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ORIGINAL RESEARCH

Uptake of and virological response to antiretroviral therapy among HIV-infected former and current injecting drug users and persons in an opiate substitution treatment programme: the Swiss HIV Cohort Study

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Objectives

The aim of the study was to investigate the influence of continued injecting drug use, enrolment in an opiate substitution treatment programme (OSTP), or cessation of injecting drug use on the uptake and course of antiretroviral therapy (ART).

Design

A prospective observational study of all participants in the Swiss HIV Cohort Study followed between 1997 and 2006 was carried out.

Methods

We distinguished four groups of former or current injecting drug users (IDUs): (i) abstinent former IDUs; (ii) persons in OSTPs without concomitant injecting drug use; (iii) persons in OSTPs with concomitant injecting drug use; (vi) current IDUs. These groups were compared with a group of patients who had never been IDUs. Factors related to ART uptake and virological endpoints were analysed using logistic generalized estimating equations.

Results

We followed 8660 participants for 48 477 person-years; 29.7% were in the IDU HIV transmission group. The likelihood of being on ART at biannual visits was lower among individuals in OSTPs with concomitant injecting drug use [odds ratio (OR) 0.79; 95% confidence interval (CI) 0.71–0.89] and current IDUs (OR 0.80; 95% CI 0.67–0.96), compared with those who had never been IDUs (reference), abstinent former IDUs (OR 1.13; 95% CI 1.02–1.25) and individuals in OSTPs without injecting drug use (OR 1.18; 95% CI 1.06–1.31). The likelihood of suppressed viral replication on ART was similar among those who had never been IDUs, abstinent former IDUs and individuals in an OSTP without injecting drug use, and lower among those in OSTPs with concomitant drug use (OR 0.82; 95% CI 0.72–0.93) and current IDUs (OR 0.81; 0.65–1.00). Adherence to ART was decreased among persons with continued injecting drug use, and correlated with virological outcome.

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[†]See Appendix A.

Conclusions
Uptake of and virological response to ART were improved among abstinent former IDUs and persons in OSTPs without concomitant injecting drug use, compared with persons with continued injecting drug use.

Keywords: antiretroviral therapy, cohort study, HIV infection, injecting drug use, opiate substitution

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Introduction

Injecting drug users (IDUs) are at risk for HIV, hepatitis B virus (HBV), hepatitis C virus (HCV) and other infections transmitted by nonsterile injection, toxicities of illicit drugs, poor nutrition, depression, and the psychosocial, economic and legal consequences of drug addiction. Sharing of contaminated injection equipment and unprotected sexual contacts with infected IDUs contribute world-wide to the transmission of HIV, HBV and HCV [1]. In 2008, the number of current IDUs world-wide was estimated as approximately 15.9 million (range 11.0–21.2 million) in 148 countries for which data were available [2].

Care of IDUs requires interdisciplinary treatment of drug addiction and its psychosocial and somatic complications. Combination antiretroviral therapy (ART) of HIV-infected IDUs is complicated by multiple factors [3], such as impaired adherence to therapy [4–7], the potential for interactions among medication, opiate substitution and illicit drugs [8], adverse effects [9], and limited access to [10,11], delayed use of [10,12,13], and decreased response to treatment [4,7]. As a consequence of such difficulties, physicians may be reluctant to offer ART to HIV-infected IDUs [14,15], resulting in less than optimal care and worse outcome [16,17].

In HIV research, the term 'IDU' is commonly used to describe the HIV transmission category or patient characteristics. When investigating the course of HIV infection and the outcome of ART in these patients, however, it is an oversimplification to consider IDUs as a homogenous group. IDUs frequently change their drug injection behaviour, drug addiction treatment status or health care setting [18,19]. We aimed to investigate the influence of injecting drug use behaviour and enrolment in opiate substitution treatment programmes on the uptake of and virological response to ART among persons classified as belonging to the IDU HIV transmission group, and to study the association between injecting drug use behaviour and adherence to ART. We distinguished four distinct groups of former or current IDUs: (i) abstinent former IDUs who had completely stopped injecting drugs; (ii) persons in opiate substitution treatment programmes (OSTPs, providing substitution with methadone or buprenorphine or legal heroin) who had stopped injecting illicit drugs; (iii) persons in OSTPs with continued concomitant injecting drug use; and (iv) current IDUs with ongoing injecting drug use who were not enrolled in a drug addiction treatment programme.

Methods

Design and data collection

Initiated in 1988, the Swiss HIV Cohort Study (SHCS; www.shcs.ch) is a prospective observational study of HIV-1-infected individuals treated at the HIV out-patient clinics of five university hospitals and two large district hospitals [20]. In addition, 25.4% of the participants are followed by private physicians and 4.8% by associated regional hospitals collaborating with the SHCS centres. As of 31 December 2006, 14 400 persons were enrolled.

Standardized data-collection forms containing demographic, clinical, laboratory and treatment information are completed every 6 months by physicians and study nurses. The forms include questions on the presumed HIV transmission category, whether the patient has ever injected drugs, whether the patient has injected drugs in the last 6 months, and whether the patient has been enrolled in an OSTP within the last 6 months. A questionnaire to document self-reported adherence to ART was introduced in July 2003, and was found to predict virological outcome of ART [21,22]. OSTPs are not carried out by the SHCS centres but by authorized specialized institutions or authorized private physicians.

Study participants

All participants of the SHCS with at least two regular biannual cohort visits between 1 January 1997 and 31 December 2006 and available CD4 lymphocyte counts and HIV-1 RNA at baseline visit ($\pm$ 30 days) were selected, including patients who were enrolled in the SHCS prior to 1997. The observation period was selected in order to include participants with access to combination ART (in Switzerland, protease-inhibitor containing ART became available in 1996). The SHCS has been approved by local ethical committees and written informed consent was obtained from all participants.

Outcomes and definitions

We assessed the following antiretroviral treatment outcomes for the four groups of former or current IDUs (as defined below) and persons categorized as never having been IDUs: (i) starting ART between the current visit and the next visit; (ii) being on ART at the current visit; (iii) currently having interrupted ART; (iv) current HIV-1 RNA below the level of detection (i.e. <400 HIV-1 RNA copies/mL until February 1998; <50 copies/mL thereafter).

At baseline (i.e. the first visit in 1997 or thereafter) and at every biannual cohort visit, the SHCS participants were categorized as never having been IDUs or, according to their injecting drug use behaviour during the previous biannual period, as (i) abstinent former IDUs, (ii) being in an OSTP without ongoing injecting drug use; (iii) being in an OSTP with concomitant injecting drug use; or (iv) current IDUs.

In terms of their ART status, patients were categorized as being treatment-naïve, having interrupted treatment, or being on treatment at every follow-up visit. For some analyses we distinguished between patients who initiated ART as mono/dual therapy and those who started with potent combination ART [at least three drugs including a protease inhibitor (PI) or a nonnucleoside reverse transcriptase inhibitor (NNRTI) or abacavir as the third drug in addition to two nucleoside reverse transcriptase inhibitors].

Antiretroviral treatment regimens were categorized as follows: two nucleoside reverse transcriptase inhibitors (NRTIs) plus (i) unboosted saquinavir, (ii) other unboosted PIs, (iii) a ritonavir-boosted PI, (iv) an NNRTI, (v) a PI plus an NNRTI, (vi) abacavir, or (vii) other combinations.

Active HCV infection was defined as HCV seropositivity and HCV RNA positivity (patients who were HCV seropositive and HCV RNA negative were considered to have inactive HCV infection). Active HBV infection was defined as HBV seropositivity and HBV surface (HBs) or envelope (HBe) antigen or HBV DNA positivity.

Statistical analysis

The characteristics of the different patient groups were compared using Wilcoxon rank sum (two groups) or Kruskal–Wallis (more than two groups) tests for continuous variables and χ^2 tests for categorical variables.

We used univariable and multivariable logistic generalized estimating equations (GEEs) to determine whether there was an association between IDU status and the binary treatment-related outcomes. Models were adjusted for calendar year, sex, age, prior clinical AIDS and $\log_2$-transformed concurrent CD4 cell counts. We also performed sensitivity analyses for the virological outcome by including time-updated antiretroviral treatment regimens to disentangle the effects of the injecting drug use behaviour from those of potentially less potent regimens prescribed. Changes in IDU status, ART status and CD4 cell count were time-updated at follw-up visits.

We used STATA (version 10.0; StataCorp, College Station, TX, USA) for analyses.

Results

Patient characteristics

Between 1997 and 2006, a total of 8772 SHCS participants had at least two biannual cohort visits; 112 persons (1.3%) were excluded because either no CD4 lymphocyte count or no HIV-1 RNA measurement was available ± 30 days of baseline. Of the 8660 participants included, 2569 (29.7%) were categorized as belonging to the IDU HIV transmission group (Table 1): Of these, 1080 (12.5%) were abstinent former IDUs reporting complete discontinuation of injecting illicit drugs; 741 (8.6%) were enrolled in an OSTP and had discontinued injecting drug use; 607 (7.0%) reported ongoing concomitant injecting drug use despite being in an OSTP; and 141 (1.6%) were current IDUs. Compared with those who had never been IDUs, the four groups of former or current IDUs included a higher proportion of women, were registered earlier in the SHCS, had longer durations of HIV infection, had a lower CD4 cell count at baseline and were more frequently coinfected with HCV. Abstinent former IDUs and persons in OSTPs without concomitant injecting drug use were more likely to have started ART with mono or dual drug combinations.

During the total observation time of 48 477 person-years, 91 838 visits were recorded. The median [interquartile range (IQR)] observation time per participant was 5.8 (2.6–9.0) years. The proportion of persons who died was 9.3%, and that of those who were lost to follow-up was 18.8%; these proportions were substantially higher among the groups of former or current IDUs (Table 1).

Adherence to antiretroviral therapy

For 5833 (67.4%) of the total of 8660 study participants, self-reported adherence to ART was assessed from July 2003 in 27 846 visits. The proportions of patients who never missed a dose of ART within the previous month among those who had never been IDUs, abstinent former IDUs, persons in OSTPs without injecting drug use, persons in OSTPs with concomitant injecting drug use and current IDUs were 78.8% [95% confidence interval (CI) 78.2–79.3%], 69.8% (95% CI 68.3–71.2%), 70.9% (95% CI 68.9–72.8%), 60.7% (95% CI 56.8–64.4%) and 54.9% (95% CI

Table 1 Baseline characteristics and outcomes at last visit for 8660 participants in the Swiss HIV Cohort Study followed between 1997 and 2006

		Baseline IDU category (at time of first visit in 1997 or thereafter)			
	Never IDU*	Abstinent former IDU	OSTP without injecting drug use	OSTP with concomitant injecting drug use	Current IDU
Baseline					
No. of persons (%)	6091 (70.3)	1080 (12.5)	741 (8.6)	607 (7.0)	141 (1.6)
Female (% of baseline category)	29.0	37.1	36.4	37.1	29.1
Age (years) [median (IQR)]	37 (32–45)	36 (32.5–39)	36 (32–39)	34 (30–38)	33 (29–39)
Median date of registration in cohort	16 Feb 1999	11 Sep 1995	18 Apr 1995	9 Jan 1997	17 Feb 1998
Years since first positive HIV test [median (IQR)]	1.27 (0.1–5.8)	9.2 (4.5–11.5)	9.0 (4.3–11.7)	5.4 (0.9–10.7)	3.6 (0.5–9.3)
Nadir CD4 cell count (cells/μL) [median (IQR)]	257 (111–432)	202.5 (81–356.5)	192 (86–357)	245 (120–470)	277 (156–512)
Prior clinical AIDS (% of baseline category)	19.0	22.1	20.4	17.3	9.2
Active hepatitis C virus infection (%)†	7.1	85.6	93.8	96.1	89.8
Active hepatitis B virus infection (%)†	4.7	3.8	3.5	4.3	5.1
Active hepatitis B and C virus coinfections (%)†	0.3	3.1	3.2	3.6	4.4
Started mono or dual therapy (% of treated)	54.2	66.1	65.5	44.8	40.4
Last visit					
Years on follow-up [median (IQR)]	5.6 (2.5–8.9)	6.9 (3.2–9.3)	5.6 (2.5–9.0)	5.4 (2.5–8.7)	5.8 (2.4–8.8)
Total person-years on follow-up	33 751	6599	4104	3253	771
No. of cohort visits/year [median (IQR)]	2.2 (1.9–2.3)	2.0 (1.7–2.1)	2.0 (1.7–2.2)	1.9 (1.5–2.1)	1.9 (1.4–2.2)
Developed AIDS-defining disease[*n* (%)]	353 (5.8)	73 (6.8)	60 (8.1)	64 (10.5)	14 (9.9)
Died [*n* (%)]	374 (6.1)	136 (12.6)	162 (21.9)	110 (18.1)	21 (14.9)
Lost to follow-up [*n* (%)]	917 (15.1)	273 (25.3)	201 (27.1)	185 (30.5)	51 (36.2)
Remained antiretroviral treatment naïve (%)‡	9.8	9.2	7.4	17.0	19.2
Discontinued antiretroviral treatment (%)§	17.9	21.7	26.6	28.2	27.0
On antiretroviral treatment (%)	72.4	69.2	66.0	54.9	53.9
HIV-1 RNA <50 copies/mL (if treated) (%)	81.4	75.6	74.4	72.7	71.1
Years on antiretroviral treatment [median (IQR)]‡	5.4 (2.4–8.8)	6.4 (3.2–9.7)	5.2 (2.0–8.9)	3.9 (1.5–7.2)	3.6 (1.3–7.1)
Not on treatment, last CD4 count <200 cells/μL (%)	11.5	26.1	29.8	30.3	24.6

*Mode of HIV transmission: heterosexual contact, 2918; men who have sex with men, 2862; other, 311 persons.
†At baseline or during follow-up. Hepatitis C virus status unknown in 118 individuals (1.4%); hepatitis B virus status unknown in 185 (2.1%).
‡Treatment history including time before cohort enrolment and during cohort follow-up.
§Of those who were alive and did not drop out.
IDU, injecting drug user; IQR, interquartile range; OSTP, opiate substitution treatment programme.

46.4–63.2%), respectively. The proportions of patients in these groups who never missed several consecutive ART doses within the previous month were 96.8% (95% CI 96.5–97.0%), 94.9% (95% CI 94.2–95.5%), 95.2% (95% CI 94.2–96.0%), 91.1% (95% CI 88.6–93.1%) and 86.1% (95% CI 79.4–91.3%), respectively.

Trajectories of injecting drug use behaviour

Changes in injecting drug use behaviour during follow-up were reported frequently. Table 2 compares the injecting drug use behaviour at baseline, throughout all biannual visits and at the last cohort visit. Of the individuals classified as abstinent former IDUs at baseline, 72.0% remained in this category throughout all cohort visits, meaning that they had no relapse of injecting drug use and were not enrolled in an OSTP while followed in the cohort. At the last follow-up visit, 84.6% of this group reported abstinence during the previous 6-month observation period. The proportions of individuals who were classified at baseline as being in the OSTP group without concomitant drug use, in the OSTP group with concomitant drug use, and current IDUs, respectively, and who remained in the same IDU category throughout all visits, were 25.2, 12.2 and 4.3%. The proportions of persons in these three IDU groups who had achieved complete abstinence from injecting drug use at the last follow-up were 23.5, 16.8 and 45.4%, respectively.

Uptake and outcome of antiretroviral therapy

During follow-up, the proportion of individuals who remained treatment-naïve ranged between 7.4 and 19.2%, and was highest among the current IDUs (Table 1). At the last follow-up visit, between 53.9% (current IDUs) and 72.4% (those who had never been IDUs) of individuals were on ART. Of those on ART, between 71.1% (current IDUs) and 81.4% (those who had never been IDUs) had suppressed viral replication. The median observation time on ART ranged between 3.6 years (current IDUs) and 6.4 years (abstinent former IDUs). Of patients with CD4 cell counts below 200 cells/μL at the last cohort visit, between 11.5%

Table 2 Trajectories of drug use behaviour during follow-up among 2580 injecting drug users (IDUs)

	Baseline IDU category			
Follow-up drug use behaviour	Abstinence, former IDU	OSTP without injecting drug use	OSTP with concomitant injecting drug use	Current IDU
Throughout all visits (%)	72.0	25.2	12.2	4.3
At last follow-up visit (%)				
Abstinence, former IDU	84.6	23.5	16.8	45.4
OSTP without injecting drug use	9.4	60.5	48.8	24.8
OSTP with concomitant injecting drug use	3.1	14.3	31.8	19.2
Current IDU	2.4	1.8	2.6	10.6

IDU, injecting drug user; OSTP, opiate substitution treatment programme.

Table 3 Antiretroviral therapy (ART) at baseline

	Baseline IDU category					
Antiretroviral therapy	Never IDU	Abstinent former IDU	OSTP without injecting drug use	OSTP with concomitant injecting drug use	Current IDU	Total
Trizivir [*n* (% of persons on treatment)]	51 (1.6)	7 (1.1)	7 (1.7)	4 (1.9)	0 (0)	69 (1.6)
2 NRTIs + unboosted saquinavir [*n* (%)]	54 (1.7)	21 (3.3)	12 (2.8)	8 (3.8)	2 (4.3)	97 (2.2)
2 NRTIs + other unboosted PI [*n* (%)]	1406 (45.0)	310 (49.2)	184 (43.3)	98 (46.5)	26 (55.3)	2024 (45.6)
2 NRTIs + boosted PI [*n* (%)]	384 (12.3)	31 (4.9)	25 (5.9)	8 (3.8)	0 (0)	448 (10.1)
2 NRTIs + NNRTI [*n* (%)]	361 (11.6)	34 (5.4)	22 (5.2)	10 (4.7)	6 (12.8)	433 (9.8)
3 class regimen [*n* (%)]	25 (0.8)	3 (0.5)	2 (0.5)	1 (0.5)	0 (0)	31 (0.7)
Other combination therapy [*n* (%)]	843 (27.0)	224 (35.6)	173 (40.7)	82 (38.9)	13 (27.7)	1335 (30.1)
Total on ART [*n* (%)]	3124 (100)	630 (100)	425 (100)	211 (100)	47 (100)	4437 (100)
Not on ART [*n* (% of all)]	2967 (48.7)	450 (41.7)	316 (42.7)	396 (65.2)	94 (66.7)	4223 (48.8)
All (no. of persons per category)	6091	1080	741	607	141	8660

IDU, injecting drug user; OSTP, opiate substitution treatment programme; trizivir, zidovudine plus lamivudine plus abacavir; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor. 'Boosted' means 'addition of ritonavir'.

(those who had never been IDUs) and 24.6% (current IDUs) were not on ART at that time.

Treatment regimens at baseline differed significantly between those who had never been IDUs and the four groups of former or current IDUs (Table 3). At baseline, the proportion of patients with unboosted saquinavir or other unboosted PI-containing ART was higher in the groups of former or current IDUs, probably because, on average, ART was initiated earlier in calendar time in these persons, before boosted PI-containing regimens were available. Furthermore, possibly because of the risk of potential interactions between NNRTIs and methadone, persons in the groups of former or current IDUs were less frequently on NNRTI-containing regimens compared with those who had never been IDUs. However, as described below, analyses including time-updated ART regimens did not explain the differences in virological endpoints among the IDU groups.

Figure 1 depicts ART uptake, ART status and suppression of HIV replication at cohort visits among persons in the four groups of former or current IDUs. The multivariable analyses were adjusted for demographic and clinical patient characteristics. The likelihood of ART uptake, treatment interruption and virological success was highly divergent between the group of patients who had never been IDUs and those in the four IDU groups. In contrast, if those who had never been IDUs were compared with those who had ever been IDUs (including all four IDU groups), differences between the groups appeared absent or minimal, except for the variable 'starting ART'.

The likelihood of being on ART at the current visit was higher in 1999 and thereafter, if CD4 cell counts were low, in the case of prior AIDS, and among men (data not shown). Compared with those who had never been IDUs (reference), abstinent former IDUs (OR 1.13; 95% CI 1.02–1.25) and individuals in an OSTP without concomitant injecting drug use (OR 1.18; 95% CI 1.06–1.31) were slightly more likely to be on ART at the current visit, whereas individuals in an OSTP with concomitant injecting drug use (OR 0.79; 95% CI 0.71–0.89) and current IDUs (OR 0.80; 95% CI 0.67–0.96) were significantly less likely to be on ART.

The likelihood of starting ART between the current follow-up visit and the next visit (if the patient was not already on treatment) was increased among persons with low CD4 cell counts and those who had never been IDUs. The likelihood of initiating ART was lower in all four groups of former or current IDUs and lowest among current IDUs (OR 0.42; 95% CI 0.28–0.62).

The likelihood of having interrupted ART since the previous visit was greatly increased among individuals in OSTPs with concomitant drug use (OR 1.52; 95% CI 1.31–1.77) and among current IDUs (OR 1.53; 95% CI 1.19–1.97).

The likelihood of having suppressed viral replication while on ART was similar among those who had never been IDUs (reference), abstinent former IDUs (OR 0.96; 95% CI 0.88–1.05) and persons in OSTPs who discontinued injecting drugs (OR 0.94; 95% CI 0.85–1.03), whereas individuals in OSTPs with concomitant injecting drug use (OR 0.82; 95% CI 0.72–0.93) and current IDUs (OR 0.81; 95% CI 0.65–1.00) were less likely to have an undetectable viral load. Differences in virological outcome among those who initiated mono or dual ART *vs.* combination ART were not significant (data not shown). Furthermore, while ART regimens showed dissimilarities among the different groups of former or current IDUs at baseline, differences in ART regimens did not explain the heterogeneity in virological outcome. The estimates remained virtually unchanged in sensitivity analyses including time-updated ART regimens categorized as in Table 3 for abstinent former IDUs (OR 1.00; 95% CI 0.92–1.10), persons in OSTPs who discontinued injecting drugs (OR 0.98; 95% CI 0.89–1.08), individuals in OSTPs with concomitant injecting drug use (OR 0.85; 95% CI 0.75–0.96) and current IDUs (OR 0.84; 95% CI 0.68–1.05).

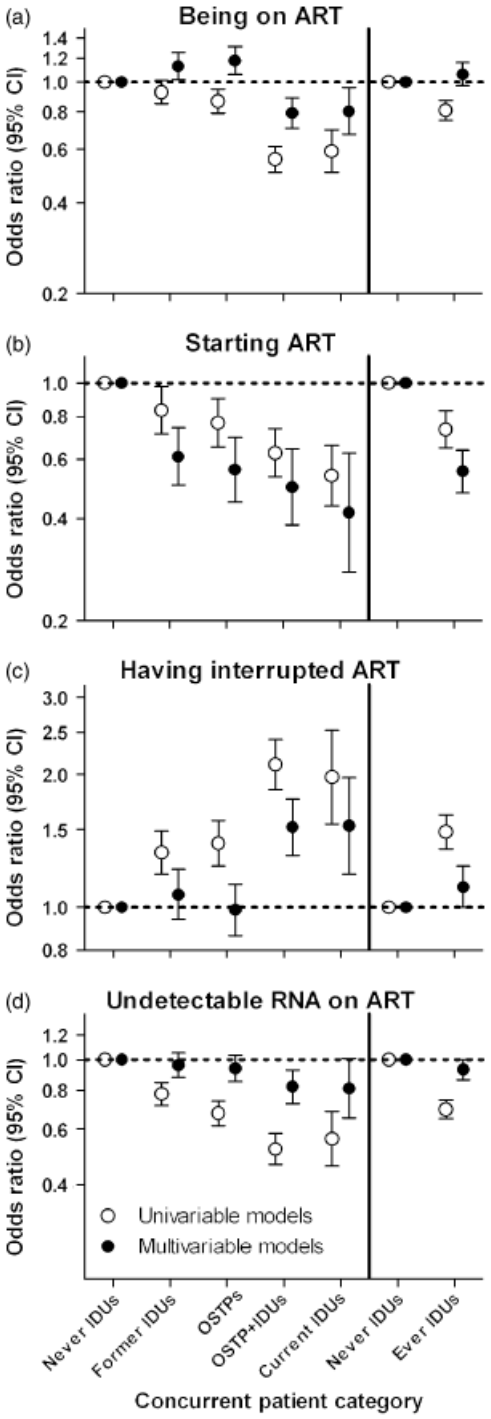

Fig. 1 Predictors of use and virological outcome of antiretroviral therapy (ART). Results of univariable (open circles) and multivariable (solid circles) logistic generalized estimating equations are presented, showing the odds ratios of (a) being on treatment at the current cohort visit; (b) newly starting treatment at or after the current cohort visit; (c) having interrupted treatment before the current cohort visit; and (d) having HIV-1 RNA below the limit of detection. The comparison between those who had never been injecting drug users (Never IDUs) and those who had ever been injecting drug users [Ever IDUs; all injecting drug users (IDUs) irrespective of current drug use or opiate substitution programme (OSTP)] is shown in the right part of each panel; the results for the four distinct IDU groups and those who had never been IDUs are compared in the left part of the panels. Multivariable models were adjusted for calendar year, gender, age, prior clinical AIDS, and $\log_2$-transformed CD4 cell counts. Terms used are as follows: former IDUs, those abstaining from injecting drug use at the time of follow-up and not in opiate substitution programmes; OSTPs, those in OSTPs without concomitant injecting drug use; OSTP + IDUs, those in OSTPs with concomitant injecting drug use; current IDUs, those with ongoing injecting drug use at the time of the cohort visit who were not enrolled in a drug treatment programme; CI, confidence interval.

Discussion

Treatment of injecting drug use and treatment of HIV infection impact one another [10,18]. We found that

enrolment in an OSTP and discontinuation of injecting drug use, respectively, were associated with improved uptake and outcome of ART. The likelihood of being on ART and having suppressed viral replication was similar among individuals who had never injected drugs, abstinent former IDUs and patients in an OSTP who completely stopped injecting illicit drugs, whereas individuals who continued to inject drugs despite being enrolled in an OSTP and current IDUs were less likely to be on ART, more frequently interrupted ART and, while on treatment, were less likely to have an undetectable viral load.

Before the availability of effective ART we found that current IDUs had a higher probability of HIV disease progression compared with patients in an OSTP or abstinent former IDUs, possibly because current IDUs did not seek or had less access to medical care, were less adherent to therapeutic interventions or suffered from non-HIV-related morbidity associated with nonsterile drug injections [23]. Furthermore, *in vitro* and animal studies found immunosuppressive effects of opiates, cocaine and other illicit substances [24–30]. Since 1996, combination ART has largely determined the outcome of HIV infection in patients with access to care [16], and mortality was found to be substantially reduced after the introduction of potent ART also among IDUs [31–33]. Therefore, drug addiction treatment programmes, which make access to somatic care possible, appear to be an important prerequisite for improved outcome of ART. In Switzerland, health insurance for all residents is mandatory, and HIV-infected IDUs have access to ART. Pharmacological and psychotherapeutic components of drug addiction treatment programmes are provided by a network of specialized institutions and authorized private physicians [34]. Opiate substitution mainly consists of oral methadone (approximately 80%), buprenorphin (15%) or legal heroin (5%) [35].

Our observation of comparatively unfavourable virological outcomes in persons who acquired HIV infection by injecting drug use may be explained by several findings: first, relapses of injecting drug use among abstinent former IDUs and those in OSTPs were frequent. Secondly, documented interruption of HIV treatment during follow-up and loss to follow-up at HIV treatment centres were particularly frequent occurrences among persons enrolled in OSTPs who continued concomitant injecting drug use and among current IDUs. Thirdly, poor adherence to ART correlated with continued injecting drug use [4,36,37]. Other factors, which were not assessed in our current study but may contribute to inferior virological outcome, may include poverty [38], lack of family support [39], alcohol use [37], smoking, depression [40,41], and psychiatric comorbidity [42]. Virological failure and failure of addiction treatment programmes among HIV-infected IDUs result in increased morbidity and mortality [19,31,42–45].

We confirm the findings of earlier studies which emphasize that successful ART is possible among former or current IDUs, and particularly effective in the setting of stable opiate substitution [5,11,18,31,32,46–48]. As a consequence, ART should not be withheld from this patient group. Also, programmes applying novel modes of administration of ART, such as directly administered ART in combination with opiate maintenance, resulted in improved virological and clinical outcome [46, 48]. In contrast, active injecting drug use and not being enrolled in an OSTP were associated with a lower likelihood of receiving ART, worse virological outcome and increased incidence of AIDS [4,5,7,18,36]. Of great concern are data showing that the incidence of AIDS has increased among some groups of IDUs in recent years compared with non-IDUs despite the availability of ART [36]. Such findings may be attributable to various barriers to the effective use of ART, including social or patient-related barriers, barriers associated with access to care or physicians' decisions [6,10,11,36], and a lower level of adherence to treatment [4,18]. In addition, direct or indirect biological effects of illicit drug use may affect the course of HIV infection and the response to ART [26]: CD4 cell recovery during successful ART in naïve HIV-infected patients was shown to be less pronounced among IDUs compared with non-IDUs [49]. Furthermore, although controversial, results obtained for our cohort indicate an impaired CD4 cell response to ART among individuals coinfected with HCV despite a similar viral response [50]. More than 85% of abstinent former or current IDUs are coinfected with HBV or HCV.

Our cohort study has notable strengths, in particular its prospective data collection over two decades and its large size, including a substantial number of abstinent former IDUs and persons in OSTPs. There are potential limitations to our analyses: because persons with injecting drug use who are not enrolled in a drug addiction treatment programme may hesitate to attend HIV referral centres or even to seek medical care, the number of current IDUs was relatively low. Further, consumption of alcohol, tranquillizers or other illicit drugs that are not injected – all of which may affect adherence to therapy or adherence to appointments with the health care provider [51] – was not documented. We assessed injecting drug use at 6-month intervals based on patients' self-reporting. Self-reporting, however, was found to be reliable with a sensitivity of at least 82% and a specificity of 88% when compared with urine tests [52,53]. Furthermore, injecting drug use behaviour was documented in our study by HIV cohort investigators and not by providers of drug addiction treatment programmes. Finally, loss to follow-up in the groups of former or current IDUs was higher than in other patients, which may lead to an underestimation of IDU-

associated mortality. We have, however, repeatedly cross-linked with the national death registry to establish the vital status of such patients [54].

Our data have important implications for the care of former and current IDUs and the conducting of clinical research. We showed that not all persons in the IDU HIV transmission group have a poor prognosis and that they are – with regard to treatment of HIV infection and drug addiction – not a homogenous group. Individuals may differ considerably with regard to the amount and frequency of illicit injecting drug use, participation in a drug addiction treatment programme and psychosocial or somatic comorbidity. Furthermore, patterns of drug use behaviour are changing frequently [18,19,55]. We found that ongoing injecting drug use is an important obstacle to ART and virological success, but, in contrast, that persons on stable opiate substitution have similar virological and clinical outcomes to abstinent former IDUs. Thus, adherence interventions for IDUs in drug addiction treatment programmes as well as for current IDUs are crucial elements of ART programmes, and will possibly contribute to the prevention of HIV transmission [56].

In conclusion, for HIV-infected IDUs, comprehensive interdisciplinary long-term strategies are needed that integrate treatment of addiction and HIV infection as well as psychosocial and somatic complications of injecting drug use. Programmes aiming for opioid abstinence or stable opiate substitution are important prerequisites for the initiation, maintenance and success of ART.

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Appendix A

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