HHS Public Access

Author manuscript

Int J Infect Dis. Author manuscript; available in PMC 2019 December 05.

Published in final edited form as:

Int J Infect Dis. 2019 October ; 87: 128–134. doi:10.1016/j.ijid.2019.08.004.

HIV-1 heterosexual transmission and association with sexually transmitted infections in the era of treatment as prevention

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Abstract

Objectives: HIV-1 heterosexual transmission among individuals on antiretroviral treatment (ART) with undetectable viremia is extremely rare. The aim of this study was to evaluate the risk of sexual HIV-1 transmission and other sexually transmitted infections (STIs) in HIV-1 serodifferent couples while the index partner is on ART.

Methods: HIV transmission was evaluated in 200 HIV-1 heterosexual serodifferent couples in a stable relationship (≥3 months). All HIV-positive individuals had been on ART for ≥3 months and had been followed up for a median preceding time of 4.5 years (range 0.3–16years) at the HIV couples clinic at Hospital Nossa Senhora da Conceição in Porto Alegre, Brazil. Following written informed consent, participants responded to demographic/behavioral questionnaires. Quantitative PCR for HIV RNA, T-cell subsets, and STI testing (syphilis, herpes, human papillomavirus, gonorrhea, and bacterial vaginosis) were performed. Self-collected vaginal swabs were obtained for quantitative HIV genital viral load testing.

Results: Among 200 couples, 70% of index partners were female. Five seroconversions were observed; the HIV infection incidence was 2.5% (95% confidence interval 0.8% to 5.7%). Mean plasma viral load results were higher in HIV transmitters compared to non-transmitters ($p = 0.02$). The presence of STIs was significantly greater in couples who seroconverted (60.0% vs. 13.3%;

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Author contributions

MGM, PMG, and KNS conceived and designed the study. MGM, BS, TMR, MS, MA, RL, and MCC were responsible for the data collection and study conduct. MGM, IV, PMG, TK, and KNS were responsible for the data analysis. MGM, IV, TK, and KNS were responsible for interpreting the data. MGM, IV, ES, and KNS drafted the manuscript. All authors critically revised the manuscript and gave final approval of the version submitted for publication.

Ethical approval

The study was approved by the institutional review boards at the Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil and at the University of California Los Angeles, CA, USA. Written informed consent was obtained from all study participants.

Conflict of interest

The authors have no competing interests to declare.

odds ratio 9.75, 95% confidence interval 1.55–61.2; $p = 0.023$). The duration of undetectable HIV viremia and presence of STIs were associated with HIV transmission.

Conclusions: Undetectable viremia was the main factor associated with non-transmissibility of HIV in this setting.

Keywords

HIV-1 transmission; Couples; STIs; ART for prevention

Introduction

In the current era, sexual transmission of HIV-1 among individuals who are on antiretroviral therapy (ART) and have an undetectable serum viral load is a rare occurrence. The estimated risk of transmission under these circumstances is so low that it is considered negligible (Attia et al., 2009; Barreiro et al., 2006; Cohen et al., 2016; Cohen et al., 2011; Grulich et al., 2015; Matthews et al., 2012; Mujugira et al., 2016; Porco et al., 2004; Quinn et al., 2000; Rodger et al., 2016; Saleem et al., 2017; Tovanabutra et al., 2002; Melo et al., 2008). Following the release of the HIV Prevention Trials Network (HPTN) 052 study results, the World Health Organization (WHO) recommended the use of ART for all HIV-infected individuals regardless of CD4 cell counts in order to reduce the risk of HIV transmission (WHO, 2015). Nevertheless approximately 1.7 million adults were recently infected with HIV according to the same organization (UNAIDS, 2016). In Brazil, the AIDS prevalence rate is 19.1 cases per 100 000, while in the city of Porto Alegre, the Brazilian epicenter of the AIDS epidemic, the number of AIDS cases is reported to be 74 per 100 000 inhabitants (Boletim, 2016).

Although it is well known that HIV suppression through ART protects individual health and reduces the transmission risk over time if sustained, the durability of viral suppression can often differ within populations (Cohen et al., 2016; Rodger et al., 2016). Although the use of condoms coupled with ART would seem to be a reasonable preventative option when the viral load is not suppressed, many studies have exhaustively demonstrated that consistent condom use in HIV serodifferent couples is imperfect (Cohen et al., 2016); adherence to condoms is often low and their use tends to be irregular across different sexual practices (Kouyos et al., 2015; Hanif et al., 2014; Suzan-Monti et al., 2016). The other challenge to prevention efforts is that the presence of co-infections with other sexually transmitted infections (STIs) may increase the genital HIV viral load and enhance the transmission risk despite adequate ART use and serum viral load suppression. This phenomenon can be observed in women with genital ulcers who may harbor residual HIV in genital secretions although serum HIV levels are undetectable (Ouedraogo et al., 2006). It is well known that an increase in inflammatory cells expressing R5 receptors on their surface favors HIV-1 tropism (Taylor et al., 2003; Fiscus et al., 2013).

The interaction between ART drug penetration into the genital tract, the suppression of viral replication with treatment, and the relevance of HIV persistence in genital secretions is not fully understood (Suzan-Monti et al., 2016; Taylor et al., 2003, Fiscus et al., 2013). Viral HIV-1 subtypes may also play a role in transmission kinetics; in areas where subtype C virus

predominates such as the south of Brazil, the epidemic tends to disseminate at a higher pace, with higher serum and genital viral loads noted overall (Boullosa et al., 2014). Nevertheless, few studies have evaluated whether the genital HIV-1 concentration is correlated with the transmission risk.

More than 90% of all new HIV infections worldwide are sexually transmitted, hence a better understanding of biological mechanisms underlying transmission is needed (Daar and Corado, 2016; Cohen et al., 2008). In this new era of ART for prevention, the focus has shifted from condom use to ART adherence, which has redefined the sexual relationships of individuals living with HIV (Rodger et al., 2016; Kouyos et al., 2015). Within this context, the main objective of the present study was to evaluate the transmission risk of HIV and other STIs in serodifferent couples in which the index case is actively using ART, as well as to investigate the risk factors for seroconversion in this setting.

Methods

A total of 200 heterosexual, HIV-1 serodifferent couples who had been in a stable relationship for at least 3 months were included in this study. They were followed up in the HIV couples clinic with partners tested for HIV every 6 months. All HIV-positive individuals were on ART and on regular follow-up at the specialized HIV/AIDS couples clinic at the Hospital Nossa Senhora da Conceição in Porto Alegre, Brazil.

Following written informed consent, all subjects responded to a detailed demographic and behavioral questionnaire on ACASI (Audio Computer-Assisted Self-Interviews), which collected details about the couples' clinical and relationship histories. Blood specimens were collected for HIV viral load and T-cell subset testing, and additional blood and vaginal specimens were collected for STI testing (syphilis and gonorrhea). Gonococcus was identified by culture, as the Brazilian public health system did not provide PCR testing for Gonococcus or Chlamydia at the time the study was performed. Syphilis was diagnosed by a positive VDRL (Venereal Disease Research Laboratory) of any titer in individuals with or without symptoms of disease, who had no prior history of syphilis treatment, and who also had a positive confirmatory treponemal test result. Herpes simplex virus (HSV) and human papillomavirus (HPV) were diagnosed by the presence of genital lesions, which were tested for these specific conditions. Self-collected vaginal swabs were obtained from HIV-positive women for HIV genital viral load. All HIV-negative partners were counseled and tested for HIV-1.

Enrollment for the demographic questionnaire and collection of multiple specimens for study purposes occurred from February 2, 2014 to December 9, 2016. The period of follow-up for the cohort began at the time the couple first visited the clinic for care, when initial HIV testing was performed and the couple were found to be HIV serodifferent (mean of 4.5 preceding years; range 3 months to 16 years); HIV partner testing was performed every 6 months thereafter.

Demographic and bio-behavioral factors were investigated to determine the risk of transmission. Alcohol use was defined as sporadic if it occurred once to four times a month

and as frequent if it occurred more than two times a week. ACASI surveys were completed by the study participants at the time of the study visit. Each participant completed the ACASI survey in a private room using a handheld device with attached headphones. Study questions and response categories were read to the participant as they appeared on the screen of the handheld device. The participant was then given time to respond to each question by selecting the appropriate answer choice on the handheld device or entering numbers via the on-screen keyboard. ACASI was used to collect data on demographics, sexual behaviors, substance use, partnership dynamics and support, and self-reported ART adherence. ACASI questions on alcohol and drug use included standardized questions for clinical screening. Questions on alcohol consumption were extracted from the WHO Alcohol Use Disorders Identification Test (AUDIT), which includes questions on hazardous alcohol use, dependence symptoms, and harmful alcohol use, in order to screen for excessive drinking that may cause a substantial risk or harm. The set of 10 standardized alcohol questions were scored in order to identify low (scores of 0 to 7), medium (scores of 8 to 15), and high (scores of 16 or above) degrees of alcohol problems, with scores of 8 and above warranting further evaluation for alcohol dependency. Questions on drug use came from the Drug Abuse Screening Test (DAST). Individuals were also asked to report the number of times they had had vaginal sex in the past month; those that had were asked how many times a condom was used. These numbers were combined to create a percentage of condom use during vaginal sex in the past month. Participants also self-reported whether they were pregnant and whether they had tried to become pregnant in the previous 12 months.

A real-time PCR (RT-PCR; Abbott) was used for the assessment of the quantitative serum HIV viral load; the cut-off value was 40 copies/ml as per the manufacturer's instructions. Quantitative genital secretion HIV RNA was determined by RT-PCR using the COBAS kit (Roche) with an undetectable cut-off value of 17 copies/ml according to the manufacturer's instructions. As a biomarker of unprotected vaginal sex, vaginal swabs were obtained and submitted to the Rapid Stain Identification of Human Semen (RSID) assay.

The statistical analysis included a bivariate analysis for the investigation of factors potentially associated with the risk of transmission. The Yates Chi-square test was used to compare categorical variables. Fisher's exact test was also used. Patterns of viral load over time were evaluated among the five couples who transmitted and those who did not. The difference in mean log viral load was calculated using the Student *t*-test. A *p*-value of 0.05 or less was considered significant. Data were processed and analyzed using the Win PEPI program version 11.5 and IBM SPSS version 22.0. The transmission incidence rate was calculated in person-months with 95% confidence intervals (CI) generated for factors found to be associated with the transmission risk in the bivariate analysis.

The study was approved by the institutional review boards at the Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil and at the University of California Los Angeles, CA, USA. Written informed consent was obtained from all study participants.

Results

Demographic and behavioral characteristics

The study population comprised 200 heterosexual, HIV serodifferent couples (400 individuals). The majority of index cases (i.e., HIV-positive) were female (70.0%) (Figure 1). Among the 400 individuals who responded to the ACASI questionnaire, the median age was 38.9 years. The majority were Caucasian and most individuals had completed elementary school (Table 1). The partnership duration ranged from 3 months to 528 months, with a median time of 72 months. At the time of the ACASI interview, partners were tested for HIV by standard HIV testing procedures using a point-of-care assay at our site, following Brazilian guidelines: HIV Tri Line, which is an immunochromatographic method for rapid and qualitative determination of anti-HIV-1 antibodies (IgM, IgG, IgA, and IgE) including subtype O and anti-HIV-2 antibodies (BioClin).

HIV-1 seroconversion was observed in five partners since the time of their last follow-up visit within the preceding 6 months; thus the incidence of acute HIV infection was 2.5% in 200 serodifferent couples (95% CI 0.8% to 5.7%). Four partners who seroconverted were male and one was female. The seroconversion incidence was greater among the 140 males who were previously seronegative as compared to the 60 females who were previously seronegative, for an HIV incidence of 2.9% (95% CI 0.8–7.2%) vs.1.7% (95% CI 0–8.9%), respectively. This finding, however, was not statistically significant ($p = 1.0$).

Extramarital relationships were not reported by the five couples who had a transmission event, but were reported by 22 of 381 HIV serodifferent individuals (5.8%) who responded to the question; 5.2% were female (10/191) and 6.3% were male (12/190), as seen in Table 2. MSM (men who have sex with men) encounters were not reported among the men who seroconverted, but were noted by three of 195 men (1.5%) who answered the question. Multiple outside partners (>1) of the opposite sex were not reported by couples who seroconverted, but were reported by two of 192 men (1%) who did not seroconvert and answered the question and by three of 194 women (1.5%) who did not seroconvert and answered the question (data not shown). All five partners who seroconverted reported unprotected vaginal sex, as opposed to 36% of partners who did not seroconvert ($p = 0.007$) (Table 2). None of the partners who seroconverted had a high school education, as compared to 53% of partners who did not seroconvert ($p = 0.025$) (Table 1).

Biological markers

Most HIV index cases had CD4 cell counts above 350 cells/μl and had undetectable serum viral loads at the time the survey was administered. The median time of undetectable serum viral load, however, was greater in couples who did not seroconvert during the observation period (Table 3). Different patterns of viral load over time were noted among the five couples who transmitted and those who did not, as shown in Figure 2. Detectable viremia was noted up to 4 years prior to when the index patients completed the ACASI interview in individuals who transmitted HIV. The mean plasma viral load was higher among individuals who transmitted HIV as compared to those who did not ($p = 0.02$). Among couples who did not transmit HIV infection, the serum viral load curve showed a steady decline along the

time of evaluation (Figure 2). Genital HIV viral load testing was performed for 140 vaginal specimens of index case women; 5% had detectable HIV in vaginal secretions. Furthermore, 4.4% of non-transmitters and 25% of transmitters had detectable vaginal HIV-1 ($p = 0.187$), and one in four women (25%) who transmitted infection to their partner had a positive vaginal HIV-1 viral load.

The RSID assay was used as the gold standard for evaluating unprotected vaginal intercourse, as it detects sperm in vaginal secretions. The test was performed by 199 women, with a positive result in 22 (12.1%), reflecting unprotected sexual intercourse in the last 72 hours. Only one female partner did not have the test performed. A total of 182 women answered this question in ACASI and 68 (37.4%) reported unprotected sex; 114 reported protected sex (62.6%). Results were concordant between the ACASI and RSID in 19.1% of cases of unprotected sex and in 92.1% of cases of protected sex (correlation coefficient = 2.8; 95% CI 1.1–6.9; $p = 0.034$). RSID testing results by transmission status among index women are detailed in Table 3. The RSID was positive in five of 58 female partners (8.6%) who did not acquire HIV. There was no positive RSID result in women who seroconverted.

STIs were identified in 85 of 400 individuals (21.3%); 56 HIV-infected participants (28%) and 29 partners (14.5%) ($p < 0.001$) (Table 3). Syphilis was the leading STI, occurring in 69 of 400 individuals (17.3%) over time, consistent with the very high rates of syphilis cases reported for the city of Porto Alegre in recent years (Boletim, 2016). HPV/condyloma was noted in 16 individuals (4%), gonorrhea in three (0.8%), HSV-2 in two (0.5%), and bacterial vaginosis in one patient (0.3%). Three of five partners (60%) who contracted HIV had recent STIs (60%); conversely, STIs were present in 13% of partners who did not acquire HIV ($p = 0.23$) (Table 3). Demographics and bio-behavioral characteristics of the couples who transmitted HIV to each other are depicted in Table 4.

Discussion

This study provides real-life data on HIV transmission in serodifferent couples in situations where the index case is prescribed ART as per current guidelines. The data suggest that there are situations even in the presence of ART where additional precautions against HIV acquisition may be warranted, such as in the presence of concurrent STIs. In this new scenario of ART for prevention, it is important when counseling couples to remember that there might be extenuating circumstances in which an HIV risk could still be present; i.e. ART has just been initiated and viral load suppression has not been fully achieved, or adherence is suboptimal and there are concurrent STIs. The study findings do not contradict U = U (Undetectable = Untransmittable). It is important to observe, however, that in real-life situations there is a residual transmission risk from the time interval between ART initiation and attainment of undetectable viremia. Individuals may assume they already have an undetectable viremia when in fact they do not, which underscores the need for continued follow-up with virological monitoring.

The main risk factors associated with HIV transmission noted included the presence of STIs and detectable viremia up to 4 years before index patients performed the ACASI interview among those who transmitted the infection. It is known from a number of studies – including

HPTN 052 – that the longer the time of ART use and complete viral suppression, the lower the likelihood of an HIV transmission event (Attia et al., 2009; Barreiro et al., 2006; Cohen et al., 2016; Cohen et al., 2011; Grulich et al., 2015; Matthews et al., 2012; Mujugira et al., 2016; Porco et al., 2004; Quinn et al., 2000; Rodger et al., 2016; Saleem et al., 2017; Tovanabutra et al., 2002; Melo et al., 2008). Durable viral suppression protects individual health and progressively reduces the risk of HIV transmission over time. One of the objectives of the present study was to evaluate the durability of viral suppression following ART initiation and its impact on transmission. It is difficult when evaluating couples in real-life clinical situations to determine exactly when HIV transmission occurred. When index case serum viral loads were first evaluated in a cross-sectional analysis, at that point in time, four of five index cases who transmitted had undetectable plasma viral loads. Nevertheless, when their viral loads were analyzed over time throughout the duration of ART up until that moment, it was noted that the index cases who had infected their partners had maintained detectable HIV viremia for a considerable period of time during follow-up. By the time their HIV RNA was measured for the cross-sectional study, their partners had already become infected. This finding corroborates data in the literature which highlight the need for complete ART adherence for at least 6 months or more with concurrent undetectable viremia and without the presence of STIs for someone to be considered a non-transmitter (Attia et al., 2009; Mujugira et al., 2016; Porco et al., 2004; Quinn et al., 2000). In the present study, the index partner had to have been on ART for at least 3 months prior to enrollment.

STIs are known to enhance HIV transmission, as they increase the HIV viral load in the genital tract, thus increasing susceptibility to HIV. There is overwhelming epidemiological evidence linking STIs to HIV, particularly the most common ones such as HSV-2 and *Trichomonas*, and also those that cause ulcerative disease (HSV-2 and syphilis) (Ouedraogo et al., 2006; Daar and Corado, 2016). Genital inflammation resulting from local infection facilitates HIV transmission (Taylor et al., 2003; Fiscus et al., 2013). With inflammation there is a greater expression of R5 co-receptors on the cell surface of HIV tropic cells, as well as enhanced migration of these cells to the inflamed area, which facilitates viral entry and infection (Taylor et al., 2003; Fiscus et al., 2013). The inflammatory reaction produced by STIs may be a contributor to HIV transmission.

A high HIV prevalence of STIs was noted in the study cohort, with 28% of index cases and 14% of partners having had an STI at some point during follow-up. As STIs enhance HIV transmission, appropriate diagnosis and treatment of these conditions is an essential component of HIV prevention efforts. In addition, the presence of STIs underscores behaviors that facilitate HIV acquisition, thus highlighting the need for urgent prevention efforts (Cohen et al., 2008). Despite the small number of couples that seroconverted in this study, the presence of STIs was associated with HIV acquisition. The high frequency of syphilis cases identified in the study population, particularly among HIV-infected participants, underscores the phenomenon of one epidemic driving the other. Syphilis has long been implicated as an important factor in HIV transmission. The presence of one epidemic fueling the other highlights the pressing need to control one in order to control the other, as they function as overlapping epidemics or a syndemic. Although a trend towards statistical significance for transmission risk when couples reported outside partnerships was

noted, the fact that some STIs were not concurrent between couples suggests the presence of other partners outside of the main relationship, far beyond what was reported on ACASI.

It was found that a higher level of education, relationships of longer duration, and less frequent sexual encounters were protective factors against HIV transmission, information that should be taken into account by the health authorities in the implementation of prevention efforts. An important finding was that unprotected vaginal/anal sex either reported by the index case or by the partner was associated with HIV transmission, increasing the transmission risk seven-fold. Although the study results, as well as those of others (Cohen et al., 2011; Grulich et al., 2015; Rodger et al., 2016), cannot clearly pinpoint the exact transmission risk of condomless sex among HIV serodifferent couples, the present study findings suggest that the combined use of condoms and ART is likely an ideal prevention strategy for this specific population. The data suggest that in the real world scenario, the risk of HIV acquisition is not always zero between serodifferent couples and that the exact risk estimate is not clearly known, but is definitely associated with the duration of undetectable viremia and STI history. In this setting it is important for health authorities to disseminate this type of information to individuals living with HIV in a clear and candid format, in order for couples to make informed decisions regarding sexual practices.

An important study limitation is that the virus of both partners was not sequenced to demonstrate genetic relatedness. By the time partners came to our attention, their viral load was undetectable and we were unable to ascertain genetic linkage. Nevertheless, there is considerable circumstantial evidence that partners were infected by the index case. For one, couples had the same viral subtype and the same genotypic susceptibility profile upon initiation of ART. In addition, both the incidence and prevalence of HIV infection in the south of Brazil among heterosexual individuals, although high for Brazil, are low as compared to HIV hotspots across the world. The prevalence of HIV in the general population of Porto Alegre is 1% or less (Boletim, 2016). At our hospital, which is an HIV referral institution, the prevalence of HIV in pregnant women is approximately 3%. So even though acquisition of HIV from another individual cannot be completely ruled out, there is the knowledge that individuals in partnership with people living with HIV would be at higher risk of HIV acquisition, that the background prevalence of HIV is not as high in the community, plus the fact that viral subtypes and genotypic susceptibility results matched those of the index case.

Subtype C virus is the most common subtype in the south of Brazil, which is different from other regions of the country (Boullosa et al., 2014). This viral subtype has been shown to have a replicative advantage in cervical epithelial cells, which may explain its strong association with heterosexual and in utero transmission (Deymier et al., 2015). In regions where subtype C prevails, there is a large number of female-to-male HIV transmission events. This was the case in the HPTN 052 study, in which most of the transmissions were from females to males and occurred in Sub-Saharan Africa (Cohen et al., 2016; Cohen et al., 2011). This has also been noted in other studies (Attiaetal.,2009;Melo et al., 2008; Fiscusetal.,2013;Hughes et al., 2012). It is also noteworthy that the south of Brazil has a closer male-to-female ratio of HIV infection than other regions in the country, which suggests transmission patterns in this region differ from those of the rest of Brazil (Boletim,

2016). Another study limitation is that a longer follow-up period would have been preferable, to enable assessment of the durability of viral suppression beyond 4 years. It was not possible to perform PCR testing for Gonococcus, Chlamydia, and HPV because the assay is not available in our public health facility, which means that the STI frequencies are likely to be underestimates. The number of seroconversion events was small, which reduced the power for assessing risk factors of potential lower magnitude.

In conclusion, ART adherence leading to undetectable HIV plasma viremia was the main protective factor against HIV transmission among serodifferent couples in this study. Risk factors predictive of transmission included prior detectable viremia and a history of STIs.

Funding source

This study was supported by the UCLA AIDS Institute and the UCLA Center for AIDS Research (CFAR), and the National Institute of Allergy and Infectious Diseases (NIAID) AI28697, National Institutes of Health (NIH).

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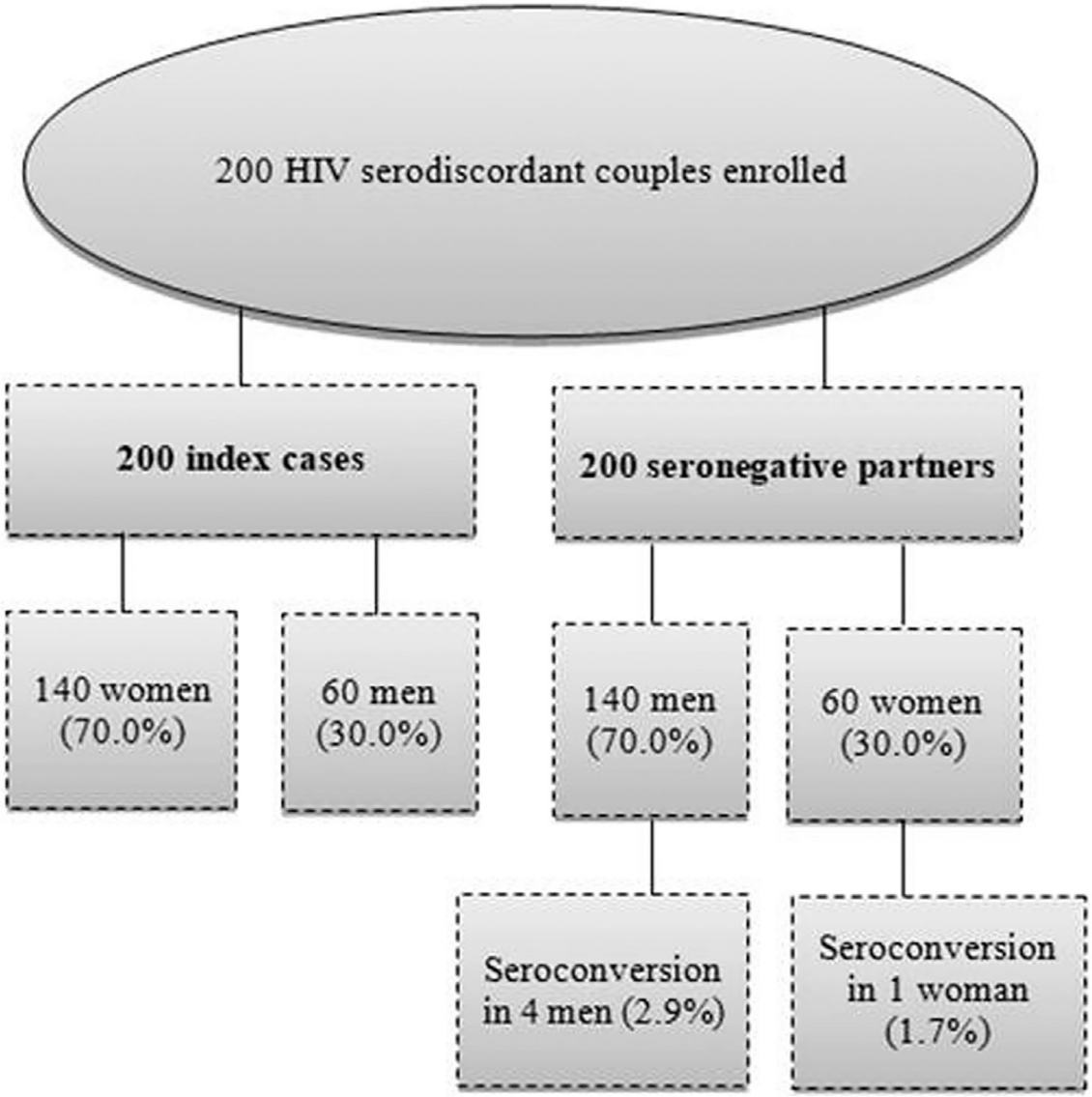

Figure 1.
Flow diagram of the study population.

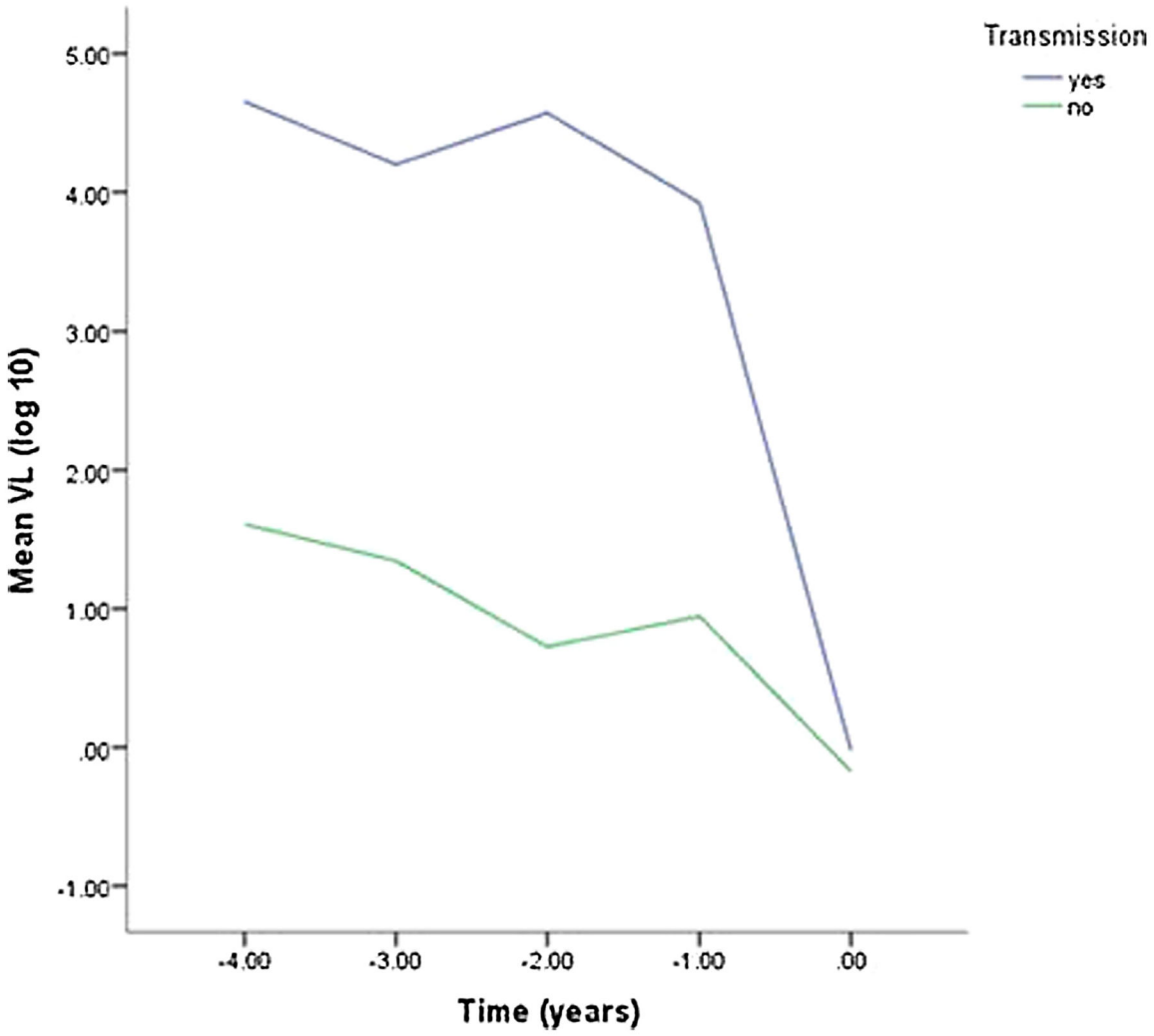

Figure 2.

Mean serum virus load in 200 couples with and without HIV transmission up to 4 years prior to ACASI interview.

Table 1

Comparison of demographic characteristics of index cases and their partners according to HIV transmission status ($N = 200$).

Characteristic	Total, *n* (%) *n* = 200	With transmission, *n (%)* *n* = 5	Without transmission, *n* (%) *n* = 195	OR (95% CI)	*p*-Value
Age, years[a]					
Index cases	38.2 ± 9.8 (18–66)	36.4 ± 16.4	38.1 ± 9.6	1.02 (0.93–1.12)	0.707
Partners	39.9 ± 11.9 (18–73)	43.4 ± 12.5	39.8 ± 11.9	0.97 (0.91–1.05)	0.506
White race					
Index cases	119/200 (59.5)	3/5 (60.0)	116/195 (59.5)	1.02 (0.17–6.25)	1.000
Partners	129/199 (64.8)	3/5 (60.0)	126/194 (64.9)	0.81 (0.13–4.96)	1.000
High school[b]					
Index cases	89/199 (44.7)	1/5 (20.0)	88/194 (45.4)	0.30 (0.03–2.74)	0.383
Partners	103/199 (51.8)	0/5 (0.0)	103/194 (53.1)	0.08 (0.01–1.15)	0.025
Own income					
Index cases	142/200 (71.0)	4/5 (80.0)	138/195 (70.8)	1.65 (0.18–15.1)	1.000
Partners	156/200 (78.0)	5/5 (100.0)	151/195 (77.4)	3.23 (0.23–46.4)	0.588
Monthly family income, reais[c]					
Index cases (*n* = 145)	1700.00 (0–3220.00) 1000.00; 3000.00	2000.00 (77.00–3000.00) 338.50; 2750.00	1650.00 (0.0–3220.00) 1.000.00; 3000.00	1.00 (1.00–1.00)	0.501
Partners (*n* = 160)	1600.00 (77.00–40 00.00) 1.000.00; 2.950.00	2000.00 (77.00–2500.00) 488.50; 2.250.00	1.600.00 (500.00–40 00.00) 1000.00; 3000.00	1.00 (0.99–1.00)	0.368
Have children					
Index cases	169/200 (84.5)	3/5 (60.0)	166/195 (85.1)	0.26 (0.04–1.63)	0.172
Partners	161/200 (80.5)	5/5 (100.0)	156/195 (80.0)	2.78 (0.19–39.92)	0.585

OR, odds ratio; CI, confidence interval

[a]Results expressed as the mean and standard deviation (range).

[b]High school = complete or incomplete.

[c]Results expressed as the median value Q1, Q3 (interquartile range 25 and 75).

Table 2

Comparison of behavioral characteristics during follow-up among index cases and their partners according to HIV transmission status ($N = 200$).

Characteristic	Total, *n* (%)	With transmission, *n* (%)	Without transmission, *n* (%)	OR (95% CI)	*p*-Value
Frequent alcohol use[a]					
Index cases	12/200 (6.0)	0/5 (0.0)	12/195 (6.2)	1.33 (0.08–22.94)	1.000
Partners	23/200 (11.5)	2/5 (40.0)	21/195 (10.8)	5.52 (0.87–34.97)	0.102
Use of illicit drugs					
Index cases	22/200 (11.0)	1/5 (20.0)	21/195 (10.8)	2.07 (0.22–19.41)	0.445
Partners	20/200 (10.0)	1/5 (20.0)	19/195 (9.7)	2.32 (0.25–21.8)	0.413
Years of follow-up of couples[b]	4.5 (0.3–21.7) 1.7; 7.5	2.0 (0.3–16.1) 0.7; 10.2	4.5 (0.3–21.7) 1.7; 7.5	1.04 (0.85–1.27)	0.704
Duration of partnership, months[b] (range) Ql; Q3	*n* = 195	*n* = 5	*n* = 190		
Index cases	72 (3–528) 24; 127	58 (8–72) 10; 66	72 (3–528) 24; 130.3	1.03 (0.99–1.05)	0.067
Partners	72 (3–528) 24; 127	60 (47–84) 49.5; 78	72 (3–528) 24; 127.8	0.99 (0.97–1.00)	0.210
Spouse has another partner					
Index cases	3/196 (1.5)	1/5 (20.0)	2/191 (1.0)	23.6 (1.8–317.0)	0.075
Partners	1/198 (0.5)	0/5 (0.0)	1/193 (0.5)	11.67 (0.53–256.6)	1.000
Number of sexual encounters in the last month[a] (range) Ql; Q3					
Index cases (*n* = 196)	5 (0–35) 2; 15	10 (2–25) 5; 22.5	5 (0–35) 2; 15	0.92 (0.85–1.01)	0.079
Partners (*n* = 198)	5 (0–30) 2; 11.3	5(2–15) 3; 11.5	5 (0–30) 2; 11.5	1.09 (0.95–1.24)	0.226
Report of unprotected vaginal sex					
Index cases	68/183 (37.2)	4/5 (80.0)	64/178(36.0)	7.1 (0.78–65.1)	0.064
Partners	67/177 (37.9)	5/5 (100.0)	62/172 (36.0)	19.5 (1.4–278.3)	0.007
Report of unprotected anal sex					
Index cases	12/200 (6.0)	1/5 (20.0)	11/195 (5.6)	4.18 (0.43–40.6)	0.268
Partners	5/49 (10.2)	2/5 (40.0)	18/195(9.2)	6.55 (1.03–41.8)	0.079

OR, odds ratio; CI, confidence interval.

[a]Occasional alcohol use was considered ingestion one to four times a month, and frequent use as ingestion two or more times a week.

[b]Results are expressed as the median (range); Q1, Q3 (interquartile range 25 and 75).

Table 3

Bivariate analysis of biological markers in index cases and their partners at the time of the ACASI interview.

	Total, n (%)	**Index cases, *n* (%)**		**OR**	**95% CI**	***p*-Value**
		With transmission	**Without transmission**			
Biological markers	*n* = 200	*n* = 5	*n* = 195			
Serum viral load in index cases, copies/ml (range) Q1;Q3[a]	0 (0–153 922) 0; 0	0(0–7652) 0.0; 3.826	0 (0–153 922) 0; 0	0.90	0.47–1.72	0.756
Genital viral load in index women	*n* = 140	*n* = 4	*n* = 136			
Detectable	7 (5.0)	1 (25.0)	6 (4.4)	7.2	0.7–80.1	0.187
Undetectable	133 (95.0)	3 (75.0)	130 (95.6)	-	-	
Genital viral load in index case women, copies/ml (range)[a] Q1;Q3	0 (0–11 200) 0; 0	0 (0–533) 0; 399.75	0 (0–11 200) 0; 0	0.484	0.021–1.11	0.089
Number of index cases with CD4 below 350 cells/µl	39/200 (19.5)	2/5 (40.0)	37/195 (19.0)	2.85	0.23–25.61	0.251
Median CD4 of index cases, cells/µl (range)[a] Q1;Q3	602.5 (41.0–1658) 389.5; 807.5	399.0 (187.0–815.0) 234.0; 798.5	606.0 (41.0–1658) 394.0; 808.0	1.00	0.99–1.00	0.337
	n = 200	*n* = 5	*n* = 195			
Median time of undetectable viral load in months in index cases[a] Q1;Q3	39.2 (0–162.6) 6.5; 74.7	0 (0–148.7) 0; 79.5	40.1 (0–162.6) 6.7; 74.7	1.01	0.98–1.03	0.419
Number of STIs[b]						
Index cases	56/200 (28.0)	2/5 (40.0)	54/195(27.7)	1.74	(0.28–10.7)	0.621
Partners	29/200 (14.5)	3/5 (60.0)	26/195 (13.3)	9.75	(1.55–61.2)	0.023*
Number of positive RSID in index women	19/140 (13.6)	2/4 (50.0)	17/136 (12.5)	7.00	0.92–53.02	0.089*

ACASI, Audio Computer-Assisted Self-Interview; OR, odds ratio; CI, confidence interval; STI, sexually transmitted infection; RSID, rapid stain identification of human semen.

*Statistically significant.

[a]Results are expressed as the median (range); Q1, Q3 (interquartile range 25 and 75).

[b]The STIs present in 400 subjects included in the bivariate analysis were as follows: syphilis *n* = 69 (17.3%); human papillomavirus (HPV)/condyloma *n* = 16 (4%); gonorrhea *n* = 3 (0.8%); herpes simplex virus *n* = 2 (0.5%); bacterial vaginosis *n* = 1 (0.3%).

Table 4

Demographic and bio-behavioral characteristics of couples with a transmission event

Characteristics	Case				
	A	B	C	D	E
Sex	Female	Female	Male	Female	Female
Age of index in years	32	45	60	27	18
Age of partner in years	40	59	54	33	31
Duration of relationship in months	84	72	60	58	52
Duration of ART use by the index in months	51.1	193.5	12.3	23.8	3.0
Index reported partner had other partners	No	No	No	No	Yes
Report of outside regular partnerships (index and partner)	No	No	No	No	No
Index response to number of vaginal sexual encounters	25	2	8	10	20
Partner response to number of vaginal sexual encounters	15	2	8	4	5
Report of unprotected sex, vaginal or anal (index and/or partner)	Yes	Yes	Yes	No	Yes
Alcohol use by index case	Occasional	Infrequent	Never	Never	Never
Alcohol use by partner	Never	Frequent	Never	Frequent	Infrequent
Response to ART adherence	No	Yes	Yes	Yes	Yes
H1V-1 subtype	C	C	C	B	B
ART regimen	MTR	STR	STR	STR	MTR
Time of ART use by index in months	51.1	193.5	12.3	23.8	3.0
Time of undetectable serum viral load in months	0	148.7	10.2	0	0
Serum viral load	7652	0	0	0	0
Genital viral load	533	0	NA	0	0
CD4 cell count, cells/μl	281	782	187	399	815
RSID	Negative	Positive	NA	Negative	Positive
Index case with ulcerative STI	Yes	Yes	No	No	No
Partners with ulcerative STI	No	Yes	Yes	No	Yes