Has the rate of progression to AIDS changed in recent years?

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Objectives: To investigate whether the rate of progression to AIDS has changed over time by testing an effect of the year of seroconversion on AIDS onset (Centers for Disease Control and Prevention 1987 revised classification), next to an effect of the calendar period of follow-up.

Design: French multicentre prospective study of 385 homosexual and heterosexual subjects and 231 subjects from a multicentre study of European injecting drug users (IDU), all with a documented date of HIV-1 seroconversion.

Method: The effect of the year of seroconversion was compared by the log-rank test. Crude and adjusted relative hazard (ARH) were quantified using the Cox model. Calendar period of follow-up was studied separately for sexual exposure group and IDU and treated as a time-dependent variable in a Cox model.

Results: In the 616 study subjects the year of seroconversion was not significantly related to AIDS occurrence (n = 108); the ARH was 0.88 [95% confidence interval (CI), 0.56–1.38] for those who seroconverted in 1988–1989, and 1.17 (95% CI, 0.61–2.25) for those who seroconverted after 1989, compared with those who seroconverted before 1988. In the sexual exposure group, a clear trend towards less rapid progression to AIDS was observed in subjects followed in 1991–1992 (ARH, 0.49; 95% CI, 0.24–0.99) and after 1992 (ARH, 0.54; 95% CI; 0.24–1.21), compared with those followed before 1991. This favorable trend was not observed in IDU despite a significant decrease over time of *Pneumocystis carinii* pneumonia as AIDS-defining illness. Conversely to sexual exposure groups, the frequency of antiretroviral treatment (mainly zidovudine) prescription was still low during the most recent calendar periods in IDU when the CD4 count threshold of 200×10^6/l was reached.

Conclusions: No evidence was found of a change in the rate of progression to AIDS in subjects who seroconverted in recent years. Furthermore, conversely to sexual exposure groups, the lack of favorable trends in IDU users followed in recent years suggest that health-care systems are not always adapted to their lifestyles.

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Introduction

AIDS occurs a median of 8–10 years after infection by HIV-1 [1,2]. Since the first cases were notified in the United States in 1981 [3], the incubation period may have changed over time for several reasons [4].

The worldwide spread of HIV since the beginning of the epidemic could have led to the emergence in recent years of new HIV-1 strains [5], HIV-1 subtypes harbouring higher viral loads [6], and transmission of resistant strains [7]. According to Ewald [8], the modifications of the sexual partner rate exchange in a population may also lead to an evolution of HIV-1. Since those events are likely to affect the host–virus response at the time of infection they raise the possibility that progression might vary according to year of infection [9].

Nonetheless, the natural history of HIV infection has probably also been modified by several external factors during the course of the disease. For example, the probable rise in the number of AIDS cases diagnosed after the extension of HIV disease classification [10] may have increased the rate of progression to AIDS after 1987. In contrast, improved medical management, especially the release of antiretroviral drugs, widespread primary prophylaxis for *Pneumocystis carinii* pneumonia (PCP), and possibly the earlier treatment of some less specific infections (e.g., thrush), probably slowed the occurrence of some AIDS-defining illnesses. At the population level, the overall effect of all these changes can be assessed by testing a calendar effect (i.e., period effect) on the progression to AIDS [9].

Analysing data from a European multicentre study of injecting drug users (IDU) and a cohort of subjects infected by the sexual route, all with a documented date of seroconversion, we investigated whether the rate of progression to AIDS has changed over time. First, the influence of the year of seroconversion on AIDS onset was studied, and then the influence of the calendar period of follow-up to determine the impact of medical management on the onset of AIDS. Since IDU like other marginalized groups [11–14] may have failed to benefit fully from medical progress in this field, this later analysis was conducted separately for IDU and sexual exposure groups.

Materials and methods

The European Seroconverter Study among IDU

IDU were defined as subjects who, since 1979, had injected drugs before their seroconversion to HIV [15]. They came from seven prospective cohorts (n = 418) in five European countries: Edinburgh Drug Addiction Study and Edinburgh City Hospital Cohort Study (n = 169); Amsterdam Cohort Study among drug users (n = 99); Geneva HIV Cohort Study (n = 60); French SEROCO Cohort (n = 38); Scottish National Collaborative HIV Testing Study (n = 31); and Innsbruck AIDS Study (n = 21). A total of 105 persons who were HIV-seronegative at enrolment subsequently seroconverted. A dated HIV-negative screening test was available for the remaining 313 subjects who were HIV-seropositive at enrolment.

The SEROCO cohort

Since 1 January, 1988, 1504 HIV-infected adults have been recruited in the Paris region and South of France [16,17]. All exposure groups except hemophiliacs were represented. A dated HIV-negative test was available for 482 persons infected by the sexual route, allowing us to determine the seroconversion interval.

In the two cohorts (European study and SEROCO), most of the retrospectively identified seroconverters were tested for reasons unrelated to disease progression.

Study population

In order to study the effect of the year of seroconversion, this analysis focused on subjects whose date of seroconversion could be estimated accurately. Those whose date of seroconversion, estimated as the midpoint between the last negative test and the first positive test, was known to be within an interval of less than 24 months (median, 6.1 months; 10th–90th percentiles; 2.0–18.2 were therefore selected). To limit any frailty selection bias due to the length of the interval between seroconversion and enrolment, subjects who were included less than 24 months after their estimated date of seroconversion were also selected. The study population comprised 281 homosexual men, 104 heterosexual subjects from the SEROCO Cohort, and 231 IDU registered in the European Seroconverter Study. The subjects who were HIV-positive at study entry were enrolled after a median of 7.8 months following seroconversion (10th–90th percentiles, 2.7–18.5).

Data collection

HIV-1 infection was diagnosed by using an enzyme-linked immunosorbent assay method and was confirmed by Western blot. Patients in all cohorts underwent clinical and laboratory examinations every 3–6 months. Lymphocyte subsets were determined by flow cytometry. Date of AIDS onset was obtained from review of medical files of participating centres and from cross-checking with local and national AIDS registries when possible. AIDS-free subjects were censored at date of death, last date known to be AIDS-free, or 1 January 1995 (the cut-off date of the analysis). Information on the start of treatment (intention to treat), such as primary prophylaxis for PCP (pentamidine aerosols, trimethoprim–dapsone, or

co-trimoxazole) and antiretroviral drugs before the onset of AIDS was available for all subjects in the SEROCO Cohort and for 126 out of 231 IDU in the European cohort. For the remaining IDU, this information was missing at the date of analysis. The term antiretroviral treatment refers here to treatment with a reverse transcriptase inhibitor alone (i.e., zidovudine) or sometimes in combination, possibly in a therapeutic trial.

Statistical analysis

Analysis of variance, Pearson's χ^2 test or the Armitage trend test, and Fisher's exact test (extended version) were used to compare medical and demographic data. Age at seroconversion was categorized according to tertiles (< 25 years, 25–30, > 30 years) of the study population. The year of seroconversion was categorized in three periods (before 1988, 1988–1989, after 1989), the reference period being prior to 1988. The median CD4 lymphocyte count measured at 24 months (±3 months) after the estimated date of seroconversion was compared according to these three periods of seroconversion using the Kruskal–Wallis test. AIDS-free survival curves (Centers for Disease Control and Prevention 1987 revised classification) [7] were compared by the log-rank test. Crude and adjusted relative hazards were determined by using the Cox proportional hazards method and tested with the likelihood ratio statistics. Adjustment for exposure group and sex was carried out using a combined variable (homosexual men, heterosexual men, heterosexual women, male IDU, female IDU).

The calendar period of follow-up was categorized in three periods [before 1991 (reference period), 1991–1992, after 1992], and then treated as a time-dependent variable in a Cox model. This allowed us to compare the risk of progression to AIDS during a given period relative to the calendar period of reference, taking into account the time since seroconversion. As explained previously, the influence of the calendar period on the progression to AIDS was studied separately for IDU and sexual exposure groups. All survival analyses were corrected for left-truncation. Hence, for subjects who were HIV-positive at study entry, survival was calculated from the estimated date of seroconversion, but they entered the risk set at the date of enrolment.

Changes over time in the frequency of treatments were studied in AIDS-free persons who reached a first CD4 cell count of less than 200×10^6/l during a calendar period. For the reference calendar period (before 1991), only those who reached this threshold value after 31 December 1987 [i.e., the release of the first antiretroviral drug (zidovudine) and primary prophylaxis of PCP] were included. The frequency of both antiretroviral treatment and primary prophylaxis of PCP was calculated at the CD4 count cut-off of 200×10^6/l [18].

The median CD4+ cell count at the AIDS onset, within 3 months of diagnosis [19], was compared according to the calendar period of follow-up by using the Kruskal–Wallis test.

Results

The first seroconversions occurred in 1986 among both homosexual and heterosexual subjects in this study (Table 1). Amongst IDU belonging to the European cohort the year of infection was uniformly distributed from 1983 to 1994. Seroconversion occurred at a significantly younger age in IDU than in the other groups. Contrary to homosexual and heterosexual subjects, in whom age at infection did not vary according to year of seroconversion ($P = 0.20$), 52% of IDU who

Table 1. Description of the study population.

	Homosexuals (n = 281)	Heterosexuals (n = 104)	IDU (n = 231)
Year of seroconversion [n(%)]			
≤ 1985	0 (0)	0 (0)	52 (23)
1986–1987	74 (26)	21 (20)	36 (15)
1988–1989	147 (52)	54 (52)	58 (25)
1990–1991	49 (18)	19 (18)	37 (16)
≥ 1992	11 (4)	10 (10)	48 (21)
Age at seroconversion (years) [n(%)]*			
< 25	69 (25)	35 (34)	100 (43)
25–30	101 (36)	35 (34)	76 (33)
> 30	111 (39)	34 (32)	55 (24)
Women [n(%)]*	– (0)	74 (71)	97 (42)
Median (IQR) follow-up (years) before AIDS	4.6 (2.9–6.2)	4.9 (3.1–6.3)	4.7 (2.3–6.9)
Pre-AIDS death [n(%)]	8 (3)	5 (5)	22 (10)
No. of AIDS diagnoses [n(%)]			
< 1991	17 (6)	4 (4)	12 (5)
1991–1992	24 (9)	2 (2)	7 (3)
> 1992	24 (9)	6 (6)	12 (5)

*$P < 0.05$. IQR, Interquartile range; IDU, injecting drug users.

Table 2. Crude and adjusted relative hazard (RH) for progression to AIDS according to period of seroconversion.

	Crude	Adjusted*	*P*
Year of seroconversion:			
< 1988	1.00		
1988–1989	1.09 (0.70–1.69)	0.88 (0.56–1.38)	0.57
> 1989	1.38 (0.73–2.62)	1.17 (0.61–2.25)	0.63

*Period of HIV seroconversion, age at seroconversion, combined exposure group/sex variable included in the model. CI, Confidence interval.

seroconverted before 1988 were under 25 years of age, compared with 34% in 1988–1989 and 33% after 1989 ($P < 0.001$).

Impact of the year of seroconversion

The median CD4 lymphocytes count at 24 months since seroconversion was 480×10^6/l for the those who seroconverted before 1988, 478×10^6/l for those who seroconverted in 1988–1989, and 451×10^6/l for those who seroconverted after 1989 ($P = 0.46$). In each exposure group, no significant difference in the median CD4 count at 24 months was observed. AIDS was diagnosed after 1987 in each of the three exposure groups, with 65 cases among homosexuals, 12 among heterosexuals, and 31 amongst IDU. Progression to AIDS (Fig. 1) did not differ significantly according to year of seroconversion in the total study population (log-rank test, $P = 0.61$) nor in the different exposure groups. The relative hazards (RH) of progression to AIDS in the total study population was 1.09 [95% confidence interval (CI), 0.70–1.69] for persons who seroconverted in 1988–1989, and 1.38 (95% CI, 0.73–2.62) for those who seroconverted after 1989 (Table 2). After adjustment for age at seroconversion, exposure group and sex, the RH were 0.88 (95% CI, 0.56–1.38) and 1.17 (95% CI, 0.61–2.25) respectively. The distribution of AIDS-defining conditions did not differ according to year of seroconversion. Choosing an earlier reference period (before 1986), which was only possible in the group of IDU, did not modify the main results.

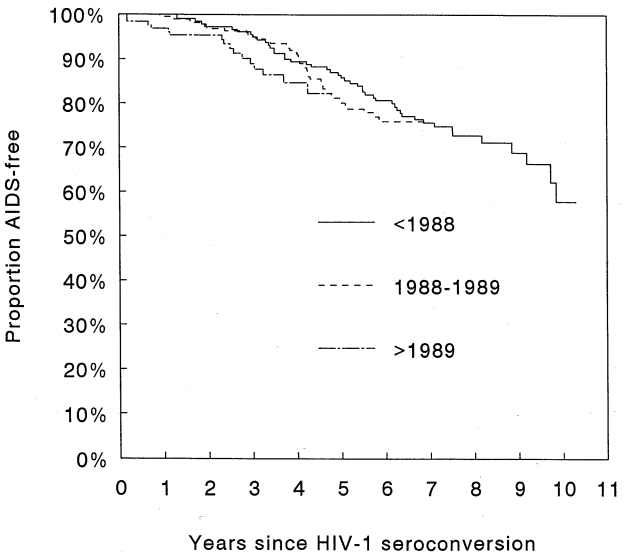

Fig. 1. AIDS-free survival curves according to period of seroconversion (curves truncated when fewer than 10 persons remained at risk).

Impact of the calendar period of follow-up

Sexual exposure groups

Among the homosexual and heterosexual persons followed during the most recent calendar period (after 1992), 21% had seroconverted before 1988, and 50% in 1988–1989. A slowing of progression to AIDS (Table 3) was suggested in the course of calendar periods 1991–1992 (RH, 0.51; 95% CI, 0.25–1.02) and after 1992 (RH, 0.58; 95% CI, 0.26–1.30) relative to the reference period (before 1991). After adjustment for age, exposure group, and sex, the RH of progression to AIDS was 0.49 (95% CI, 0.24–0.99) in persons followed in 1991–1992, and 0.54 (95% CI, 0.24–1.21) in those followed after 1992. These relative risks were unaffected by adjustment for the year of seroconversion. The median CD4+ cell count at the time of AIDS diagnosis declined from 179×10^6/l before 1991, to 94 and 102×10^6/l in 1991–1992 and after 1992, respectively, although this decline was not statistically significant due to small numbers (n = 68).

Table 3. Crude and adjusted relative hazard (RH) for progression to AIDS by calendar period of follow-up.

	No. persons at risk within calendar period	RH (95% CI) Crude	RH (95% CI) Adjusted	*P*
Sexual risk group* (n = 385)				
Calendar period:				
< 1991	(344)	1.00		
1991–1992	(309)	0.51 (0.25–1.02)	0.49 (0.24–0.99)	0.05
> 1992	(269)	0.58 (0.26–1.30)	0.54 (0.24–1.21)	0.14
Injecting drug users† (n = 231)				
Calendar period:				
< 1991	(170)	1.00		
1991–1992	(176)	0.87 (0.33–2.30)	0.70 (0.23–2.09)	0.51
> 1992	(181)	1.38 (0.57–3.33)	1.00 (0.32–3.12)	0.99

*For adjusted RH: calendar period, age at seroconversion, and exposure group/sex included in the model. †For adjusted RH: calendar period, age at seroconversion, sex, and study sites included in the model. CI, Confidence interval.

Table 4. Prescription of reverse transcriptase inhibitors and primary prophylaxis of *Pneumocystis carinii* pneumonia (PCP) before AIDS onset, according to the calendar period of follow-up.

	No. subjects who reached CD4 < 200 × 10^6/l within calendar period	Zidovudine*	PCP prophylaxis
Sexual risk groups			
Calendar period			
< 1991	37	11	5
1991–1992	40	48	33
> 1992	55	53	35
P value		0.001	0.004
Injecting drug users			
Calendar period			
< 1991	4	0	0
1991–1992	11	9	9
> 1992	7	14	57
P value		0.99	0.05

Proportion of subjects (%) receiving antiretroviral drugs and PCP prophylaxis at the CD4 count threshold of 200 × 10^6/l among those who reached this threshold during calendar period of follow-up. Data on treatment were available for 126 injecting drug users, 22 of whom reached a CD4 count < 200 × 10^6/l after 1987. *Zidovudine or other reverse trancriptase inhibitors.

Table 5. Proportion (%) of opportunistic infections, including *Pneumocystis carinii* pneumonia (PCP), and frequency of Kaposi's sarcoma among all first AIDS-defining illnesses according to calendar period of follow-up.

	n	Opportunistic infections (including PCP)	PCP	Kaposi's sarcoma
Sexual risk groups				
Calendar period				
< 1991	21	57	29	33
1991–1992	26	50	15	34
> 1992	30	77	17	17
P value		0.10	0.51	0.25
Injecting drug users				
Calendar period				
< 1991	12	100	67	–
1991–1992	7	71	29	–
> 1992	12	83	17	3
P value		0.60	0.05	

All *P* values calculated with Fisher's exact test (extended version).

Antiretroviral treatment was prescribed earlier in the course of the infection after 1991 (Table 4). Indeed, 11% of AIDS-free subjects who had reached the CD4 count threshold of 200 × 10^6/l before 1991 were already receiving treatment, compared with 48 and 53% of those who reached this threshold in 1991–1992 and after 1992, respectively ($P = 0.001$). Primary prophylaxis for PCP also became more frequent from 1991 onwards. When the first CD4+ cell count fell below 200 × 10^6/l, 5, 33, and 35% of AIDS-free patients in each calendar period respectively, were on prophylaxis ($P = 0.004$). Indeed, PCP was less frequently diagnosed as first AIDS-defining conditions from 1991 onwards, although the difference was not statistically significant (Table 5). However, the fall in the frequency of Kaposi's sarcoma in the most recent period led to an overestimation of the relative frequency of PCP during the same period. After censoring subjects not having developed PCP as first AIDS-defining disease at the date of diagnosis, the risk of developing PCP fell from 1991 onwards, the adjusted RH being 0.30 (95% CI, 0.06–1.39) in 1991–1992, and 0.29 (95% CI, 0.05–1.93) after this date.

IDU

Amongst IDU monitored during the most recent calendar period, 33% had seroconverted before 1988, and 22% in 1988–1989. The crude RH of progression to AIDS was 0.87 (95% CI, 0.33–2.30) in the calendar period 1991–1992, and 1.38 (95% CI, 0.57–3.33) in the following calendar period. After adjustment for age, sex and the participating centres, progression to AIDS was still stable during the different calendar periods, with respective adjusted RH of 0.70 (95% CI, 0.23–2.06) and 1.00 (95% CI, 0.32–3.12) compared with the reference calendar period. No decline in the CD4 count at AIDS diagnosis (n = 22) was observed over time. Treatment (intention to treat) was given in few IDU before their first CD4+ cell count fell below 200 × 10^6/l (0% before 1991, 9% in 1991–1992, and 14% after 1992; $P = 0.99$). Six months after reaching this threshold, a more marked increase was observed over time (0, 27 and 43%, respectively). Primary prophylaxis of PCP was increasingly prescribed over the course of the study period (0, 9, and 57%, respectively, at the first CD4 count < 200 × 10^6/l, $P = 0.05$). Six months after reaching this threshold, those proportions were 0, 27, and 71%, respectively. A significant decrease of PCP as AIDS-defining illness (Table 5) was observed amongst IDU ($P = 0.05$). Consequently, the risk of developing PCP fell regularly over the three periods, the adjusted RH being respectively 0.31 (95% CI, 0.05–1.92) and 0.15 (95% CI, 0.02–1.20) after censoring those having developed another AIDS-defining disease at the date of diagnosis.

Discussion

This study conducted in various exposure groups did not provide evidence of a more rapid progression of the disease in subjects who seroconverted in recent years compared with those who seroconverted between 1983 and 1987. In contrast, investigating the effect of calendar period of follow-up, a clear although not significant trend towards less rapid progression to AIDS was observed in sexual exposure group from 1991 onwards, although we did not find this favorable trend in IDU.

The AIDS incubation period can be influenced by factors linked to the immunological response [20,21] and to the virus itself [17,22]. The possibility of secular changes in HIV-1 pathogenicity has been raised by some authors [23,24]. Indeed, nearly 40% of US military personnel infected at the end of the 1980s reached the CD4 count threshold of 500×10^6/l within months of HIV seroconversion. This unusual high percentage suggests that a large proportion of these subjects were likely to progress rapidly to AIDS and, by implication that progression rates to AIDS may vary according to the year of seroconversion. Nonetheless, large studies conducted in the United States in homosexual men and in Italy in various exposure groups suggested that the rate of decline in the CD4+ cell count during the months following infection remained stable between 1984 and 1992 [5,25]. When comparing the median CD4+ cell count at 24 months since seroconversion in our study population, we found very similar results according to year of seroconversion. However, using CD4 cell measurement close to seroconversion to evaluate secular changes in HIV-1 suppose an early effect of those changes on HIV infection, even though these effects might only be detectable at a later stage [25]. We found no evidence of a more rapid progression to AIDS according to year of seroconversion. The use of another method to estimate the date of infection [15] or a different categorization of years of seroconversion did not affect the results (data not shown). However, our results were not in agreement with those recently published by Sinicco *et al.* [26], and further studies are needed to assess trends on longer periods and in different regions of the world. The discordant results obtained in studies of US army personnel [23,24] still raise the possibility of more pathogenic HIV-1 strains in other regions, as most of the personnel served in non-European areas.

In contrast, progression to AIDS slowed among homosexual and heterosexual subjects monitored from 1991 onwards, as shown by the relative risks associated with the most recent calendar periods of follow-up and the fall in the CD4+ cell count at AIDS onset [27]. Adjustment for the year of infection did not influence the results. Our observations differ from those of Hessol *et al.* [9], which suggested faster progression to AIDS in homosexual men monitored in 1991–1992. However, the reference period (before July 1987) in this previous study was before the adoption of the extended AIDS classification of 1987, which enlarged the subsequent diagnosis of AIDS-defining illnesses. In our study, the first cases of AIDS occurred in 1988 in each of the exposure groups, ruling out this potential source of bias.

The fall in the incidence of PCP among sexual exposure groups and IDU cannot alone explain the slowing of disease progression recently observed in the sexual exposure groups because there was no clear trend in favor of a recent slowing of progression to AIDS in IDU. Due to the limited number of AIDS cases among IDU, and the merging of different subcohorts, this finding on the overall progression to AIDS must be interpreted with care. Nevertheless, there was no significant difference in progression to AIDS among the original cohorts [15] and no temporal trend in pre-AIDS mortality was observed (data not shown). In addition, according to Graham *et al.* [28], primary prevention of PCP significantly reduces the incidence of this opportunistic infection, but would not alone slow the progression to AIDS at a population level, contrary to zidovudine use. Among sexual exposure groups, a significant increase of antiretroviral prescription (mainly zidovudine alone) at the threshold of 200×10^6/l was observed in 1991–1992 and later, suggesting that antiretroviral drugs were prescribed earlier from 1991 onwards. In the United States, the fall in the incidence of AIDS among homosexual men observed after 1987 and the lack of a favorable trend amongst IDU were attributed to differences in zidovudine prescription, alone or combined with other antiretroviral drugs [12]. Despite regular follow-up in a cohort, very few IDU were receiving antiretroviral treatment when their CD4+ cell count fell below 200×10^6/l, suggesting that treatment was delayed [29,30]. Although the effect of zidovudine on the progression to AIDS is limited [31,32], treatment before the CD4+ cell count falls below 200×10^6/l is more effective than later treatment [33,34]. The efficacy of zidovudine before this cut-off is transient, however, and the improvement observed in the first year of treatment disappears thereafter [35]. Indeed, in our study, the reference calendar period (before 1991) was essentially limited to follow-up during the first 5 years after seroconversion, as most subjects were infected after 1986. The comparison of the different calendar periods of follow-up is thus equivalent to estimating relative risks on the basis of data on subjects who are likely to develop AIDS rapidly. Hence, in terms of RH, the impact of this short time effect of early zidovudine use could be lower with much longer periods of follow-up.

Contrary to sexual exposure groups, the proportion of IDU treated with zidovudine before their CD4+ cell count reached 200×10^6/l was probably too small for a favorable trend to be observed during the recent calendar periods. In addition, compliance with these heavy treatments is probably poor in some patients, especially active IDU [28] and those not part of methadone programmes [11]. Finally, exclusion of IDU from clinical trials limits their access to early medical surveillance, including some non-specific treatments delaying the onset of opportunistic infections (e.g. the effect of fluconazole on the onset of invasive candidiasis and cryptococcal infection) [36]. This latter information was not available in our study population.

In conclusion, we did not observe a faster progression to AIDS in persons infected in recent years. A clear trend towards less rapid progression to AIDS was observed for those followed from 1991 onwards in the sexual exposure groups who had early medical management, including appropriate prescription of zidovudine or other reverse transcriptase inhibitors. This favorable trend was not found amongst IDU, who were treated later in the course of the disease. A fall in the incidence of PCP was observed in all the three exposure groups, probably attributable to primary prophylaxis. IDU did not appear to benefit rapidly from medical progress made since the beginning of the HIV epidemic, suggesting the fact that health-care systems are not always adapted to their lifestyles. In the promising era of early combined therapy including protease inhibitors, further investigations are urgently needed in IDU to improve their level of care.

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