Effectiveness of Highly Active Antiretroviral Therapy in Reducing Heterosexual Transmission of HIV

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Summary: Highly active antiretroviral therapy (HAART) has been shown to be highly effective in reducing plasma levels of HIV RNA; therefore, these treatments could diminish the risk of transmission. We analyzed 393 steady heterosexual couples, of which one partner had been previously diagnosed with HIV infection (index case) and where the nonindex partner reported his or her sexual relationship with the index case as the unique risk exposure. These couples were consecutively enrolled in the period 1991 through 2003 when the nonindex partners took their first HIV test. HIV prevalence among partners of index cases who had not received antiretroviral therapy was 8.6%, whereas no partner was infected in couples in which the index case had been treated with HAART (P = 0.0123). HIV prevalence among nonindex partners declined from 10.3% during the pre-HAART period (1991–1995) to 1.9% during the late HAART period (1999–2003; P = 0.0061). In the multivariate analysis, this decline held (odds ratio = 0.14, 95% confidence interval: 0.03–0.66) after adjusting for length of partnership, unprotected coitus, and pregnancies as well as gender, $CD4^+$ lymphocyte count, AIDS-defining diseases, and sexually transmitted infections in the index case. When HAART became widely available, a reduction of approximately 80% in heterosexual transmission of HIV was observed, irrespective of changes in other factors that affect transmission.

Key Words: HIV infection, HIV transmission, heterosexual transmission, antiretroviral therapy

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HIV transmission risks in unprotected sexual relationships vary considerably according to different factors such as type of sexual practice,[1] stage of HIV infection,[2] presence of sexually transmitted infections,[2,3] and plasma viral load in the HIV-infected partner.[4–6] Highly active antiretroviral therapy (HAART) has been shown to be highly effective in reducing plasma levels of HIV RNA among infected persons[7]; therefore, these treatments could diminish the risk of HIV transmission.[4] Reduction of infectiousness among individuals who receive antiretroviral therapy has been demonstrated in mother-to-child transmission[8] but has not been fully established in sexual transmission, in spite of the important influence it could have on the course of the pandemic.[9–12]

In the absence of changes in other relevant factors, a reduction in the sexual transmission of HIV after the introduction of HAART would be indicative of the effectiveness of this treatment to prevent new infections. With this aim in mind, we studied first-time HIV testers whose sole risk exposure was having a steady heterosexual partner who was infected. We compared HIV prevalence among those who were recruited during the years before the introduction of HAART and those included during the period when HAART was being used.

PATIENTS AND METHODS

Study Population

The study was conducted in a clinic in Madrid that launched a specific program for HIV-serodiscordant sexual couples in 1987. To each patient who was diagnosed with HIV infection, it was recommended that his or her sexual partner also visit the clinic for voluntary counseling and testing. With the informed consent of both partners, stable heterosexual couples attending this program were prospectively included in an observational study to analyze HIV sexual transmission risk, determinant factors, and needs related to prevention and reproduction aspects. Couples were recruited when the nonindex partner came to the clinic for his or her first HIV test in the period from January 1991 to December 2003. For the present analysis, 393 couples were selected with the following criteria: ongoing sexual relationship during the past 6 months, in which one of the partners ("index case") had been diagnosed with HIV-1 with a well-identified probable route of infection and the nonindex partner had not had a previous diagnosis of HIV and where the sexual relationship with the index case was the sole known risk exposure.

Interviews and Laboratory Tests

Both members of each couple were interviewed separately during a medical visit by means of a structured questionnaire before the serologic HIV result for the nonindex partner was known. The information collected for index cases

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included sociodemographic characteristics, probable route of infection, date of HIV infection diagnosis, AIDS-defining diseases, last $CD4^+$ lymphocyte count, and antiretroviral treatments. Plasma HIV RNA level (Branched-DNA; Bayer Diagnostics, France) was available since 1997. The information concerning nonindex partners contained sociodemographic data, date of the beginning of their relationship as a couple, and frequency of intercourse without a condom in the past 6 months. Women were also asked about pregnancies with their partner. For both members, the history of sexually transmitted diseases and presence of dysuria, genital discharge, ulcers, or warts were obtained through anamnesis and medical examination. Serologic study of syphilis was conducted using the reaginic test, and positive samples were confirmed by *Treponema pallidum* hemagglutination assay (TPHA) or the fluorescent treponemal antibody absorption test (FTA-ABS). For all participants, blood specimens were tested for HIV by an enzyme-linked immunosorbent assay, and reactive sera were confirmed by Western blot analysis.

Statistical Analyses

The most complete of all antiretroviral therapies received by the index case since the beginning of the couple's relationship was considered in the analyses. For the whole of the period from 1991 through 2003, HIV prevalence among nonindex partners was compared according to index case's antiretroviral regimen (no treatment, mono- or bitherapy, 3 or more drugs).

In accordance with current international guidelines,[13] HAART has been available free of charge in Spain to all patients since 1997. With this fact in mind, HIV prevalence among nonindex partners was compared for 3 calendar periods: pre-HAART (1991–1995); early HAART (1996–1998), the transition period; and late HAART (1999–2003), corresponding to the full implementation of this therapy.

A 2-sided χ^2 test and the Fisher exact test were used to compare proportions. Differences in continuous variables were tested with the Wilcoxon test and Kruskal-Wallis test. The bivariate analysis was followed by a multivariate logistic regression used to identify the isolated effect of the calendar period, adjusting by confounder covariables. The association between variables was quantified by means of the prevalence odds ratio (OR) and its 95% confidence interval (CI).

RESULTS

Couples' Characteristics According to Enrollment Period

Table 1 shows characteristics of the 393 couples grouped according to the enrollment period. In all 3 periods, the man was the initially HIV-infected partner in most couples and most index cases were infected through risk practices related to

TABLE 1. Characteristics of the Couples Enrolled During the 3 Treatment Periods

	Pre-HAART 1991–1995 n (%)	Early HAART 1996–1998 n (%)	Late HAART 1999–2003 n (%)	P*
All	214 (100.0)	73 (100.0)	106 (100.0)	
Male index case	176 (82.2)	61 (83.6)	81 (76.4)	0.3743
Prior injection drug use in index case	180 (84.1)	55 (75.3)	68 (64.2)	0.0003
Age of women (y), mean (SD)	27.7 (5.8)	29.7 (6.7)	32.7 (6.9)	<0.0001
Age of men (y), mean (SD)	30.3 (5.2)	33.2 (6.6)	35.7 (6.9)	<0.0001
Duration of relationship (y), median (P25–P75)	3.51 (0.92–7.12)	1.71 (0.84–9.64)	2.22 (0.74–5.22)	0.3377
Known duration of HIV infection (mo), median (P25–P75)	15.5 (1.2–45.0)	31.6 (1.8–84.7)	97.6 (30.6–148.5)	<0.0001
Beginning of relationship after diagnosis of HIV in index case	73 (34.1)	35 (47.9)	63 (59.4)	<0.0001
Previous pregnancy	102 (47.7)	32 (43.8)	43 (40.6)	0.4736
Present pregnancy	20 (9.3)	7 (9.6)	7 (6.6)	0.6790
Sexually transmitted infection in index case	21 (9.8)	3 (4.1)	1 (0.9)	0.0063
Bacterial vaginosis or genital infection in nonindex partner	54 (25.2)	19 (26.0)	10 (9.4)	0.0026
Coital acts without condom in past 6 months	123 (57.5)	44 (60.3)	49 (46.2)	0.0980
Index case $CD4^+$ cells/μL, median (P25–P75)	460 (272–724)	503 (308–685)	550 (271–700)	0.9072
Index case viral load (log copies/mL), median (P25–P75)†	—	3.65 (2.95–4.17)	2.70 (ND–4.27)	0.0083
AIDS-defining disease	21 (9.8)	10 (13.7)	21 (19.8)	0.0453
Antiretroviral therapy				<0.0001
Mono- or bitherapy	14 (6.5)	6 (8.2)	0 (0)	
HAART	0 (0)	8 (11.0)	52 (49.1)	

*P values were obtained from a χ^2 test for categoric variables and the Kruskal-Wallis test for continuous variables.
†Only available for 135 patients, all of them recruited after 1996.
ND indicates nondetectable viral load, below 1.70 log copies/mL; P25–P75, interquartile range.

TABLE 2. Prevalence of HIV Infection Among Heterosexual Partners of HIV-Infected Index Cases According to Characteristics of Couple

	Infected/Analyzed (n/N)	HIV Prevalence (%)	*P*
Enrollment period			0.0254
Pre-HAART (1991–1995)	22/214	10.3	
Early HAART (1996–1998)	5/73	6.8	
Late HAART (1999–2003)	2/106	1.9	
Gender of index case			0.8072
Male	23/318	7.2	
Female	6/75	8.0	
Age of man			1.0000
<30 y	10/140	7.1	
≥30 y	19/253	7.5	
Age of woman			0.7000
<30 y	17/212	8.0	
≥30 y	12/181	6.6	
Mode of HIV transmission in the index case			0.8213
Intravenous drug use	22/303	7.3	
Sexual transmission	7/90	7.8	
Coital acts without condom in past 6 months			0.0233
No	6/177	3.4	
One per month or less	5/49	10.2	
More than 1 per month	18/167	10.8	
Index case antiretroviral therapy			0.0129*
No	27/313	8.6	
Mono- or bitherapy	2/20	10.0	
HAART	0/60	0	
Index case $CD4^+$ cells/μL			0.0029
≥350	12/269	4.5	
<350	17/124	13.7	
Index case viral load, log copies/mL†			0.0778
<4	1/95	1.1	
≥4	3/40	7.5	
Time since beginning of the relationship			0.1437
<1 y	5/117	4.3	
≥1 y	24/276	8.7	
Time since HIV diagnosis of index case			0.3046
<6 mo	12/127	9.4	
≥6 mo	17/266	6.4	
Beginning of relationship			
Before diagnosis of HIV infection in index case	21/222	9.5	0.0816
After diagnosis of HIV infection in index case	8/171	4.7	
Sexually transmitted infection in index case			1.0000
No	28/368	7.6	
Yes	1/25	4.0	
Bacterial vaginosis or genital infection in nonindex partner			1.0000
No	23/310	7.4	
Yes	6/83	7.2	
AIDS-defining diseases in index case			0.0856
No	22/341	6.5	
Yes	7/52	13.5	
Previous or present pregnancies			0.0062
No	8/207	3.9	
Yes	21/186	11.3	

*HAART versus all other options.
†Only available for 135 patients.

injecting drug use, although in the late HAART period, the proportion of individuals infected by a sexual route rose to 35.8% ($P = 0.0003$). The mean length of the couple relationships was 2.7 years, and 8.7% of women were pregnant at the time of their first visit to the clinic, without any significant variation between periods.

The index case's $CD4^+$ cell count at the time of inclusion in the study remained stable ($P = 0.9072$); nevertheless, the percentage of those diagnosed with an AIDS-defining disease rose from 9.8% to 19.8% ($P = 0.0453$), and the proportion of index cases with antiretroviral therapy increased from 6.5% to 49.1% ($P < 0.0001$). Whereas all patients who were treated during the first period underwent mono- or bitherapy, they all received combinations of 3 or more antiretroviral drugs in the last period.

Among index cases, the frequency of sexually transmitted infections decreased from 9.8% to 0.9% ($P = 0.0063$). None of the nonindex partners had received postexposure prophylaxis.

HIV Prevalence Among Nonindex Partners

For the nonindex partners, HIV prevalence declined from 10.3% in the pre-HAART period to 6.8% in the early HAART period and to 1.9% in the late HAART period ($P = 0.0254$). HIV prevalence among partners of index cases who had not received any antiretroviral therapy was 8.6%, whereas no partner was infected in couples in which the index case was being treated with HAART ($P = 0.0123$). Other variables associated with a higher HIV prevalence among nonindex partners were unprotected coital acts in past 6 months, $CD4^+$ count less than 350 cells/μL in the index case, and pregnancy during that couple's relationship. Moreover, the presence or history of AIDS-defining diseases and high levels of HIV RNA for index cases were close to statistical significance, although this last information was only available for some couples. No association was found with gender, age, length of the relationship, time since HIV diagnosis in the index case, and presence of genital or sexually transmitted infections (Table 2).

The decrease in HIV prevalence among nonindex partners was especially pronounced when index cases had a $CD4^+$ count less than 350 cells/μL and when they took antiretroviral drugs (Table 3). As a consequence, in the late HAART period, there was no difference in HIV prevalence between couples whose index case received HAART (0%) and those whose index case had received no treatment (3.7%; $P = 0.4954$).

Multivariate Analysis

Using logistic regression analysis, we evaluated changes in HIV prevalence between the 3 periods, which corresponded to different levels of HAART availability, adjusting them by possible confusion factors (Table 4). The results confirmed the pronounced decrease in HIV prevalence among nonindex partners recruited during the late HAART period when compared with the prevalence observed among those included during the pre-HAART period (OR = 0.14, 95% CI: 0.03–0.66; $P = 0.0127$). Other variables independently associated with higher HIV prevalence were $CD4^+$ count less than 350 cells/μL, sexual intercourse without a condom in the previous 6 months, and pregnancy during that couple's relationship. In the multivariate analysis, the gender of the index cases, the length of the couples' relationships, antiretroviral therapy, and the presence or history of AIDS-defining diseases and sexually transmitted infections were not significantly associated with a higher HIV prevalence among nonindex partners. Interaction terms between calendar period and other covariables were not statistically significant.

TABLE 3. Prevalence of HIV Infection Among Heterosexual Partners of HIV-Infected Index Cases According to Enrollment Period

	Pre-HAART 1991–1995		Early HAART 1996–1998		Late HAART 1999–2003		
	Infected/Analyzed (n/N)	Prevalence (%)	Infected/Analyzed (n/N)	Prevalence (%)	Infected/Analyzed (n/N)	Prevalence (%)	P*
$CD4^+$ cell count in index case (cells/μL)							
≥350	8/147	(5.4)	2/50	(4.0)	2/72	(2.8)	0.5035
<350	14/67	(20.9)	3/23	(13.0)	0/34	(0)	0.0022
Gender of index case							
Male	18/176	(10.2)	4/61	(6.6)	1/81	(1.2)	0.0090
Female	4/38	(10.5)	1/12	(8.3)	1/25	(4.0)	0.6399
Coital acts without condom in past six months							
No	4/91	(4.4)	2/29	(6.9)	0/57	(0)	0.2986
Yes	18/123	(14.6)	3/44	(6.8)	2/49	(4.1)	0.0646
Index case antiretroviral therapy							
No	20/200	(10.0)	5/59	(8.5)	2/54	(3.7)	0.1799
Yes	2/14	(14.3)	0/14	(0)	0/52	(0)	0.0424
Total	22/214	(10.3)	5/73	(6.8)	2/106	(1.9)	0.0061

*P values were obtained from χ^2 tests that compare pre-HAART and late HAART periods.

TABLE 4. Multiple Logistic Regression Analysis of HIV Prevalence Among the Steady Heterosexual Partners of HIV-Diagnosed Index Cases

	Prevalence OR	95% CI	*P*
Coital acts without condom in past 6 months			
No	1		
Yes	2.66	1.00–7.05	0.0488
Index case $CD4^+$ cells/μL			
≥350	1		
<350	2.68	1.13–6.35	0.0250
AIDS-defining diseases in index case			
No	1		
Yes	1.86	0.66–5.23	0.2369
Gender of index case			
Female	1		
Male	0.74	0.27–2.05	0.5624
Beginning of relationship			
Before diagnosis of HIV infection in index case	1		
After diagnosis of HIV infection in index case	1.15	0.39–3.40	0.8013
Time since beginning of relationship			
<1 year	1		
≥1 year	1.05	0.30–3.76	0.9346
Sexually transmitted infection in index case			
No	1		
Yes	0.37	0.04–3.20	0.3634
Previous or present pregnancies			
No	1		
Yes	2.38	0.95–5.97	0.0655
Enrollment period			
Pre-HAART (1991–1995)	1		
Early HAART (1996–1998)	0.55	0.19–1.61	0.2763
Late HAART (1999–2003)	0.14	0.03–0.66	0.0127

DISCUSSION

These results demonstrate an important reduction in the heterosexual transmission of HIV and provide evidence showing that such a reduction can be attributed to HAART. On the one hand, none of the HIV-infected index cases who received HAART had transmitted HIV to his or her partner compared with 8.7% of the index cases who had not received this therapy. On the other hand, HIV prevalence among individuals with a stable heterosexual partner previously diagnosed with HIV infection is 5 times lower since HAART has been widely available than during the period before the introduction of HAART.

Comparison between calendar periods with different levels of HAART availability, once the influence of changes in other variables that affect HIV transmissibility has been excluded, enables us to evaluate the effectiveness of these therapies in reducing transmission when applied under uncontrolled conditions. Antiretroviral therapy is prescribed for patients with worse clinical, immunologic, or virologic states,[13] who are thus more infectious toward their sexual partners.[2–4] This could help to explain why the impact of HAART on HIV transmission has been important, although only half of the index cases underwent such therapy. With the introduction of HAART, the context in which antiretroviral therapy was prescribed was enlarged, and this could account for the fact that HIV prevalence among partners of index cases who did not receive antiretroviral drugs also decreased.

The inclusion criteria applied in our study allow us to state, with a rather high level of probability, that HIV infections detected among nonindex partners are attributable to heterosexual transmission by their index case partner. The information was collected before the nonindex partner's serologic status was known, which reduces possible biases.

The major limitation of our results is that they do not completely enable us to rule out the effect of factors other than antiretroviral therapy on the reduction of HIV prevalence among the nonindex partners. The proportion of couples who practiced unprotected coital acts decreased as well as the frequency of sexually transmitted infections, which would contribute to a lower transmission rate. In any case, the marked decrease in HIV prevalence of the nonindex partners in the HAART period was maintained after adjusting for all these changes.

Several arguments suggest that antiretroviral therapy can reduce sexual transmission of HIV. The viral load in genital secretions seems to decline, together with the viral load in plasma, after combination therapy.[14,15] A prospective study established a link between zidovudine use and a decrease in the rate of HIV transmission from infected men to their partners,[16] and another more recent study suggests that homosexual men have lower infectivity after the introduction of HAART.[17]

As shown by other studies, the fact of having practiced unprotected coitus[2,3] and the low levels of $CD4^+$ cell counts were 2 of the major explanatory variables of HIV transmission to the sexual partner. The low levels of $CD4^+$ cell counts can be justified mainly because of the presence of high viral load values and/or a long duration of the infection,[18] and both of these circumstances could have contributed to a higher likelihood of HIV transmission. We did not find any association between the presence of sexually transmitted infections and HIV transmission to the partner,[2–4] although such an association has been described in various studies.[1] Nevertheless, a genital discharge was not present in any of these infections, and only 1 subject had genital ulcers.

Although not a single case of HIV transmission was found when the index case had received HAART, the existence of some risk could not be totally excluded, because the persistence of HIV in genital secretions of patients with HAART has been described.[19] Some increases in risky practices have been observed for various population groups and were attributed to a slackening in preventive measures because of HAART.[20–23] Other studies have revealed no change[24,25] or even a decrease of risky behavior frequency that coincides with HAART introduction, however.[26] A rise in risky behavior could thus cancel out or even reverse the preventive effect on sexual transmission obtained though antiretroviral therapies. This is why it is important not to forget that the main preventive measure for HIV sexual transmission remains the avoidance of risky sexual practices.

In conclusion, after the introduction of HAART, an important decrease in HIV transmission has been observed in a thoroughly studied group of steady heterosexual couples, irrespective of any changes in other factors that affect transmission. These results strongly suggest that combined antiretroviral treatments applied according to current guidelines have a great potential for preventing HIV transmission to sexual partners. The accessibility to HAART for HIV-infected people around the world, as long as it is not accompanied by a relaxation of other prevention measures, could greatly contribute to controlling the spread of HIV among similar populations.

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