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The impact of methadone or buprenorphine treatment and ongoing injection on highly active antiretroviral therapy (HAART) adherence: evidence from the MANIF2000 cohort study

Perrine Roux[1,2,3], M. Patrizia Carrieri[1,2,3], Virgine Villes[1,2,3], Pierre Dellamonica[4], Isabelle Poizot-Martin[5], Isabelle Ravaux[6] & Bruno Spire[1,2,3]

Inserm U912 (SE4S), Marseille, France,[1] Université Aix Marseille, IRD, UMR-S912, Marseille, France,[2] ORS-PACA, Observatoire Régional de la Santé Provence Alpes Côte d'Azur, Marseille, France,[3] Hôpital de l'Archet, Service des Maladies Infectieuses, Nice, France,[4] Hôpital Sainte-Marguerite, Unité CISIH Sud Hématologie VIH, Marseille, France[5] and Hôpital La Conception, Service des Maladies Infectieuses, Marseille, France[6]

ABSTRACT

Aims To date, no data exist assessing the impact of either methadone or buprenorphine on adherence to highly active antiretroviral therapy (HAART) in the long term. This study was conducted in order to evaluate whether receiving take-home methadone and buprenorphine may ensure better adherence to HAART in individuals infected with human immunodeficiency virus (HIV) through injection drug use (IDU). **Design** Longitudinal data on adherence, opioid substitution treatment (OST) and patient behaviours starting from their first HAART prescription were collected for 276 individuals HIV-infected through drug use ($n = 1558$ visits). **Setting** Out-patient hospital services delivering HIV care in Marseilles, Avignon, Nice and Ile de France. **Measurements** At any given visit, patients were classified both according to the type of OST received and ongoing injection. Patients who reported no injection and no OST over the whole study period were considered as 'abstinent' and used as a reference category. A logit model based on generalized estimation equations (GEE) was used to identify predictors of non-adherence. **Findings** After adjustment for alcohol consumption, depression and self-reported side effects, patients ceasing injection during OST and abstinent patients exhibited comparable adherence. Patients reporting injection, on OST or not, had a twofold and threefold risk, respectively, of non-adherence compared with abstinent patients ($P < 0.01$ linear trend). Duration on OST without injecting was associated significantly with virological success. **Conclusions** Both access to and effectiveness of OST contribute to sustaining adherence to HAART in HIV-infected IDUs. These results advocate strongly the need of wider use of OST in countries scaling-up HAART where HIV is driven by IDUs.

Keywords Adherence, antiretroviral therapy, buprenorphine, drug users, injection, methadone, opioid substitution treatment.

Correspondence to: M. Patrizia Carrieri, 23 rue Stanislas Torrents, 13006 Marseille, France. E-mail: pmcarrieri@aol.com
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INTRODUCTION

In France in 2005, at least 13% of the human immunodeficiency virus (HIV)-positive population who had access to HIV care were HIV-infected through injection drug use (IDU) [1]. Although the introduction of highly active antiretroviral treatment (HAART) is known to have revolutionized the course of HIV disease, even in late-stage HIV-infected injection drug users (IDUs) [2], this population still has higher mortality rates due to other competing causes of death, such as hepatitis, suicide or overdose [3,4]. Since the scaling-up of opioid substitution treatments (OST) such as methadone and buprenorphine, and the introduction of needle exchange programmes, HIV prevalence among IDUs in France has decreased dramatically from 40% to 11% [5,6]. One of the possible reasons for this is that wider use of OST may play a role in reducing injecting behaviours and HIV transmission [7–9]. Although OST can foster access to HIV care [10], delays in access to HAART have already been observed [11]. This observation underlines the need for the prescribing physician to

identify appropriate strategies to deliver care and ensure sustained adherence to HAART, especially in IDUs [12].

HAART efficacy requires a high level of adherence to achieve viral suppression [13], prevent possible clinical progression [14] and the risk of resistance [15]. Following the prescribed HAART schedule is a challenge for HIV-infected IDUs, considering that HAART-related side effects are reported more frequently in IDUs [16] and are a determinant of poor adherence [17]. Ongoing drug injection has been found consistently to be associated with non-adherence to HAART [18], and has been shown to be predictive of adherence failure [19]. Moreover, Lucas *et al.* have suggested that effectively targeting and treating active drug use may lead to improved HIV clinical outcomes [20], as demonstrated already in methadone-substituted patients receiving directly administered antiretroviral therapy [21,22].

To date, no studies have assessed the impact that take-home buprenorphine or methadone can have on adherence to HAART in HIV-infected individuals in the long term and to what extent receiving OST can modify the known correlates of non-adherence and influence HAART efficacy [18]. In France, while methadone was the first drug to be introduced in 1995, and initialized only in specialized centres for drug dependence, high-dose buprenorphine was introduced in 1996 as a harm reduction tool, available in primary care. In France, both treatments are delivered as take-home medications, the only exceptions to this being some scattered low-threshold structures where they are administered directly. Buprenorphine take-home dispensing by community pharmacists is possible for 28 days with the written agreement of a physician. In terms of methadone dispensing, take-home is authorized for 14 days, but its availability is very limited within community pharmacies because of the administrative burden, as methadone is classified as a narcotic. Easy access to buprenorphine through primary care has resulted in a rapid scale-up of buprenorphine treatment in IDUs (80 000 patients on buprenorphine at the end of 2000 [23]).

Longitudinal data from the MANIF2000 study gave us the opportunity to assess the impact of take-home methadone or buprenorphine treatment and ongoing drug injection on both adherence to HAART and virological response, while taking into account known determinants of adherence.

METHODS

In 1995/96, the French MANIF2000 cohort enrolled 467 patients who were HIV-infected through injection drug use. Inclusion criteria for enrolment in the cohort included only patients with a $CD4^+$ cell count >300/ul in the last visit prior to enrolment and in clinical stages A or B. This cohort was designed to focus upon social and behavioural aspects of HIV-positive IDUs and particularly on their access [11] and adherence to antiretroviral treatment [19], as well as the OST outcomes [24]. Data collection (every 6 months) was based on medical records, a face-to-face interview and a self-administered questionnaire.

Study group

In this specific study, we focused primarily upon patients who started HAART while in the cohort. For each selected patient in the cohort, we considered his/her first visit following initial HAART prescription as the first visit on HAART.

Among the 467 patients included in MANIF2000 study, 317 patients received HAART at least once. Forty-one patients had no data on adherence to HAART. Therefore, the present analysis was conducted on 276 patients receiving HAART and with at least one assessment of adherence data during follow-up after HAART initiation. Only visits with complete adherence data were considered (1558 visits).

As the cohort was based on 6-month interval assessment, the first HAART prescription could occur between two scheduled visits. For this reason, in the majority of cases the first visit on HAART corresponded to the MANIF2000 visit after starting HAART (at most 6 months after starting HAART), but it may have occurred soon after HAART initiation. This explains why there are patients with high viral load at the first visit on HAART, as the time since HAART initiation is perhaps not long enough to observe an effect on viral replication.

Data collection

The face-to-face interview was based on a standardized questionnaire, administered by trained nurses, which gathered psychosocial information as well as patients' personal experience with HIV infection and care. The questionnaire included socio-demographic data, incarceration, several items about substance use and related behaviour, exposure to OST, consumption of psychotropic drugs (sedatives, benzodiazepines, other anxiolytics, antidepressants and hypnotics) and alcohol. Alcohol was measured in alcohol units (AU), where one unit corresponds to a glass of wine, a can of beer or a measure of spirits and is equivalent to 10/12 g of alcohol [25]. All the data collected referred to the 6 months prior to the given visit. To improve the sensitivity of the definition and compensate for possible under-reporting by patients, the definition of a specific behaviour (e.g. cocaine use) at each visit was based on a combination of several questions about the specific substance. Self-reports about

Table 1 Distribution of visits according to exposure to opioid substitution treatment (OST) and injection status ($n = 1558$ visits) from the MANIF2000 cohort.

	No OST	*On methadone*	*On buprenorphine*
Injection	43	53	81
No injection	319	106	294
Always abstinent from injection	662	–	–

heroin and morphine use were validated at enrolment by morphine detection in urine samples [26].

Injection drug use at any given visit thereafter was defined as the injection of heroin or morphine, psychotropic drugs, cocaine, buprenorphine or any other drugs in the 6 months before that visit. This variable defining drug injection status (with three categories: injection, no injection and always abstinent over the whole MANIF2000 follow-up) was then combined with the information about exposure to OST so that at any given visit, patients could be classified according to the six following categories: 'methadone and no injection', 'buprenorphine and no injection', 'no OST and no injection', 'methadone and injection', 'buprenorphine and injection' and 'no OST and injection' (Table 1). Those who reported being abstinent from injection and not receiving OST over the whole MANIF2000 follow-up period constituted an additional category, which was used as the reference group in the analysis. It is important to underline that those classified as 'no OST and no injection' constituted individuals cycling in and out of treatment or characterized by cessation or relapse into drug injection during follow-up.

Information about adherence to HAART was collected in the self-administered questionnaire and the structured face-to-face interview. The questionnaire included five questions about patient's adherence to HAART in the 4 days and in the 4 weeks prior to the interview. Those questions were included in all self-administered questionnaires according to the methodology established by the AIDS Clinical Trial Group [15]. We assessed adherence to HAART using a dichotomous score already validated in previous studies [27,28]. Patients were first asked to list, for each drug included in their HAART regimen, the number of pills they had actually taken on each of the 4 days before the visit. Those who reported having taken all their prescribed doses in the 4 days before the visit were classified as adherent, unless they also reported in subsequent answers that they had skipped a dose during the previous weekend or had 'almost totally' followed their HAART regimen, or had modified the prescribed scheduling several times or had taken all their medication at one time each day, in which case they were classified as non-adherent. In addition, the visual analogue scale was used to reclassify as non-adherent those whose score was <100%. At any given visit, patients were considered 'non-adherent' if they reported in the interview that they had taken less than 100% of the total dose of prescribed drugs during the week prior to the visit and/or during the previous month. This approach has been validated previously using serum protease inhibitor concentrations [29]. When a patient reported HAART interruption more than once during the previous month, he/she was classified as non-adherent. However, if the patient discontinued HAART totally during the follow-up, all visits subsequent to this interruption were excluded from the analysis.

Depression was measured using the French version of the Center for Epidemiological Studies Depression Scale (CES-D) [30]. Although CES-D cannot be considered as a clinical tool for diagnosing depression, patients were considered to be presenting depressive symptoms if their CESD score was greater than 17 (for men) or greater than 23 (for women) [31].

The self-administered questionnaire included a 13-item scale asking whether patients had experienced any of the following HAART-related side effects at least once during the previous 4 weeks [32]: diarrhoea, nausea, stomach pain, headache, change in taste, skin itching, muscle pain, heartburn, sore mouth, vomiting, fever, kidney stones or fatigue. A summary score based on the sum of all self-reported side effects was computed to obtain a quantitative assessment of the burden of perceived HAART-related toxicity.

The variable 'psychotropic drugs consumption' consisted in collecting information about all prescribed or non-prescribed psychotropic drugs consumed by the patient during the previous 6 months. We built an algorithm using a combination of several questions about the consumption of different classes of psychotropics (antidepressants, anxiolytics, hypnotics, . . .). If the patient reported using at least one of these drugs, he/she was classified by this variable as a user of psychotropic drugs.

Other clinical and laboratory data as well as further information about OST came from the physician or from medical records which were collected every 6 months. In order to obtain a cumulative indicator of exposure to 'effective' OST to be correlated with virological success at any visit, time on OST without injection was computed for all individuals at any follow-up visit.

Statistical methods

The relationship between possible predictors of adherence to HAART, including substitution treatment and drug injection, was assessed using a logit model based on

generalized estimating equations (GEE) [33]. Variables with *P*-values <0.25 in the univariate analysis were considered eligible for the final model, which was built using a forward procedure based on the log-likelihood ratio test and a *P*-value <0.05 to enter the variables in the model. All the analyses were performed using Stata version 9.0.

RESULTS

First visit after HAART initiation

Of the 467 patients enrolled in the MANIF2000 cohort, 276 (59.1%) received HAART during follow-up. They accounted for 1558 visits (799 person-years).

Median [interquartile range (IQR)] patients' age was 35 years [32–38]; 200 (72.5%) were men. At their first visit on HAART, 140 (50.7%) were living in a stable relationship, 186 (67.4%) were unemployed and 145 (52.5%) had a history of incarceration. Only 66 patients (24%) had a high school certificate and 108 (39.1%) reported being the owner or tenant of their house. Only nine (3.3%) patients could be classified as acquired immune deficiency syndrome (AIDS) cases (stage C), while 148 (53.6%) were in stage B. Median (IQR) CD4 cell count (cells per μl) and HIV viral load ($\log_{10}$ copies per ml) in the visit before HAART initiation were, respectively, 386 (290–508) and 4.1 (3.2–4.7). Ninety-one patients (33%) had an undetectable viral load.

The median (IQR) calendar year of HAART initiation was 1998 (1997–98). When comparing immunovirological characteristics of patients before HAART initiation between those receiving and those not receiving HAART (this latter group including untreated patients or those receiving a double combination therapy), those receiving HAART had a significantly lower CD4 count and higher values of plasma HIV RNA viral load.

Fifty-nine patients (21.4%) were receiving buprenorphine while 32 (11.6%) were being treated with methadone. Median (IQR) time since first injection was 16 years [13–18] and 114 (46.9%) patients presented depressive symptoms. Approximately 16% reported no alcohol consumption in the 6 months prior to the visit. The median (IQR) number of AU/month was 3.8 (1.5–45.0), but in those reporting alcohol consumption this rose to 14 (4–56) while the median (IQR) number of self-reported side effects was 2 (0–4).

Longitudinal data

During the whole follow-up among the 276 patients receiving HAART, the number of patients who were being treated with either buprenorphine or methadone at least at one follow-up visit was 117 (during 375 visits) and 51 (during 159 visits), respectively.

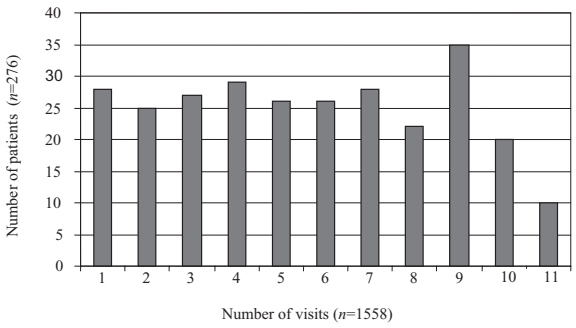

Figure 1 Distribution of visits in patients receiving highly active antiretroviral therapy from the MANIF2000 cohort

Individuals on HAART but 'abstinent' from injection and not receiving OST during the whole study period ($n = 106$, 38% accounting for 662 visits) were used as a reference group.

Among all the visits of patients receiving HAART (1558 visits), 42.5% (106 patients) represented those who had always been abstinent during follow-up while 46.1% of visits (226 patients) represented those who reported no injection practices in the previous 6 months at any given visit (but who reported either OST or injection at a different visit). In addition, 5.2% of visits (81 visits, 42 patients) concerned patients receiving buprenorphine and reporting injection, while 18.9% of visits (294 visits, 104 patients) concerned those receiving buprenorphine but not reporting injection. For those patients reporting access to methadone, injection during the previous 6 months was reported in 53 of the 159 visits. Patients reporting no use of OST and drug injection in the previous 6 months accounted for 2.8% of all visits (43 visits, 26 patients) (Table 1).

Figure 1 reports the distribution of patients according to the number of visits on HAART in the MANIF2000 follow-up. The average number of visits per patient was 5.6. Only 28 patients had only one visit. Among them, eight patients were classified as abstinent over the whole MANIF2000 study period and five patients were classified as 'no OST and no injection', as they had already reported injecting drugs before initiating HAART.

In order to evaluate whether individuals without data about adherence to HAART differed from those included in the analyses, we compared socio-demographic and clinical characteristics. Clinical stage C was the only factor discriminating patients with adherence data ($n = 276$) from those without ($n = 41$).

Univariate analyses

Table 2 shows the crude and adjusted odds ratios (ORs) of possible determinants of non-adherence.

The variable combining exposure to OST and injection was associated significantly with the outcome as well as

Table 2 Predictors of non-adherence to highly active antiretroviral therapy (HAART) in human immunodeficiency virus (HIV)-infected injecting drug users: crude and adjusted odds ratios (ORs) based on generalized estimation equation (GEE) logit models (MANIF2000 cohort, $n = 276$ individuals, 1558 visits)[c].

	No. of visits (%) or median (IQR)	*No. of patients*	*OR (95% CI)*	*P-value*	*Adjusted OR (95% CI)*
Exposure to OST and drug injection[c,d,i]					
Always abstinent during the whole study period	662 (42.5)	106	1		1
Buprenorphine and no injection	294 (18.9)	104	1.2 (0.8–1.8)	0.3	1.0 (0.6–1.6)
Methadone and no injection	106 (6.8)	37	1.1 (0.7–1.9)	0.7	1.0 (0.5–1.8)
No OST and no injection	319 (20.5)	85	1.7 (1.1–2.4)	0.008	1.4 (0.9–2.2)
Buprenorphine and injection	81 (5.2)	42	2.5 (1.5–4.2)	0.001	2.3 (1.2–4.4)
Methadone and injection	53 (3.4)	29	2.3 (1.2–4.3)	0.01	2.2 (1.1–4.5)
No OST and injection	43 (2.8)	26	2.9 (1.5–5.7)	0.002	3.3 (1.4–8.1)
Gender[g]					
Men	1101 (70.7)	200	1		
Women	457 (29.3)	76	1.1 (0.8–1.6)	0.55	
Age	36 (33–39)		0.99 (0.96–1.02)[f]	0.53	
Child(ren)					
Yes	325 (209)	117	1		
No	1233 (79.1)	266	1.0 (0.8–1.2)	0.78	
High school certificate[g]					
Yes	374 (24.0)	66	1		
No	1184 (76.0)	210	1.1 (0.7–1.5)	0.71	
Employment[e]					
Yes	561 (36.0)	123	1		
No	997 (64.0)	219	1.2 (0.9–1.5)	0.25	
Depressive symptoms[d,e]					
Yes	659 (44.8)	190	1.5 (1.2–1.9)	0.001	1.4 (1.1–1.9)
No	813 (55.2)	209	1		1
Number of weekly prescribed pills[d,e]					
<80	414 (28.0)	164	1		
≥80	1065 (72.0)	229	1.2 (0.9–1.5)	0.13	
Monthly alcohol consumption[d,e]	3.8 (1.5–45.0)		1.15 (1.08–1.23)[h]	$<10^{-3}$	1.19 (1.10–1.28)
Cocaine use[d,e]					
Yes	174 (13.8)	74	1.6 (1.1–2.2)	0.01	
No	1091 (86.3)	252	1		
Heroine use[d]					
Yes	126 (10.0)	61	1.2 (0.8–1.8)	0.37	
No	1140 (90.0)	252	1		
Cannabis use[d,e]					
Yes	776 (61.3)	192	1.6 (1.2–2.0)	0.001	
No	491 (38.8)	171	1		
Psychotropic drugs consumption[d,e]					
Yes	472 (31.8)	159	1.3 (1.0–1.7)	0.002	
No	1013 (68.2)	237	1		
Incarceration[d,e]					
Yes	36 (3.4)	25	2.1 (1.1–4.1)	0.03	
No	1019 (96.6)	268	1		
Time since HAART initiation	14.7 (5.5–26.5)		1.01 (1.00–1.01)[a]	0.07	
Number of self-reported side effects[d,e]	3 (1–6)		1.08 (1.04–1.13)[b]	$<10^{-3}$	1.07 (1.02–1.12)

[a]Per 1-month increase. [b]Per one-event increase. [c]Non-adherence was reported in 650 visits (41.7% visits). [d]In the 6 months prior to the visit. [e]Eligible for the multivariate model ($P < 0.25$). [f]Per 1-year increase. [g]At baseline. [h]Per 30 alcohol units (AU) increase per month [as approximately 20% of individuals reported no alcohol use, the median [interquartile range (IQR)] monthly AU units in those reporting alcohol use was 14 (4–56)]. [i]Linear trend $P < 0.01$ across abstinent, not injecting during opioid substitution treatment (OST), injecting during OST and active injection.

variables concerning other addictive behaviours (alcohol consumption, use of cocaine, cannabis or psychotropic drugs). Problems with the police and incarceration were also associated with non-adherence behaviours. There was a significant relationship between depressive symptoms, the number of self-reported side effects, the number of negative life events and the outcome.

Multivariate analysis

First of all, as shown in Table 2, the number of weekly prescribed pills was not associated with adherence in the patients included in our analysis. The results show that after adjustment for the number of self-reported side effects [OR = 1.07, 95% confidence interval (CI) (1.02–1.12)], depressive symptoms [OR = 1.4, 95% CI (1.1–1.9)] and monthly alcohol consumption [OR = 1.19 per 30 AU increase per month, 95% CI (1.10–1.28)], those individuals reporting no injection and exposure to OST (buprenorphine or methadone) did not differ significantly from abstinent individuals in terms of non-adherence [OR = 1.0, 95% CI (0.6–1.6)] for those on buprenorphine and for those receiving methadone [OR = 1.0, 95%CI (0.5–1.8)].

Interestingly, individuals neither injecting nor receiving OST at any given visit had an increased risk of non-adherence of 1.4 (0.9–2.2) with respect to abstinent patients, although this difference did not reach statistical significance in the multivariate analysis.

By contrast, individuals reporting injection, whether or not on OST, exhibited a significantly higher risk of non-adherence than abstinent ones with a twofold increased risk for both individuals injecting while on buprenorphine [OR = 2.3, 95% CI (1.2–4.4)] and for those injecting while receiving methadone [OR = 2.2, 95% CI (1.1–4.5)]. This rose to a threefold increased risk for those injecting but not receiving OST [OR = 3.3, 95% CI (1.4–8.1)]. It is interesting to note a significant linear trend ($P < 0.01$, Table 2) in the adjusted ORs across the different categories: abstinent, not injecting during OST, injecting during OST and injection without OST.

Furthermore, it is important to underline that, at any follow-up visit, exposure to OST without injection (expressed as a duration in months) was associated significantly with virological success, as expressed by an undetectable HIV viral load [OR = 1.02 per one more month of OST, 95% CI (1.01–1.04)].

DISCUSSION

This is the first study to demonstrate the long-term positive impact of both take-home buprenorphine and methadone on adherence to HAART and HAART efficacy in HIV-infected individuals. The major conclusion of the present study is that when drug users have easy access to methadone or buprenorphine, and do not inject during substitution treatment, their adherence is comparable to that reported by abstinent HIV-infected patients. It is important to note that the majority of patients on OST do not practice injection (three of four patients on buprenorphine and two of three on methadone). These results remain valid even when taking into account major determinants of non-adherence such as self-reported side effects, depressive symptoms or alcohol consumption.

Conversely, patients on buprenorphine or methadone reporting injecting behaviours have at least a twofold higher risk of being non-adherent. These results suggest that when OST cannot suppress injection practices in opioid-dependent patients, these patients have difficulty adhering to their HIV treatment. Moreover, patients reporting injection while not on OST have a threefold higher risk of being non-adherent than abstinent patients. Interestingly, the significant linear trend found across the different 'OST/injection' categories confirms that OST can contribute to sustain adherence to HAART in active IDUs. As the evaluation of OST receipt and injection is retrospective over the previous 6 months, it is possible that injection may have occurred before receiving OST, after OST discontinuation or during treatment in the 6 months prior to the visit. In these two last cases, injection in those receiving substitution may be interpreted, respectively, as a proxy of non-retention in OST or non-adherence to OST recommendations, due probably to inadequate dosage prescription [34]. It is known that, in populations still dependent upon opioids, the risk of cycling in and out of treatment may be high, and that relapse into injection practices in patients whose dependence and/or social conditions are not stabilized are relatively frequent [35]. The present study confirms previous results and evaluates the role that OST stabilization may play in sustaining adherence even in the maintenance phase of HAART.

Despite the fact that most cohort studies have found HAART to be associated with substantial declines in morbidity and mortality for all transmission categories, there is growing evidence that IDUs have not benefited to the same degree as other risk groups [18]. This could be related to a constellation of factors, including the fact that physicians often perceive IDUs as being at high risk of non-adherence [36,37]. Some previous studies have already shown higher rates of HAART failure among IDUs [38] because of higher viraemia at HAART initiation and poor immunological response to HAART [39]. The results from the present study confirm these findings and highlight the positive impact of take-home OST on adherence even in the long term, provided that it is also effective in stabilizing patients by suppressing injection. Notably, the relationship between such a positive effect of

methadone or buprenorphine on adherence is confirmed by the significant positive association between the duration of OST without injection and virological success.

Adherence to HAART among IDUs has already been investigated in some studies focusing upon specific populations receiving either buprenorphine [40] or methadone [41], showing that active drug users had lower self-reported adherence to HAART compared with former or non-drug users. The role that specific models of OST delivery can play in sustaining adherence has already been investigated [18,42]. A prospective study, integrating directly administered ART (DAART) into a methadone clinic setting, showed that this delivery model was associated with improved virological and immunological outcomes, compared with findings from a cohort of IDUs whose HAART intake was self-administered [21]. While there is increasing evidence about the negative impact of drug injection on adherence to HAART, data comparing the role played by stabilization of opioid dependence through buprenorphine or methadone in sustaining adherence to HAART have never been investigated. This is especially true for take-home OST prescribed mainly in primary care.

One of the principal outcomes in evaluating OST efficacy and its ability to induce patients into stabilization of their opioid dependence is the reduction in injecting behaviours. However, in our study some patients injected during OST, and this seems to be particularly present among patients on methadone. Historically, in France, initialization of methadone is possible only in specialized centres for drug dependence, while access to buprenorphine is available in primary care [5]. This differential access could explain why methadone in France is initialized more frequently in patients presenting a severe addictive profile, and therefore the significantly higher proportion of injection practices in patients receiving methadone.

Alcohol consumption appears to be associated with non-adherence, as reported already in previous research [43]. Alcohol use may reduce the efficacy of OST in sustaining adherence, as reported by Palepu *et al.*, who demonstrate that among HIV-infected people with alcohol problems substance abuse treatment does not have a significantly positive effect on adherence to HAART [44]. Moreover, depression, which is frequent among IDUs, has also been reported in long-standing cohort studies as being a major risk factor of non-adherence [19,45]. Consequently, besides an appropriate OST for each patient, comprehensive management of health problems such as perceived toxicity, depression or alcohol dependence should be implemented to optimize adherence to HAART [46].

Some limitations of this study should be acknowledged. First, the small number of patients in the three injectors' categories could be explained by the impact of access to HAART on injection among IDUs. Bouhnik *et al.* have already shown in the MANIF2000 cohort the association between drug injection cessation and HAART initiation [47]. In the present study, missing adherence data existed for those individuals who failed to attend one or more scheduled visits, for those who did not answer the self-administered questionnaire and for those who were lost to follow-up. It is possible that non-adherent patients may have been slightly under-represented in this study, as individuals excluded from the analyses due to missing data were more likely to be at HIV clinical stage C.

In France, the health insurance system allows even marginalized populations to have free access to care [48], not only for HIV but also for drug dependence. More specifically, HIV-infected individuals are classified by the French health insurance system as patients affected by a chronic disease, which allows them to benefit from additional rights (e.g. reimbursing the cost of transportation to the care centre). This is a key point in understanding to what extent the population of the study may be representative of the general HIV-infected population in France. Because of this free access to care, it may be supposed that drug users are represented adequately.

As in most studies in this field, our assessment of drug use and injection behaviour was based upon self-reports. The validity and reliability of self-reports about active drug use have been established in many studies which used similar methods for collecting information about addictive behaviours [49], as well as in a previous study in which we documented substantial agreement between self-reported heroin use and morphine detection in urine [26]. A meta-analysis by Nieuwkerk & Oort [50] has already shown the validity of self-reported measures of adherence. As social desirability is still possible, the use of a high cut-off score and an algorithm reclassifying patients reporting non-adherence at least once in the adherence questionnaire allowed us to minimize such bias and improve the validity of the instrument used.

The results presented in this study represent a step forward in the understanding of the complex relationship between exposure to OST, OST outcomes and HAART success. When methadone and buprenorphine are successful in stabilizing opioid dependence, they can ensure sustained adherence to HAART. Other research questions remain—first, whether or not these results would hold in a randomized controlled trial; and secondly, to what extent methadone and buprenorphine can mediate the relationship between depression or self-reported side effects and adherence.

These data also suggest that adequate models of care need to be evaluated and implemented to provide more patient-adapted services, able to fulfill the specific needs of

IDUs in care for other comorbidities and psychosocial support.

In conclusion, both access to and effectiveness of OST contribute to sustaining adherence to HAART in HIV-infected IDUs. These results clearly support the need for wider access to OST in countries which are scaling-up HAART in IDUs and those which face alarming epidemics in IDUs. The wider the spectrum of OST options, the higher the coverage will be and the stronger the public health benefits will become.

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Declarations of interest

None.

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