High HIV seroconversion rate in hepatitis C virus-infected drug users followed in a harm reduction unit: a lost opportunity for preexposure prophylaxis

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Objectives: Current harm reduction strategies will probably remain insufficient to eliminate HIV transmission among drug users. We aimed to estimate the HIV seroconversion rate among drug users followed at a harm reduction unit (HRU) to evaluate the potential use of preexposure prophylaxis as a prevention tool.

Design and methods: A cohort of drug users has been followed at an HRU in Madrid between 2013 and 2016. Individuals who were HIV negative at baseline and who had at least one retest for HIV infection were eligible. Kaplan–Meier methods were employed to estimate the incidence density.

Results: A total of 954 drug users had at least an HIV test. At baseline, 260 were HIV negative and had at least one follow-up HIV test. After 330.89 person-years of risk for HIV infection, 10 (3.8%) seroconverted. Overall incidence density of HIV seroconversion was 3.02 [95% confidence interval (CI); 1.4–5.5] per 100 person-years, with differences according to hepatitis C virus (HCV) serostatus: 1.17 (95% CI; 0.1–4.2) per 100 person-years in negative HCV individuals and 4.98 (95% CI; 2.1–9.8) per 100 person-years in positive HCV individuals. In the multivariable analysis, infection with HCV remained independently associated with time to HIV seroconversion (adjusted hazard ratio = 6.43; 95% CI; 1.1–36.5, $P = 0.035$).

Conclusion: Despite efforts in HIV prevention in a HRU, a high incidence of HIV was found among active drug users. Positive HCV status is a strong predictor of HIV seroconversion. In this context, preexposure prophylaxis implementation should be considered as an additional tool for HIV prevention in this population.

AIDS 2018, **32**:1157–1163

Keywords: drug users, harm reduction, hepatitis C virus, HIV seroconversion, preexposure prophylaxis

Introduction

According to WHO reports, there were 2.1 million new HIV infections at the end of 2015 [1]. In Western and Central Europe, and North America, 15% of the new HIV infections were in people who injected drugs (PWIDs) [2]. The Joint United Nations Programme on HIV and AIDS reports that in Western and Central Europe and North America, the number of new infections among PWID has remained stable during the last 15 years, but there are regions such as Eastern Europe and Central Asia where it has increased by 30% in the same period [1].

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Received: 3 October 2017; revised: 19 January 2018; accepted: 23 February 2018.

DOI:10.1097/QAD.0000000000001806

ISSN 0269-9370

HIV incidence rates fluctuate according to regions [3–8] and to the total or partial implementation of harm reduction services [9–12]. Factors associated with HIV seroconversion have been identified and have included heroin and cocaine injections [13], receptive syringe sharing [12], sexual work [14], longer length of engagement in drug injection and fentanyl drug injections [15,16].

There are several evidence-based interventions that have been shown to reduce HIV transmission among PWID [17–19]. Needle/syringe programs [20,21], medication-assisted treatment for substance use disorders, opiate substitute therapy (OST) [22] and antiretroviral treatment for HIV infection [23] reduce HIV transmission among PWID. In addition, the low-threshold harm reduction programs (LTHRP) are flexible intervention programs that attend a marginalized population of heroin addicts with unstable lifestyle, who would not have access to regular programs characterized by restrictive selection criteria and limited availability, reducing barriers to admission and improving retention in treatment [24,25]. Despite effective harm reduction strategies, these measures alone are and will remain insufficient to eliminate HIV transmission completely [23].

Antiretroviral preexposure prophylaxis (PrEP) reduces sexual transmission of HIV. WHO and others international and local organizations recommend PrEP to all population groups at substantial risk of HIV infection [26–28]. Offering PrEP should be a priority for populations with an HIV incidence of about three per 100 person-years or higher [29]. In addition, recent results of the randomized, double-blind, placebo-controlled Bangkok Tenofovir Study showed that taking tenofovir daily as PrEP can reduce the risk of HIV infection by 49% in PWIDs [30].

HIV and hepatitis C virus (HCV) infection are readily transmitted among PWID. However, parenteral transmission of the HCV appears to be extremely efficient [17]. HCV is transmitted very efficiently through nonsterile injection practices, contamination of needles and syringes, as well as contaminated injection paraphernalia, creating a need for both more stringent adherence to safe injection techniques and adequate supplies of paraphernalia and syringes in comparison with HIV [31]. As to different biological, social, behavioral and historical–epidemiologic factors in PWID [31], the HCV global prevalence remains high in PWID, compared with HIV [32] and the degree of risk reduction required for population level impact appears to be greater [31,33,34]. Recently, an outbreak of HIV infection centered in the rural town of Austin in Scott County, Indiana, the HCV status was highly prevalent among the newly diagnosed HIV-infected persons [35].

HIV incidence and seroconversion predictors among cocaine and heroin injectors in the era of harm reduction and treatment as prevention is largely unknown in Spain as in most European countries. We therefore measured the HIV incidence density and factors associated with HIV seroconversion among illicit drug users followed in a harm reduction unit (HRU) in Madrid with the goal of assessing if current reduction harm strategies are sufficient to reduce new HIV infections to desirable levels, or if the implementation of PrEP should be considered as part of a comprehensive prevention plan.

Methods

For the current observational study, we pooled data from a cohort of drug users who actively consume heroin and/or cocaine, either smoked, injected or both, and are being followed at an HRU located in the outskirts of Madrid, Spain.

The HRU attends active drug users who have limited access to standard health care. This population consumes mainly heroin and cocaine in a marginalized way and has comorbidities such as blood-borne virus infections, skin and soft tissue infections, overdoses and emergency-derived aggressions. Also, most of them have impaired physical conditions and poor access to standard medical care. Also, they are psychologically disrupted, socially excluded and with frequent criminal records and behaviors.

The study was designed to estimate the time to HIV seroconversion among active drug users followed in an HRU in the period from January 2013 to December 2016. This HRU consists of mobile units that offer LTHRP such as sex and blood-borne infections counseling and testing, risk-reduction counseling, social services, primary medical care, directly observed treatment for chronic and acute infections that included HIV and HCV, OST, condoms, clean injection equipment, sterile needle and syringes, all free of charge. Methadone is prescribed at the mobile HRU on a daily basis and as a low threshold program. All individuals recruited during the study period were eligible for the analysis of baseline HIV prevalence, whereas individuals who were HIV negative at baseline and who had at least one follow-up visit (to retest for HIV infection) were eligible for the analysis of HIV incidence density.

An HIV enzyme-immunoassay and rapid tests were used as screening. All HIV tests initially reactive on ELISA were later confirmed by western blot analysis. Individuals with an initial HIV-positive test were excluded from the incidence density analysis and considered for the prevalence calculation. The seroconversion was considered as the change of HIV antibody from negative to positive. Baseline characteristics were collected for analysis of HIV seroconversion predictors in seroconverters and nonseroconverters.

Statistical analysis

Data for the analysis were collected from the HRU database that registered the unit's activity between 2013 and 2016. As an initial step, Kaplan–Meier methods were employed to estimate the global incidence density and incidence density stratified by HCV status and reported at 95% confidence intervals (CIs) calculated with normal approximation given the frequent events. The date of HIV seroconversion was estimated as the midpoint between an individual's last negative and first positive test. Although this is a frequently used method, it can be a limitation as presumably recent risk-taking behavior may prompt the service user to be retested. Participants remaining persistently HIV negative were censored at the time of their most recent available HIV antibody test result prior to December 2016. Pearson's chi-squared or Fisher's tests were used to compare categorical variables, and continue variables were compared using the Wilcoxon rank-sum test for independent variables.

We also calculated the unadjusted relative hazard of HIV seroconversion using Cox proportional hazard regression, and stratified for HCV status, to assess the independent effect of HCV status on time to HIV seroconversion. HCV status was determined as positive or negative according to the outcome of the first HCV serology performed after January 2013. We also considered secondary variables that might potentially confound the relationship between the HCV status variable and the outcome. These included in the adjusted analysis: sex (male vs. female), age (per 10 years older), methadone use (yes or not), injected drug use (yes or no) and nationality (Spanish vs. non-Spanish). For the multivariate analyses, all variables described above were adjusted.

Analyses were conducted using R software (R Foundation, Vienna, Austria), and the threshold for statistical significance was set at P less than 0.05. All P values were two sided.

Results

During the study period, 954 illicit drug users were seen and had performed at least an HIV test as part of the individual, initial intervention in our HRU. A total of 648 individuals were excluded, as they had a single HIV test, and 46 due to being HIV-infected at the first visit (Fig. 1). At baseline, 260 drug users were HIV negative and had at least one follow-up HIV test and were therefore included in the analysis of HIV incidence density. Six variables, which were routinely collected at screening (age, sex, nationality, methadone use, intravenous drugs use and HCV status), were available for all the participants and were included in the analyses. A comparison of the 694 HIV-negative drug users excluded from the analysis and the 260 included in the analysis revealed no significant

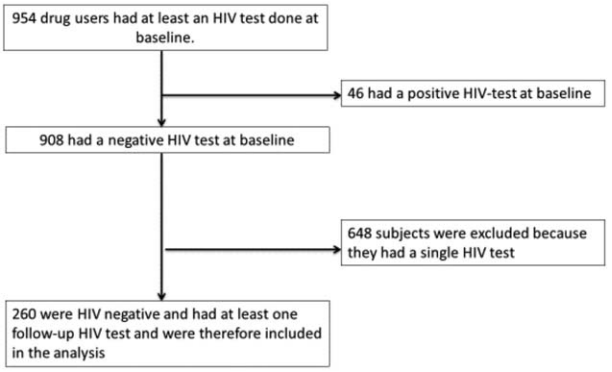

Fig. 1. Flowchart of the study population.

differences between the groups with respect to any of the sociodemographic characteristic considered: age (39.1 vs. 38.4; $P = 0.351$), male sex (76.0 vs. 70.2%; $P = 0.110$) and Spanish nationality (74.2 vs. 72.1%; $P = 0.672$).

Among the 260 baseline HIV-negative drug users, the median age was 36.8 [interquartile range (IQR) 32.3–41.5] and 165 (70.2%) were men. Overall, 85 (32.7%) individuals had a positive HCV test and 55% reported injected drug use. After a median 2.30 (IQR 1.1–3.2) years of follow-up, with a total of 330.89 person-years, 10 individuals (3.8%) seroconverted for HIV. Baseline characteristics of the drug users stratified for HIV nonseroconverters and seroconverters are shown in Table 1. The 10 HIV seroconverters drug users had a median age of 33 years (IQR 28.5–38.5); 70% were Spanish; eight (80%) had a positive HCV status; three (30%) were women, nine (90%) reported injecting drugs and five (50%) had ever received methadone prior to their HIV seroconversion in our HRU. All HIV seroconverters drug users reported to be heterosexual and denied the use of slam or chemsex.

The incidence density of HIV seroconversion for the entire sample was 3.02 (95% CI; 1.4–5.6) per 100 person-years. Stratified by HCV status, the incidence density rates of HIV infection were as follows: 1.17 (95% CI; 0.1–4.2) cases per 100 person-years among participants with negative HCV status at baseline, compared with 4.98 (95% CI; 2.1–9.8) cases per 100 person-years among those with positive HCV status at baseline (Fig. 2).

Table 2 shows the results of the unadjusted and adjusted Cox proportional hazard regression analyses of the time to HIV infection for baseline characteristics. In univariate analysis, the positive HCV status was positively associated with time to HIV seroconversion (hazard ratio = 8.34; 95% CI; 1.8–39.4, $P = 0.007$). In the multivariable analysis, after adjusting for sex, age, nationality, injected drugs use and methadone, the positive HCV status remained independently and positively associated with

Table 1. Baseline characteristics of drugs users stratified by HIV seroconversion.

Characteristics	HIV seroconversion		*P* value
	No, *n* = 250 (96.15%)	Yes, *n* = 10 (3.85%)	
Age, median (IQR)	39 (32–46)	33 (28.5–38.5)	0.074
Sex, male, *n* (%)	158 (70.2%)	7 (70%)	0.057
Spanish nationality	109 (72.2%)	7 (70%)	0.999
Methadone treatment	156 (66.9%)	5 (50%)	0.478
HCV status, positive	77 (30.8%)	8 (80%)	<0.001
Use of injected drugs	101 (52.1%)	9 (90%)	0.022

HCV, hepatitis C virus; IQR, interquantile range.

time to HIV seroconversion (adjusted hazard ratio = 6.43; 95% CI; 1.1–36.5, $P = 0.035$).

Discussion

In the current study, we found a high HIV incidence density among drug users followed in an HRU of Madrid (Spain) between January 2013 and December 2016 despite the implementation of LTHRP. Furthermore, a positive HCV status was independently associated with an increased rate of HIV seroconversion after adjusting for various confounders.

The finding of a high incidence in our population is consistent with other studies conducted in different countries [11,36], although some worrying disparities still persist. HIV incidence remains above 10 cases per 100 person-years in Southwest Asia and Eastern Europe, primarily as a result of sharing of injection equipment among heroin injectors and the lack of OST [37]. In contrast, HIV seroincidence densities lower than two

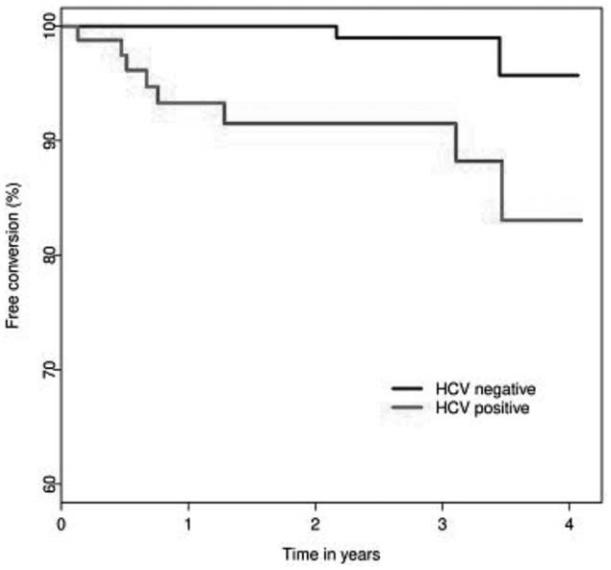

Fig. 2. Kaplan–Meier seroconversion-free survival curve.

cases per 100 person-years have been reported in some regions, although this might be explained by short follow-up periods [13,38] or that the places of participants recruitment were heterogeneous and included persons with nonactive consumption [14,15]. The different publications in the literature illustrate the vast heterogeneity of the studies that analyze the incidence of HIV seroconvertion in drug users. This is related to the different sociodemographic data between countries which include high heterogeneity in the degree of implementation of harm reduction strategies, time of follow-up and the selection of drug users for analysis.

A key finding of the current study is the independent association between a positive HCV status and acquiring HIV after adjusting of injected drug use. There is, however, a substantial overlap in the CI of HIV seroconversion by HCV status, which most likely is related with the low number of seroconversions recorded. To our knowledge, there are no published cohort studies comparing HIV incidence in populations according to HCV status. A cross-sectional survey performed in China found that HCV infection was significantly associated with being HIV positive [11]. HCV and HIV are infections readily transmitted through drug injection [39]. However, HIV is about 10 times less infectious than HCV [34,40]. The risk of HCV infection among PWID is greater than that of HIV infection due to biological, behavioral, social and epidemiological factors [40]. Therefore, the rapidity with which PWID may acquire HCV creates a need to reduce risk among PWID very early in injection careers. Currently, the HCV seroconversion rate remains high in Spanish drug injectors [41], and the HCV prevention efforts are insufficient to control the HCV epidemic among PWID [31], possibly for the inability of identify higher risk individuals of HCV acquiring. Conversely, in HIV, the presence of HCV infection would create a situation that precedes a potential risk of other blood transmitted infections, included HIV, and know the HCV status, could be a relevant tool that to help identify drug users at a higher risk of acquiring HIV infection.

As in other populations, PrEP should be an additional prevention tool inside of a comprehensive package of

Table 2. Univariate and multivariate Cox proportional hazard analyses of the time to HIV seronconvertion.

	Overall baseline	HIV nonseroconverts	HIV seroconverts	HR (95% CI)	*P* value	AHR (95% CI)	*P* value
Time invariant characteristics							
Sex							
Male	165 (70.2%)	158	7	0.82 (0.21–3.20)	0.780	0.34 (0.08–1.54)	0.162
Female	70 (29.8%)	67	3	1			
Spanish nationality							
Yes	116 (72.1%)	109	7	1.01 (0.25–3.87)	0.999	1.33 (0.30–5.97)	0.706
Not	45 (27.9%)	42	3	1			
Time varying exposure							
Median age (years, IQR)	36.8 (32.3–41.5)	39 (32–46)	33 (28.5–38.5)	0.93 (0.86–1.01)	0.104	0.95 (0.87–1.03)	0.222
Methadone exposure							
Yes	161 (65.5%)	156	5	0.53 (0.15–1.85)	0.324	1.17 (0.31–4.41)	0.819
No	85 (34.5%)	80	5	1			
HCV status							
Positive	85 (32.7%)	77	8	8.34 (1.76–39.42)	0.007	6.43 (1.13–36.50)	0.035
Negative	175 (67.3%)	173	2	1			
IDUs							
Yes	110 (55%)	102	9	7.61 (0.96–60.09)	0.054	3.78 (0.37–38.51)	0.260
No	92 (45%)	90	1	1			

Adjusted covariates include age, nationality, sex, methadone use and injected drugs use. AHR, adjusted hazard ratio; CI, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; IQR. interquartile range.

services [26]. The risk of becoming HIV infected varies largely among different subgroups of PWID, mainly associated with needle/syringe and paraphernalia sharing. Estimating this risk may be important as it has been suggested that the decision to take PrEP by PWID is based, at least in part, on their perceived risk of incident HIV infection [30]. But the graduation of the risk may be difficult, due to the fact that needle/syringe sharing behavior is underreported possibly because of stigmatization [42]. As shown in this report, HCV serostatus may help objectively identify and stratify an increased risk of HIV seroconversion among drug users. We agree with Bruneau *et al.* in that, rather than a polarizing debate around HIV PrEP contrasting biomedical tools and other harm-reduction strategies for HIV prevention, a better focus now would be to determine how we can integrate PrEP use into the existing arsenal of harm reduction programs for PWID [43]. Considering that PWID are approximately 24 times more likely to acquire HIV than the general adult population [15], omitting the evaluation of PrEP for use by PWID would represent a lack of opportunities of prevention, as well as a lack of ethical accountability [30].

The current study has several limitations. First, the current study does not include a random sample of PWID in our area. Drug users who return for HIV screening to the HRU could be at lower risk of HIV infection than those who are not engaged, and this fact could underestimate the incidence. Nevertheless, in a low threshold harm reduction setting, drug users who are offered screening are those with riskier behaviors. Also, proactive search of those at risk is carried out by healthcare providers at the HRU. Second, this study was carried out under extreme conditions, in which follow-up and engagement are variable and fluctuant due to prison admissions and relapsed and abstinence periods, frequents in drug addiction. This is a limitation that reduces the sample size, but nevertheless we think that it is still a representative sample of drug users seen at the HRU. Moreover, the extension of the conclusions is limited by the small numbers of HIV and HCV conversions, although the association is still significant. Third, the information related with the characteristics of the population studied, including the drug injection practices and the sexual behavior, were not collected at inclusion. We estimate the impact on sexual transmission may be minimal given that the risk of acquiring HIV through sexual route is much lower than injection practices in PWID as previously reported by El-Bassel *et al.* [33]. Although HIV seroconversion has been adjusted by current intravenous drug use, which is the main transmission risk factor, the results should be interpreted taking into account the missing data and that other needle-sharing behaviors were not analyzed. Fourth, there were 28 cases of HCV seroconversion during follow-up which have not been considered for the association with HIV infection as HCV screening with rapid tests was not available in the HRU during a large part of the study period. Further studies could evaluate the impact of recent HCV seroconversions. The findings of this investigation may not necessarily be generalizable to all persons who inject drugs or who live in other communities or countries. Our population represents a precarious one with high consumption of heroin and cocaine and with few o null periods of abstinence.

In summary, although a decreasing trend of new HIV infections in PWIDs is reported worldwide, there is still a high rate of HIV seroconversion in specific subgroups of

drug users. A positive HCV status remained independently associated with time to HIV seroconversion. In light of the above, our findings have major implications for HRU providers and for outreach workers' efforts to identify target drug users with more HIV acquired risk, doubling the prevention and educational services and HIV retesting more frequently. Therefore, during the time of active consumption, the HCV-infected PWID should be the target of more complex strategies for risk reduction, that could include PrEP as part of combination HIV prevention approaches.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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