 204 (160–305) cells per μL in women (p=0·05). 18 (34%) of the 53 participants initiating ART at CD4 cell counts of 350 cells per μL or higher began combination ART while pregnant. Of the 349 participants who initiated ART, 45 (13%) later reported no ART use at a subsequent follow-up visit. HIV-1 susceptible partners were followed up for a median 8·2 months (IQR 3·9–12·3) after their partners initiated ART.

103 genetically linked HIV-1 transmission events occurred during follow-up for which ART use was known (incidence 2·13 per 100 person-years). An additional 39 unlinked transmissions (HIV-1 transmissions from non-study partners) occurred during follow-up (incidence 0·81 per 100 person-years). 102 of the 103 linked transmissions were from HIV-1 infected participants who had not yet initiated ART; only one transmission event was recorded in 349 couples in whom the infected partners had initiated ART (table 3). In analysis adjusted for time since study enrolment and stratum of CD4 cell count, ART use by HIV-1 infected participants was associated with a 92% reduction in risk of transmission (table 3).

The one ART-exposed HIV-1 transmission event was a female-to-male transmission in which the infected woman's CD4 cell count was 302 cells per μL at enrolment and 201 cells per μL at the 6-month study visit. At the 9-month study visit, she reported having started 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). 90 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 per mL at the 6-month study visit (before ART initiation); at the 12-month study visit plasma viral load was undetectable (<240 copies per mL) and CD4 cell count was 637 cells per μL.

The rate of HIV-1 transmission from infected participants not receiving ART was highest for those with CD4 cell counts lower than 200 cells per μL and was similar across the three higher CD4 cell count strata (p=0·09 for comparison of rates in the three highest strata; table 3). No HIV-1 transmission events were reported in couples in whom the infected participant initiated ART at a CD4 cell count lower than 200 cells per μL, and risk of transmission in this stratum was significantly reduced by ART initiation (table 3). For combined CD4 cell count strata of 200 cells per μL or more, ART use was not significantly associated with reduced risk of HIV-1 transmission (table 3).

For participants infected with HIV-1 who initiated ART, median plasma HIV-1 concentration before ART initiation fell from 4·88 $\log_{10}$ copies per mL (3·97–5·41) to less than 2·38 $\log_{10}$ copies per mL (<2·38–3·53) (the limit of quantification) at the final study visit (p<0·0001), both measurements available for 344 participants), with 241 (70%) achieving virological 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 (3·4–12·1).

Reports of high-risk sexual behaviour in this cohort decreased substantially after study enrolment, with unprotected sex reported by HIV-1 infected participants at only 7% of all follow-up visits.[13] In infected participants

	Number of HIV-1 transmissions	Length of follow-up (person-years)	HIV-1 incidence per 100 person-years (95% CI)	Proportion of HIV-1 transmissions*	Proportion of person-years*
Plasma HIV-1 concentration, at CD4 cell counts of 200–349 cells per μL					
≥50 000 copies per mL	32	687	4·66 (3·19–6·58)	34%	15%
10 000–49 999 copies per mL	8	413	1·94 (0·84–3·82)	9%	9%
<10 000 copies per mL	1	367	0·27 (0·01–1·52)	1%	8%
Plasma HIV-1 concentration, at CD4 cell counts of ≥350 cells per μL					
≥50 000 copies per mL	34	804	4·23 (2·93–5·90)	36%	18%
10 000–49 999 copies per mL	9	887	1·02 (0·46–1·93)	10%	20%
<10 000 copies per mL	10	1309	0·76 (0·37–1·41)	11%	29%

*Proportion of HIV-1 transmissions occurring from HIV-1 infected partners who had CD4 cell counts greater than 200 cells per μL and who were not on antiretroviral therapy (total n=94).

Table 4: **HIV-1 transmission rates by CD4 cell count and plasma HIV-1 concentration in couples in whom the HIV-1 infected partner had not initiated antiretroviral therapy**

who initiated ART, the proportion of visits at which reports of sex was unprotected by condoms decreased further after ART initiation, from 6·2% before to 3·7% of visits after (adjusted odds ratio 0·63, 95% CI 0·41–0·96, p=0·03), an effect that did not differ between female and male participants. Notably, the mean number of sexual acts per month did not change significantly after compared with before ART initiation (p=0·6). Further adjustment for sexual activity unprotected by condoms did not appreciably change the estimated effect of ART on reduction of HIV-1 transmission risk (incidence rate ratio 0·09, 95% CI 0·00–0·61, p=0·005).

For HIV-1 infected participants with CD4 counts higher than 200 cells per μL, transmission risk was highest for those with plasma HIV-1 concentrations of more than 50 000 copies per mL, irrespective of whether their CD4 cell count was 200–349 cells per μL or greater than 350 cells per μL (table 4). Of the 94 HIV-1 transmissions from infected participants not on ART who had CD4 cell counts greater than 200 cells per μL, 66 (70%) occurred from those with plasma HIV-1 concentrations higher than 50 000 copies per mL, although these participants accounted for only 1491 (33%) person-years of total follow-up (table 4).

Discussion

In this analysis of almost 3400 HIV-1 serodiscordant heterosexual couples from seven African countries, ART use by the infected person was accompanied by a 92% reduction in risk of HIV-1 transmission to their partner. An important strength of our study was phylogenetic linkage of HIV-1 transmissions within the study partnerships, which probably reduced misclassification of the source of transmission and improved precision of 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 showed that plasma HIV-1 RNA concentrations decreased significantly after ART initiation, probably serving as the mechanism by which ART reduced risk of HIV-1 transmission, and we recorded a small but significant increase in condom use after treatment was initiated. The greatest effect of ART on HIV-1 transmission risk was in participants with CD4 cell counts lower than 200 cells per μL, emphasising the potential synergy of clinical and prevention benefits of ART in those with CD4 cell counts lower than this threshold.

Our results are highly consistent with those of a meta-analysis that estimated a 92% reduction in HIV-1 transmission risk as a result of ART, from 5·64 to 0·46 transmissions per 100 person-years.[10] Results of mathematical modelling studies have predicted that universal testing of HIV-1 serostatus and immediate initiation of ART (a strategy called test and treat) could greatly reduce new HIV-1 transmissions.[16] Few empirical data are available for the rate of HIV-1 transmission from patients receiving ART, and our findings provide valuable information about the degree of HIV-1 prevention benefit that might be achieved with ART during a 2-year period.[17]

In our cohort, the highest rate of HIV-1 transmission occurred from infected participants with CD4 cell counts lower than 200 cells per μL, and ART had the greatest absolute benefit in reduction of HIV-1 transmission risk in this group. Less than 50% of patients worldwide with CD4 cell counts lower than this threshold are currently receiving ART.[18,19] Our data emphasise that an HIV-1 transmission benefit would be achieved with maximum ART coverage of patients with CD4 cell counts lower than 200 cells per μL. Moreover, we report HIV-1 transmissions across all strata of CD4 cell counts, including a consistent rate of HIV-1 transmission (roughly 2% per year) at CD4 cell counts greater than 200 cells per μL. Notably, these findings suggest that use of ART to reduce HIV-1 transmission will necessitate coverage of patients with high CD4 cell counts as well as those with counts lower than 200 cells per μL.

WHO has recommended that the threshold for ART initiation for HIV-1 treatment be raised from a CD4 cell count of 200 cells per μL to 350 cells per μL.[12] In our study, 70% of transmissions from HIV-1 infected

participants with CD4 cell counts greater than 200 cells per µL occurred from those who also had plasma HIV-1 concentrations higher than 50 000 copies per mL. This result suggests that targeting of HIV-1 infected individuals with high plasma HIV-1 concentrations could achieve maximum HIV-1 prevention benefits of ART. Development of inexpensive point-of-care tests for plasma HIV-1 concentration could allow ART provision to be targeted to patients with high CD4 cell counts and high plasma HIV-1 concentrations.[1,20,21]

Similarly to the meta-analysis of effect of ART on HIV-1 transmission risk,[10] we recorded a low rate of transmission (<0·5% per year) after ART initiation. The one ART-exposed transmission event that we recorded happened less than 4 months after treatment was started, and thus transmission probably occurred before complete HIV-1 suppression by ART. A 2008 statement from the Swiss Federal Commission for HIV/AIDS argued that patients with undetectable plasma and genital HIV-1 concentrations as a result of ART can be regarded as sexually non-infectious.[22,23] Little is known about the timecourse of infectiousness for patients starting ART, and durable suppression of both semen and blood HIV-1 concentrations is not achieved in some treated patients.[2,6,7] In mathematical modelling studies, investigators have shown that if HIV-1 risk is low but non-zero in patients with suppressed HIV-1 concentrations, population-level increases in HIV-1 incidence could result if condom use fell in patients starting ART.[22] Our data reinforce previous findings that ART initiation does not lead to increased sexual activity or decreased condom use in heterosexual couples.[17,24–27] However, follow-up in this study was short compared with the lifetime duration of treatment that will be required of patients who start ART. Reliable information is needed about the long-term transmission benefits and behavioural risks associated with ART, especially when initiated at high CD4 cell counts. The US National Institutes of Health, through the HIV Prevention Trials Network, has a continuing 5-year clinical trial of ART initiation at CD4 cell counts of 350–550 cells per µL (*vs* at <250 cells per µL), which will be invaluable for understanding the balance of long-term risks and benefits of ART for treatment and prevention.[28]

In our study, information about ART initiation was obtained by self-report, thus there is potential for misclassification of ART-exposed time, although the one instance of HIV-1 transmission after initiation seemed to be truly in the context of ART use, in view of the change in plasma HIV-1 concentrations recorded in the HIV-1 infected participant. Some study participants were unwilling to initiate ART despite repeated efforts by site staff to link participants to treatment clinics, and thus we had some follow-up time for participants with CD4 cell counts lower than 200 cells per µL. We did not obtain data for the reasons for ART initiation for participants who started treatment at CD4 cell counts higher than national guidelines, but of those occuring above CD4 cell counts of 350 cells per µL, roughly a third occurred in pregnant women, potentially indicating early ART initiation for prevention of mother-to-child HIV-1 transmission. We had restricted numbers and follow-up for partners of participants initiating ART at CD4 cell counts higher than 250 cells per µL, so cannot reliably estimate the effect of ART on HIV-1 transmission at high CD4 cell counts. We also did not obtain information about ART adherence, although we did note substantial reductions in plasma HIV-1 RNA concentrations, with undetectable concentrations recorded in 70% of participants at a median 7 months after ART initiation. All HIV-1 infected participants in this study were HSV-2 seropositive; however, HSV-2 is common in patients with HIV-1 worldwide (seroprevalence 50–90%), and thus this study entry requirement is unlikely to restrict the generalisability of our findings.

Although the 92% reduction in HIV-1 transmission that we report is highly encouraging, on an individual basis, counselling is needed to reinforce understanding that potential for HIV-1 transmission to partners remains after ART initiation. This cohort received frequent counselling during 3-monthly follow-up, and we noted no evidence of behavioural risk disinhibition after ART initiation. We recorded HIV-1 transmissions across the range of CD4 cell count strata, with most transmissions occurring from participants who had low CD4 cell counts or high plasma HIV-1 concentrations. The greatest priority for ART provision for both treatment and prevention of HIV-1 coincides in patients with CD4 cell counts lower than 200 cells per µL. As countries strategise for optimum use of resources to expand ART provision beyond individuals with low CD4 cell counts, targeting of treatment to those with high plasma HIV-1 concentrations could be a cost-effective strategy to achieve maximum population-level reductions in HIV-1 transmission, as a step toward universal ART provision to all patients with HIV-1.

Contributors

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

Conflicts of interest

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