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Time to AIDS From 1992 to 1999 in HIV-1–Infected Subjects With Known Date of Infection

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Summary: To estimate the change in AIDS incubation time during three periods characterized by different availability of antiretroviral treatments, data from the French Hospital Database on HIV of 4702 HIV-1–positive subjects with a documented date of infection were analyzed. Times from seroconversion to AIDS were compared in three periods: period 1 from January 1992 to June 1995 (monotherapy); period 2 from July 1995 to June 1996 (dual therapy); and period 3 from July 1996 to June 1999 (triple therapy). Nonparametric survival analyses were performed to account for staggered entries in the database and during each period. From periods 1 to 3, antiretroviral treatments were initiated earlier after infection, more subjects were treated, and the nature of regimens changed (25.6% of subjects were treated with monotherapy in period 1, 34.6% were treated with dual therapy in period 2, and 53.4% were treated with triple therapy in period 3). Compared with period 1, the relative hazard (RH) of AIDS was 0.31 in period 3 (95% confidence interval [CI]: 0.24–0.39). When comparing period 3 with period 2, the RH of AIDS was 0.36 (CI: 0.29–0.45). Assuming a log normal distribution, the median time to AIDS was estimated as 8.0 years in period 1 (CI: 6.0–10.6), 9.8 years in period 2 (CI: 8.5, 11.2), and 20.0 years in period 3 (CI: 17.1–23.3). This lengthening in time to AIDS from 1992 to 1999 was particularly marked in the period after the introduction of triple therapy, including protease inhibitors. **Key Words:** AIDS—Cohort study—Disease progression—HIV—Highly active antiretroviral therapy—Incubation duration.

The quantitative estimate of time to AIDS in observational studies is an important parameter in public health to assess the impact of the HIV epidemic and its control. It provides a measure of the population effectiveness of therapies (1) in contrast to clinical trials, which measure the therapeutic efficacy at an individual level. Importantly, it can also contribute to an estimation of the size of the HIV-infected population, using back-calculation approach accounting for treatment effect and guiding public health interventions (2).

Changes in treatments (antiretroviral and prophylactic) together with global health care, HIV strain virulence, AIDS events classification, and diagnosis ability are factors capable of influencing the time between HIV infection and the development of AIDS (3,4). In a population, the clinical impact of the spread of a new therapy might be assessed by comparing clinical progression rates across different calendar periods. Using this approach, previous studies on HIV seroconverters focused on progression to death only (5,6), whereas Detels et al. (7) also considered the progression to AIDS.

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The French Hospital Database on HIV, whose data are provided by HIV-specialized hospitals, represents an opportunity to evaluate the change in time to AIDS. The goal of our study was to estimate the time to AIDS during three periods of follow-up characterized by different availability of antiretroviral treatments.

MATERIALS AND METHODS

Database

The French Hospital Database on HIV is a clinical epidemiologic network started in 1989 with 29 Centers d'Information et de Soins de l'Immunodéficience Humaine especially involved in the medical care of HIV-infected persons at 68 French university hospitals (8). National coverage was achieved in 1992. In brief, patients with a documented HIV infection who have signed an informed consent form are enrolled during their first hospital visit. Trained research assistants collect data on a standardized form at inclusion, at each visit or hospital admission for an HIV-related clinical diagnosis, at the time of a new treatment prescription, or at least every 6 months. Data are computerized locally using the French Ministry of Health software, DM12. Sex, transmission group, date of birth, and date of first HIV-positive test are systematically collected at inclusion. When available, date of last negative HIV test, date of contamination, and date of primary HIV infection are also collected. Data collected during each follow-up visit include biologic markers, clinical HIV-related manifestations, nature of treatments prescribed, and date of death. At the time of the study, the last update was in December 1999.

Date of HIV-1 Infection

Eligible patients for the current study were those whose date of HIV-1 infection could be documented on the basis of the date of a patient's last negative HIV test, date of primary infection, or date of contamination. Primary infection, defined by the presence of typical signs and symptoms followed by HIV seroconversion, was ascertained by a physician. The date of contamination was the date of the risk exposure assessed by a physician according to a patient's history. The date of HIV-1 infection was estimated as the midpoint between the date of the last negative and first positive HIV tests (test interval) within an interval of 24 months when the dates of primary infection or contamination were not documented. Otherwise, we assumed the date of infection to be the date of primary infection, if available, or as the date of contamination.

Inclusion Criteria

Inclusion was restricted to the HIV-1–infected adults whose date of infection was documented after 1985, who were AIDS-free as of December 1991, and who had at least one follow-up visit, except in the case of a first AIDS-defining event diagnosed at the first visit. Subjects involved in a double-blind antiretroviral trial during their follow-up period ($n = 246$), diagnosed with AIDS before database entry ($n = 372$), or with a follow-up interval of less than 6 months ($n = 99$) were excluded.

Estimation of Incubation Time

Patients were followed until AIDS, death, last follow-up, or June 1999, whichever occurred first. AIDS was defined according to the Centers for Disease Control and Prevention's 1993 clinical classification. Three calendar periods were defined according to the availability of antiretroviral regimens in France: January 1992 to June 1995 (period 1: mainly nucleoside reverse transcriptase inhibitor [NRTI] monotherapy), July 1995 to June 1996 (period 2: mainly NRTI dual therapy), and July 1996 to June 1999 (period 3: mainly triple combination therapy). Patients AIDS-free and alive were considered as lost to follow-up in period 1 and period 2 if their last visit occurred in period 1 or 2, respectively. Patients followed in period 3 were considered as lost to follow-up if they had no hospital visit after June 1998.

Recruitment in our cohort implies that subjects with a shorter incubation time have less chance to enter the database AIDS-free and, consequently, less chance to be included in the analysis than subjects with a longer incubation time (9,10). To overcome this survival bias, patient follow-up was left truncated until the first hospital visit (11,12). Moreover, a subject contributed to the risk set in each calendar period he or she was followed while AIDS-free; therefore, we left-truncated the follow-up at the beginning of each calendar period in which he or she contributed (13,14).

Nonparametric AIDS-free probabilities in the three periods were assessed using the Kaplan-Meier method and compared by the Cox proportional hazards model. The Cox model was adjusted for age at infection, transmission group (homosexual, intravenous drug user, heterosexual, and other), period of seroconversion (1986, 1987–1991, 1992–June 1995, July 1995–June 1996, after July 1996), and calendar periods, entered as time-dependent covariates.

Parametric estimates of the median incubation time in the three calendar periods were derived from log-normal distribution, which has been shown to better suit the time variation in the hazard of AIDS than a Weibull model (15–17). To overcome the departure from the log-normal model at the tail of the observed times, which is most relevant for predictions, left truncation was extended to 5 years after the seroconversion as recommended by Muñoz and Xu (16). Log-exponential and Weibull models were used to assess the robustness of the lognormal model in the third period.

Antiretroviral and Prophylaxis Treatments

For each subject followed in a given period, we examined the treatments prescribed at the last follow-up visit while the patient was still AIDS-free. Antiretroviral regimens were analyzed according to the time lag from infection at this visit and classified in three categories according to the number of drugs used: monotherapy, dual therapy, and triple therapy. Triple therapy was defined as the concomitant use of three or more antiretroviral drugs. *Pneumocystis carinii* prophylaxis was defined as any use of sulfamethoxazole/trimethoprim, aerosolized pentamidine, dapsone, or atovaquone.

Statistical analyses were performed using SAS (version 6.12; SAS Institute, Cary, NC, U.S.A.) and S+ (version 5.0; MathSoft, Seattle, WA, U.S.A.) computer programs and a C program for estimating AIDS-free probabilities.

RESULTS

Overall, 4702 subjects fulfilled the inclusion criteria. Of these, 2962 (63.0%) had a test interval within 24 months. The remaining subjects were documented on the

basis of primary infection (609 subjects [13.0%]) and contamination (1131 subjects [24.0%]).

In the study sample, 3406 subjects (72.4%) were male, 2257 (48.0%) were homosexual men, 1700 (36.2%) were heterosexuals, and 509 (10.8%) were intravenous drug users. For 236 subjects (5.0%), the transmission group was unknown. The median age at infection was 28.8 years. Overall, 1982 subjects were infected between 1986 and 1991: 1636 during period 1, 387 during period 2, and 697 during period 3.

After infection, the median time before the first hospital visit was 12 months (interquartile range: 5–40 months). The median follow-up interval was 63 months (5.2 years). From 1992 to June 1999, 862 subjects (18.3%) developed a first AIDS-defining event, and 67 (1.4%) died while AIDS-free. More patients were lost to follow-up in period 3 (11.5%) than in period 1 (7.5%) or period 2 (4%). Overall, patients were lost to follow-up after a median interval while AIDS-free of 53 months.

Table 1 presents the characteristics of the subjects followed during the three calendar periods. Infection duration before the first hospital visit was similar in the three calendar periods. The three groups were relatively similar regarding age at infection, sex, and transmission group distribution. In all periods, approximately two thirds of the dates of infection were documented on the basis of test interval.

Figure 1 shows the Kaplan-Meier estimates of AIDS-free probabilities in the three calendar periods. The probability of remaining AIDS-free at 5 years was estimated as 69.2% in period 1 (95% confidence interval [CI]: 66.1– 72.2), 77.6% in period 2 (CI: 73.3–81.9), and 89.9% in period 3 (CI: 87.9–91.9).

Table 2 presents the results of relative hazard (RH) of progression to AIDS across the calendar periods in univariate analysis and after adjusting for age at infection, transmission group, and period of infection. The RH of progression to AIDS was significantly reduced in period 3 compared with period 2 or period 1 and remained similar after adjustment. The reduction in the hazard of AIDS observed between periods 2 and 1 was borderline significant in the multivariate analysis. Under a lognormal assumption, the median time between HIV-1 infection and the development of AIDS was estimated to be 8.0 years (CI: 6.0–10.6) in period 1, 9.8 years (CI: 8.5–11.2) in period 2, and 20.0 years (CI: 17.1–23.3) in period 3. In period 3, whether the log-exponential model or the Weibull model was used, estimates were similar;

TABLE 1. *Characteristics of the 4702 HIV-1–infected subjects according to the period of follow-up*

	Calendar period		
	1/1/92–6/30/95 Period 1	7/1/95–6/30/96 Period 2	7/1/96–6/30/99 Period 3
Number of patients followed during the period	2684	2540	3732
Total person-years	4829	2109	7817
General characteristics			
Median date of infection	April 1991	February 1992	June 1993
Date of infection during the period (%)	39.3	5.7	18.7
Median age at infection (years)	28.1	28.0	28.8
Male (%)	72.1	71.1	71.7
Men who have sex with men (%)	48.2	47.5	47.1
Inclusion and date of infection			
Last negative and first positive HIV-1 test within 24 months (%)	66.1	65.4	62.4
Date of first infection only (%)	13.0	12.1	13.0
Date of contamination only (%)	20.9	22.4	24.6
Staggered entries			
Number of patients with first visit before the period[a]	681	1998	2256
Median infection duration at the beginning of the period and 25% through 75% percentiles (months)	36 (20–54)	46 (27–72)	51 (30–77)
Number of patients with first visit during the period[b]	2003	542	1476
Median infection duration at first visit and 25% through 75% percentiles (months)	13 (6–42)	14 (6–42)	12 (5–47)
Follow-up from infection to the end of the period			
Median duration and 25% through 75% percentiles (months)	46 (26–71)	51 (30–77)	67 (38–97)
Number of AIDS cases (%)	453 (16.9)	171 (6.7)	238 (6.4)
Number of deaths before an AIDS diagnosis (%)	32 (1.2)	11 (0.4)	24 (0.6)
Number lost to follow-up (%)[c]	201 (7.5)	102 (4.0)	431 (11.5)

[a] Left truncation at the beginning of the period.
[b] Left truncation at the first hospital visit.
[c] Subjects AIDS-free at the last hospital visit occurring during the period or before July 1998 for the third period.

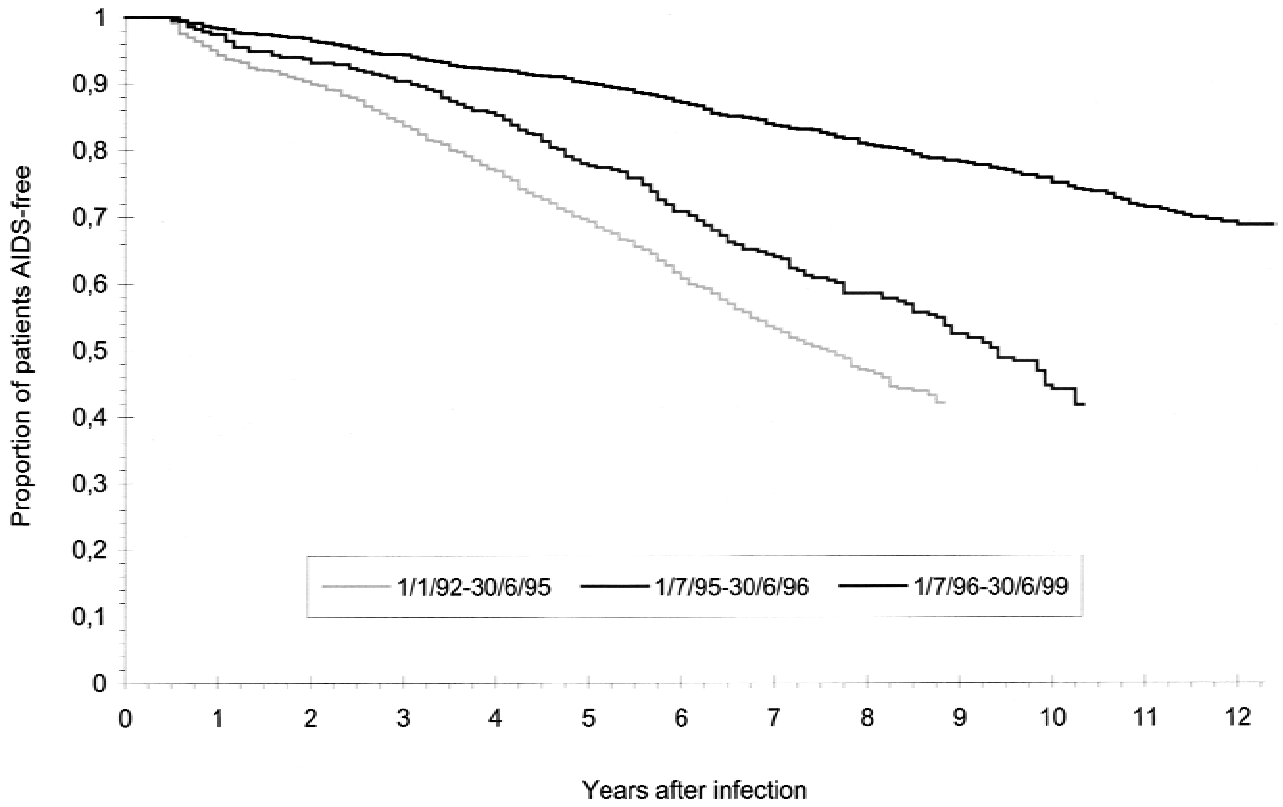

FIG 1. Kaplan-Meier estimates of AIDS-free survival in the three calendar periods of follow-up.

they were 20.8 years (CI: 17.8–24.5) and 19.8 years (CI: 17.6–22.3), respectively.

Whatever the infection duration, the proportion of subjects receiving antiretroviral treatment strikingly increased over the three periods, and the nature of regimens changed (Fig. 2). The increase in antiretroviral prescriptions was particularly marked for the persons recently infected. In period 1, 16.4% of the subjects infected for less than 1 year were treated versus 29.2% in period 2 and 54.5% in period 3. Overall, 34.4% of the subjects were treated in period 1 compared with 47.1% in period 2 and 75.5% in period 3. Treatments prescribed were monotherapy for 74.4% of subjects treated in period 1, dual therapy for 73.4% of subjects treated in period 2, and triple therapy for 70.7% of subjects treated in period 3.

In period 1, 23.0% of the subjects received *P. carinii* prophylaxis versus 21.0% in period 2 and 14.2% in period 3.

DISCUSSION

Our study of the quantitative changes of time to AIDS after infection across successive periods revealed a major lengthening of AIDS-free times concomitant with the introduction of triple therapy for HIV in the late 1990s. Parametric and nonparametric estimates provided evidence of a reduction in the progression to AIDS across

TABLE 2. *Estimated relative hazard of AIDS according to the period of follow-up*

		Crude RH	CI	Adjusted RH[a]	CI[a]	Adjusted RH[b]	CI
Period 2 versus period 1	7/1/95–6/30/96 versus 1/1/92–6/30/95	0.79	0.66–0.94	0.78	0.65–0.94	0.86	0.71–1.05
Period 3 versus period 1	7/1/96–6/30/99 versus 1/1/92–6/30/95	0.27	0.22–0.32	0.26	0.22–0.31	0.31	0.24–0.39
Period 3 versus period 2	7/1/96–6/30/99 versus 7/1/95–6/30/96	0.34	0.28–0.42	0.33	0.27–0.41	0.36	0.29–0.45

[a] Adjusted for age at infection and transmission group.
[b] Adjusted for age at infection, transmission group, and period of infection.
RH, relative hazard; CI, 95% confidence interval.

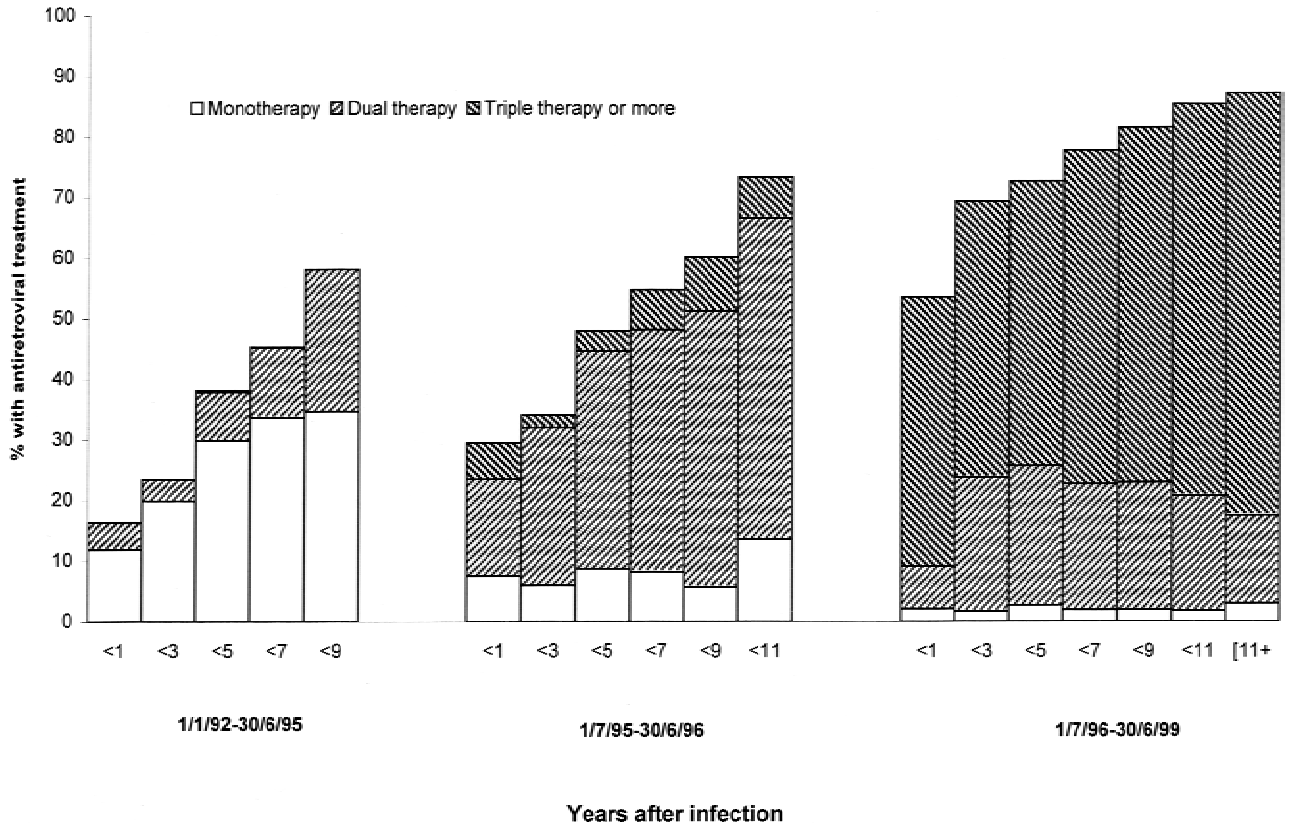

FIG. 2. Antiretroviral regimen at patients' last follow-up visit while AIDS-free in each period according to the duration of incubation at this visit.

successive periods, which was particularly marked in the most recent period. The probability of remaining AIDS-free 5 years after infection increased from 69.2% before mid-1995, to 77.6% between mid-1995 and mid-1996, to 89.9% after mid-1996. Similarly, we observed a 64% reduction in the hazard of AIDS after mid-1996 compared with the previous period. The hazard of AIDS between the periods after and before mid-1995 was also reduced but not significantly. The median time to AIDS was estimated as 8.0 years before mid-1995, 9.8 years from mid-1995 to mid-1996, and 20.0 years from mid-1997 to mid-1999.

Our results are consistent with those previously published in seroconverter cohort studies with known duration of infection. For the Multicenter AIDS Cohort Study, Detels et al. (7) compared subjects with the same infection duration in four calendar periods with different regimen availability. This study demonstrated a reduction in the hazard of AIDS or death in the latest period after introduction of potent antiretroviral therapy compared with the period when only monotherapy was available (AIDS RH = 0.35). In the Italian HIV Seroconversion Study, the RH of death and the RH of AIDS-related death were both estimated to be 0.54 in 1997 compared with before 1991 (5). A pooled analysis of 38 studies concluded that there was a significant survival benefit 10 years after infection in the period from 1997 to 1998 compared with before 1997 (6). Our results are also consistent with results estimated in prevalence cohorts by comparing progression since a defined level of prognostic markers instead of the date of infection (18).

Several biases and potential confounding factors that could interfere with the results should be discussed. First, to address a potential survival bias, time duration was restricted for each patient to the period of active follow-up since the first hospital visit.

Second, among factors known to influence AIDS incubation time, age at infection is the most often reported (19–21) and was introduced in the multivariate analyses, and it did not modify the estimates. This can be explained by a similar median age at infection for patients in the three periods. Host genetic factors (22,23) have also been reported to influence the progression to AIDS, but it is rather unlikely that these genetic characteristics of HIV-infected patients have changed over time. In contrast, one can imagine that changes in viral

virulence might have occurred over time. Adjustments for periods of seroconversion did not affect the results, however.

Third, it has been reported that when Kaposi sarcoma, a tumor almost exclusively diagnosed in homosexual men, is not excluded from the AIDS definition, the risk of progression to AIDS is higher in homosexual men than for other transmission groups (24). This was accounted for in the analysis by adjusting for transmission groups, and, again, the results did not vary.

Fourth, in the literature, the date of HIV infection is most often documented on the basis of a test interval (5,7,24). In our study, test intervals were not available for one third of the patients, and only the dates of primary infection or contamination were. Nevertheless, a sensitivity analysis restricted to subjects with a date of infection documented on the basis of a test interval (n = 2692) showed similar risk of progression to AIDS (data not shown).

Finally, concern could be raised about a possible bias caused by an informative censoring of the 11.5% of patients followed in the last period who were lost to follow-up. We performed a sensitivity analysis assuming that these patients had a diagnosis of AIDS the day after their last visit. The RH of AIDS remained significantly reduced in period 3 compared with period 1 (RH = 0.88; CI: 0.77–0.99).

Thus, none of the factors discussed previously could really explain the lengthening in time to AIDS that we observed. The fact remains that over the three periods, the most striking difference was the change in the use of antiretroviral regimens. Antiretroviral treatments were initiated earlier after infection and with more potent regimens (see Fig. 2). It is therefore likely that the lengthening in time to AIDS should be attributed to the introduction of NRTI combinations and that it has been greatly marked since the introduction of triple therapy, including protease inhibitors. By providing quantitative estimates of the impact of antiretroviral combination therapy, including protease inhibitors, at the population level, our results complement the efficacy results of antiretroviral combination demonstrated in clinical trials in advanced patients and the effectiveness described in observational studies (25–27).

In conclusion, we observed a lengthening in time to AIDS from 1992 to 1999, which was particularly marked in the most recent period. Although this improvement may reflect differences in calendar periods, it is most likely related to the change in antiretroviral regimen management over time and the introduction of triple therapy, including protease inhibitors.

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