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ORIGINAL PAPER

Low Non-structured Antiretroviral Therapy Interruptions in HIV-Infected Persons Who Inject Drugs Receiving Multidisciplinary Comprehensive HIV Care at an Outpatient Drug Abuse Treatment Center

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Abstract Continuous HIV treatment is necessary to ensure successful combined antiretroviral therapy (cART). The aim of this study was to evaluate the incidence of patient-initiated non-structured treatment interruptions in HIV-infected persons who inject drugs and who received a multidisciplinary comprehensive program, including medical HIV care, drug-dependence treatment and psychosocial support, at a drug outpatient addiction center. Non-structured treatment interruptions were defined as ≥30 consecutive days off cART without medical indication. During a median follow-up of 53.8 months, 37/132 (28 %) patients experienced the first non-structured treatment interruptions. The cumulative probability of cART interruption at 5 years was 31.2 % (95 % CI 22.4–40.0). Current drug use injection ≥1/day (HR 14.77; 95 % CI 5.90–36.96) and cART naive patients (HR 0.35, 95 % CI 0.14–0.93) were predictive factors for non-structured treatment interruptions. HIV care provided at a drug addiction center is a useful strategy to sustain continuous cART, however, drug abstinence is essential for the long-term maintenance of cART.

Resumen El tratamiento continuado del VIH es necesario para garantizar la eficacia de la terapia antirretroviral combinada (TAR). El objetivo de este estudio fué evaluar la incidencia de las interrupciones no estructuradas de tratamiento iniciadas por el paciente en personas infectadas por el VIH usuarias de drogas intravenosas y que recibieron un programa multidisciplinario, incluyendo atención médica del VIH, tratamiento de las drogodependencias y apoyo psicosocial, en un centro ambulatorio de atención médica a la adicción de drogas. Las interrupciones no estructuradas fueron definidas como el abandono de la TAR ≥ 30 días consecutivos sin indicación médica. Durante una mediana de seguimiento de 53.8 meses, 37/132 (28 %) pacientes tuvieron una primera interrupción no estructurada de la TAR. La probabilidad acumulada de interrupción fué del 31.2 % (IC 95 %: 22.4-40.0) a los 5 años. El consumo de drogas inyectables ≥1/día (HR14.77; IC del 95 %: 5,90 a 36,96) y los pacientes naive a la TAR (HR 0.35; IC del 95 %: 0.14-0.93) fueron factores predictivos de interrupciones no estructuradas de la TAR. La atención médica del VIH proporcionada en un centro ambulatorio de atención médica a la adicción de drogas es una estrategia útil para conseguir el mantenimiento de la TAR, sin embargo, la abstinencia de drogas es esencial para el mantenimiento a largo plazo.

Keywords Antiretroviral · Therapy · HIV · Interruptions · Drugs

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Introduction

The use of combined antiretroviral therapy (cART) has enhanced the quality of care and life expectancy of HIV-positive individuals [1–3]. However, a sustained optimal use of cART is necessary to ensure maximum therapeutic benefits [4]. The continuity of treatment is not only a vital

component of care but also the best predictor of an HIV-positive individual's successful long-term HIV management [4]. As a consequence, consistent adherence and uninterrupted treatment represent major challenges [5, 6].

Treatment interruptions (TI), whether physician-directed (structured) or patient-initiated (non-structured; NTI) as a result of treatment fatigue or cART toxicities, have been found in observational studies and prospective clinical trials to promote viral rebound and CD4 cell loss and increase the risk of retroviral rebound syndrome, person-to-person transmission, opportunistic infections, non-AIDS events, and death [6–15]. Consequently, the use of structured TI in the management of HIV-positive individuals is no longer recommended [15].

Despite recognition of the detrimental effects of TI, patient-initiated non-structured treatment interruptions are a reality of routine clinical care and a high prevalence has been reported, particularly among HIV-infected persons who inject drugs (HIV-PWID) [6, 16–22]. Moreover, HIV-PWID have worse immune recovery, lower virologic suppression outcomes, and more rapid disease progression compared to HIV-infected individuals who do not inject drugs [23, 24]. This adverse clinical picture highlights the need for additional therapeutic strategies to prevent NTI and to improve the benefits of cART in HIV-PWID.

In addition to drug-dependence disorders, HIV-PWID present several medical co-morbidities (hepatitis C, tuberculosis), psychiatric comorbidities (depression), and social issues (homelessness, unemployment, incarceration) which severely complicate the continuity of HIV treatment and result in inferior clinical HIV outcomes [25, 26]. It is essential for all these medical and psychosocial issues to be addressed in order to improve the success of cART.

HIV medical care, drug treatment, and social support are, however, traditionally delivered in separate settings by different providers which are not necessarily interconnected. This fragmentation of care raises the risk for poorer treatment adherence, limited follow-up, treatment interruption, and worse clinical outcomes [27]. Thus, multifaceted and interdisciplinary approaches, including the integration of health service delivery, are recommended in international guidelines since they have great potential for improving health outcomes in HIV-PWID [28]. In this respect, the provision of cART at methadone-dispensing centers has led to an improvement in the physical health of patients, increased use of cART, and better virologic suppression [29, 30]. Nevertheless, the impact over time of strategies for providing HIV-1 therapy at a drug abuse treatment center on NTI has not been previously evaluated.

The present study aimed to evaluate the incidence and predictive factors of NTI in a cohort of HIV-PWID who initiated cART at an outpatient drug addiction center. They received integrated and multidisciplinary care of HIV and substance abuse disorder as well as psychosocial support. As secondary objectives, immunologic and virologic effectiveness were also analyzed.

Methods

This longitudinal study included HIV-PWID who met the criteria for DSM-IV-TR substance dependence disorder and were receiving simultaneous treatment for both HIV and substance dependence, as well as psychosocial support, at CAS (Centro de Atención y Seguimiento a las drogodependencias; Center of Attention and Monitoring of drug addiction) Barceloneta in Barcelona, Spain.

All patients who started cART at CAS Barceloneta after January 2005 and were monitored until December 2014 were included.

CAS-Barceloneta is a free of charge, drug outpatient addiction center located in the old part of the city of Barcelona (Spain). Individuals come to the center requesting drug abuse treatment, they are either self-referred or referred by their primary care physician. The subjects are informed and sign a consent form prior to being admitted to the program.

The multidisciplinary health team includes two psychiatrists, a physician, a social worker, a psychologist, and four trained nurses. According to individual characteristics, this team designs the most suitable drug abuse treatment modality for each case (detoxification, methadone maintenance, naltrexone maintenance, inpatient detoxification referral, and residential treatment). The subjects are monitored on a regular basis at multidisciplinary sessions where the medical and psychosocial issues for each subject are discussed.

The physician is a specialist in internal medicine and takes care of the subjects' health problems, in particular HIV-1 infection, tuberculosis prophylaxis or treatment, and hepatitis C co-infection. He decides when to initiate cART and assesses the monitoring of patients according to local guidelines, which recommend starting cART with CD4 counts <500 cells/μL in asymptomatic HIV-infected patients [31].

The nurses dispense methadone, perform blood extractions, and supervise urine tests. They also review the side effects of medication, identify adherence problems, provide instruction on adherence, and make note when an individual patient fails to attend the scheduled appointments. They are responsible for locating the subjects and ensuring they attend a new appointment to facilitate treatment continuation.

Communication among patients and staff takes place within confidentiality, in an empathetic, non-judgmental, and non-punitive manner, and with the regular use of motivational interviews.

More details on the functioning of CAS-Barceloneta have been published elsewhere [32].

On the day of outpatient admission, subjects completed a brief questionnaire for the collection of information on socio-demographic variables, drug use, and ongoing risk behaviors, and underwent a comprehensive medical examination and routine laboratory testing including biochemistry, blood analysis, and HIV, hepatitis A, B, and C, and syphilis screening. T cell lymphocyte sub-populations and plasma HIV-1 RNA were measured every 3 months in HIV-infected patients. T-cell lymphocyte sub-populations were measured by standard whole-blood flow cytometry and plasma HIV-1 RNA was quantified using RT-PCR (COBAS TaqMan VIH, Roche Diagnostics) with a minimum detectable level of 20 copies/mL.

During follow-up, urine analysis were carried out weekly to detect the presence of metabolites of major abuse drugs (heroin, cocaine, benzodiazepines) and a brief questionnaire on current drug use was completed monthly by all patients. The questionnaire was drawn up by the center and included the following questions/answers: Did you inject drugs in the previous month? (Yes/No). How often do you inject drugs? (Once a day/More than once a day).

cART was free of charge and dispensed monthly at the hospital pharmacy where patients had to collect the treatment in person. It was self-administered and patients were seen every 3 months by the physician. Patients under directly-observed cART were excluded from the study.

Non-structured treatment interruption (NTI), the primary outcome, was defined as a non-medically supervised interruption of antiretroviral treatment of at least 30 consecutive days after cART was initiated. NTI were identified through pharmacy dispensation records indicating that a participant had not collected any cART for 30 days or longer after the end of the prescription refill date.

Loss to follow-up was considered as no clinical contact by patients with the drug addiction center for more than 6 months.

cART status was classified as naive (patients who initiated cART for the first time) or pretreated (patients who reported previous cART experience in another HIV medical center and had discontinued it).

Qualitative drug use was classified according to main drug type as stimulant or non-stimulant drugs, and the intensity of drug use injection as heavy ($\geq$day) or non-heavy ($<$day).

Substance dependence and mental disorders were diagnosed according to DSM-IV-TR.

Virologic response was calculated as a percentage of patients who had RNA HIV-1 $<$20 copies/mL at the end of follow-up.

Data were expressed as number and percentage of subjects or the median and interquartile range. Cumulative NTI was estimated using the Kaplan–Meier method, and the relationship between clinical and psychosocial covariates with the primary outcome was estimated using the Cox regression model. Covariates that were statistically significant ($P < 0.05$), or marginally significant on the univariate Cox proportional hazards model were included in the multivariate model. Hazard ratios with their 95 % confidence interval and P values of Walds test were shown in both analysis. Analysis were performed using SPSS (Chicago, Illinois, USA; release 17.0.0, August 2008).

Results

One hundred and thirty-two patients were included in the study. Clinical characteristics of the HIV patients included are shown in Table 1. Median age was 43 (IQR 36–48), 63.6 % were males, and 90.2 % were Spanish.

The presence of any kind of social problem was observed in 129 (97.2 %) patients and a severe mental disorder was diagnosed in 39 (29.5 %).

One hundred and nine patients (82.6 %) were polysubstance users and 78 (59 %) were using stimulants. Current drug use injection $\geq$1/day was observed in 37 (28 %) patients and methadone therapy maintenance was initiated in 114 (86.4 %).

Forty-three patients (32.6 %) were naive to cART. In contrast to pretreated patients, they were younger (39.8 vs. 45.4 years; *P* 0.000), with a higher number of men (76.7 % vs. 57.3 %; *P* 0.022), lower AIDS prevalence (27.9 % vs. 49.4 %; *P* 0.19), and lower current drug use injection $\geq$1/day (21.6 % vs. 78.4 %; *P* 0.04), respectively. No differences were observed in the median CD4 cell count at cART initiation or in the current cART regimen between groups.

Side effects that required a cART change were observed in 13.6 % (18/132) of patients but did not lead to an NTI. Documented side effects were gastrointestinal (12), liver (4), renal (1), and cutaneous (1).

Over a median clinical follow-up of 53.8 months (range 13–104), 37 patients (28 %) had at least one NTI. Figure 1 shows the Kaplan–Meier estimates of the cumulative probability of a first NTI. The probability of a first NTI was 17.2 % (95 % CI 10.6–23.8) at 2 years and 31.2 % (95 % CI 22.4–40.0) at 5 years. Of all first NTI, 7 (18.9 %) occurred in the first year after cART initiation, 16 (43.3 %) in the second, 9 (24.3 %) in the third, 4 (10.8 %) in the fourth, and 1 (2.7 %) in the fifth. The patients' reasons for discontinuing therapy were chaotic life style after drug use relapse (24 patients), mental disorder (5 patients),

Table 1 Baseline characteristics of HIV-infected persons who inject drugs initiating cART at an outpatient drug abuse center (N = 132)

Variables	N(%) or median and (IQR)
Patients	132
Age	43 (36–48)
Male	84 (63.6 %)
Origin	
Spanish	119 (90.2 %)
Non-Spanish	13 (9.8 %)
Psychiatric disorder	
Depressive disorders	23 (17.4 %)
Psychotic disorders	16 (12.1 %)
Previous incarceration	82 (62.1 %)
Homelessness	26 (19.7 %)
Currently employed	11 (8.3 %)
Main drug	
Heroin + cocaine	64 (48.5 %)
Heroin	54 (40.9 %)
Cocaine	14 (10.6 %)
Current drug use	
<day	95 (72 %)
≥day	37 (28 %)
Methadone therapy	114 (86.4 %)
Hepatitis C	123 (93.2 %)
AIDS	56 (42.4 %)
cART naive patients	43 (32.6 %)
CD4 count (cells/μL)	237 (41–468)
CD4 count <200 (cells/μL)	57 (43.2 %)
Viral load	5.02 (4.1–5.9)
Viral load >log10	42 (31.8 %)
Current cART regimen	
Boosted PI	108 (81.8 %)
NNRTI	18 (13.6 %)
IGI	2 (1.5 %)
Salvage therapy	4 (3.0 %)

cART combined antiretroviral therapy; *IQR* interquartile range; *PI* protease inhibitor; *NNRTI* non-nucleoside reverse-transcriptase inhibitor; *IGI* integrase inhibitor

incarceration (2 patients), conflict with medical staff (1 patient), and unspecified reason (5 patients).

Cox regression models examining factors predicting first NTI are shown in Table 2. Gender, age, stimulant drug use, current drug use injection ≥1/day, and being naive to cART were included in the multivariate Cox proportional hazard model which showed that current drug use injection ≥1/day and being naive to cART were predictive factors for NTI.

cART was resumed in the thirty-seven patients who presented a first NTI, four of whom had a second interruption. Three of the latter restarted therapy and one was lost to follow-up. Median time to resuming therapy after NTI was 4.0 months (range 2–12).

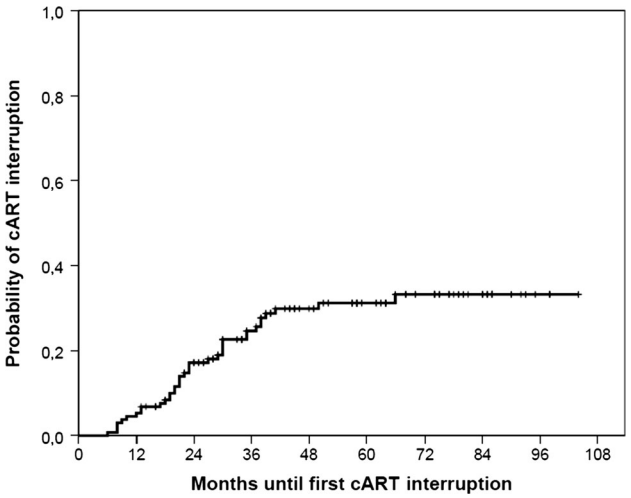

Fig. 1 Kaplan–Meier probability curve depicting time from cART initiation to first non-structured treatment interruption among HIV-infected persons who inject drugs. Cumulative probability of cART interruption at 5 years: 31.2 % (95 % CI 22.4–40.0)

None of the subjects developed a retroviral rebound syndrome after NTI and none died during follow-up.

At baseline, no difference was observed in median CD4 cell count between patients with or without NTI (197 cells/μL vs. 239 cells/ml; *P* 0.826). Overall, at the end of follow-up, median CD4 cell count was 481 cells/μL and only 12 % (17/132) of patients had a CD4 cell count <200 cells/μL; however, median CD4 cell count was lower in patients with some NTI compared to those who did not (CD4 cell count 365 cells/μL vs. 517 cells/μL; *P* 0.007).

Virologic response was observed in 89.4 % (118/132) of the patients at the end of follow-up and was lower in patients who had a NTI compared with those who did not (94.7 % vs. 75.7 %; *P* 0.003).

Salvage therapy was used in 3 % (4/132) of the patients, and no differences were observed between patients who interrupted cART and those who did not (*P* 0.26).

Discussion

The results obtained in this cohort of HIV-PWID show that only 28 % of the patients had one NTI for the first time during a follow-up of more than 4 years. The NTI incidence reported in the present study is lower than that in the North American cohort (Alive; AIDS Link to the Intravenous Experience) which reported a NTI incidence of 78 % in a similar period of time (median follow-up of 4.5 years) [21] and the Canadian cohort (Access; AIDS Care Cohort to Evaluate Access to Survival Services)

Table 2 Cox proportional models of factors predicting time to first NTI among HIV-infected persons who inject drugs

Factor	Univariate analysis hazard ratio (CI 95 %)	Walds test P value	Multivariate analysis adjusted hazard ratio (CI 95 %)	Walds test P value
Age	0.95 (0.90–1.01)	0.094	0.93 (0.86–1.002)	0.056
Gender				
Men	1	0.016	1.21 (0.61–2.4)	0.574
Women	2.21 (1.16–4.22)			
Origin				
Spanish	1	0.261		
Non-Spanish	1.36 (0.71–22.43)			
Mental disorder				
No	1	0.247		
Yes	1.58 (0.72–3.47)			
Previous Incarceration				
No	1	0.189		
Yes	1.75 (0.91–3.34)			
Homeless				
No	1	0.242		
Yes	1.54 (0.74–3.18)			
Unemployment				
No	1	0.182		
Yes	23.79 (0.22–249)			
Methadone therapy				
No	1	0.238		
Yes	0.62 (0.28–1.36)			
Stimulant drug use				
No	1	<0.001	2.20 (0.81–5.95)	0.595
Yes	5.83 (2.26–15.04)			
Current drug use ≥ day				
No	1	<0.001	14.77 (5.90–36.96)	0.001
Yes	21.21 (8.76–51.34)			
AIDS				
No	1	0.158		
Yes	1.59 (0.83–3.03)			
CD4 cell count (cells/μL)	1.77 (0.92–3.38)	0.832		
Viral load log10	1.35 (0.69–2.63)	0.371		
cART naive patient				
No	1	0.091	0.35 (0.14–0.93)	0.043
Yes	0.51 (0.23–1.11)			

NTI non-structured therapy interruption; *CI* confidence interval; *cART* combined antiretroviral therapy

which reported a NTI incidence of 63 % in a shorter period of time (median follow-up 2.3 years) [22].

The North American and Canadian cohorts were conducted on the cART era and the clinical characteristics of the patients included were similar to those observed in the present study with respect to age, gender, and drug use. However, the fundamental difference between cohorts is that the present study is a clinical cohort and all subjects are in care. By contrast, the ALIVE and the ACCESS cohorts are study cohort and all subjects are in the study, but may not be in care. In the present study all subjects were receiving treatment addiction and 86.4 % of them were on methadone maintenance therapy. In contrast, only 25 % of the subjects were on methadone maintenance therapy in the North American cohort and 60 % were receiving treatment addiction in the Canadian cohort, in which it was also reported that engagement in methadone maintenance therapy was negatively and independently

associated with antiretroviral therapy discontinuation. Therefore, addiction treatment is a major aspect to take into consideration with respect to optimizing HIV outcomes among individuals who inject drugs.

It is important to note that methadone therapy was often dispensed daily together with antiretroviral therapy to improve adherence in the North American and Canadian cohorts. In contrast, in the present study cART was self-administered by the patients. The NTI incidence observed in our study is, moreover, comparable to data reported in other HIV non-drug user cohorts. In a recent systematic review including seventy studies, the median proportion of patients interrupting treatment was 23 % for a median duration of 150 days [6].

Active intravenous drug use is a major obstacle to effective cART in HIV-PWID [23, 24, 33]. According to the results of the Alive Cohort [21], a higher intensity of injecting was the main predictive factor for NTI, as was observed in the present study. These results are contradictory to those reported by the Access Cohort in which patterns of injecting drug use were not predictive of cART interruption in comparison to abstinence from drug injecting [22]. The differences between studies could be explained by the fact that drug use and related behaviors are highly stigmatized and such activities may have been under reported by the patients in the semi-annual questionnaires of the Access Cohort [34]. Moreover, injection patterns in HIV are dynamic and some patients may relapse into injection despite having been previously abstinent [35]. As a result, changes in drug use status were time-updated in the present study.

Cocaine and other stimulant drugs pose a challenge for optimal substance treatment. The psychological consequence of stimulant drug use, the absence of replacement therapy, the shorter half-life and the need for a greater number of administrations may lead to more chaotic drug-seeking behavior than heroin and therefore unsuccessful HIV management [36, 37]. However, a recent study reported that patterns of active drug injecting at the time of cART initiation did not affect plasma HIV-1 RNA suppression rates [38]. In the present study, the use of stimulant drugs was predictive of NTI in the univariate model; however, this association lost statistical significance in the multivariate analysis. This result could be explained by the fact that almost all the patients using non-stimulant drugs had drug use injection <1/day, while nearly half of those employing stimulant drugs had drug use injection ≥ 1/day, although no differences were observed in methadone maintenance therapy between the two groups (data not shown).

Mental disorders and social problems have been associated with poorer results of cART in HIV-PWID [39, 40]. These issues were addressed immediately prior to cART initiation and were not predictive of an increased risk of NTI in the present study. These results underline the importance of including social support and psychiatric evaluation in comprehensive HIV care to improve the success of cART in this population.

The resumption of cART after NTI should be a priority to avoid the harmful effects of discontinuing cART in HIV-PWID. The ALIVE cohort reported that 51 % of the patients had multiple NTI and 20 % never resumed cART after the first NTI [22]. However, in the present study, four of the thirty-seven patients who interrupted cART had a second NTI and all except one resumed cART after NTI, thereby indicating an additional benefit of the comprehensive program.

Finally, it is important to note that a high percentage of patients maintained virologic suppression and CD4 cell count above 350 cells/μL after follow-up, especially when considering that they had started treatment with a low median CD4 cell count. Nevertheless, patients who had an NTI had worse immune recovery and virologic response than those who had not, in agreement with previous studies [6].

The present observational study had some limitations. An intrinsic selection bias existed in the inclusion of patients who voluntarily attended the drug abuse center for drug dependence assistance. Subjects who were concerned for their own medical health, and thus more motivated to start drug abuse and HIV treatment may have contributed to improved outcomes.

However, the patients stemmed from a particularly troubled urban catchment area and represented a group with a notably high incidence of poor adherence surrogate markers, including mental illness, unemployment, homelessness, criminal records, and history of previous cART interruption, and thus constituted a representative sample of HIV-PWID. Furthermore, the median follow-up of the study was sufficiently long, nearly 5 years, for the appearance of the outcome variable to be detected.

An important aspect reinforcing the results of the study is the definition of NTI used in the study. There is no consensus on the definition and methods of determining cART interruptions [6]; thus, in the present study, NTI was defined according to the viral replication and immune damage observed 1 month after effective antiretroviral therapy ceased in HIV-1 RNA-suppressed patients [7]. Furthermore, NTI was confirmed by pharmacy prescriptions, thereby reducing the prevalence of under reporting in the self-administered questionnaires [34].

In conclusion, medical programs to maintain cART and improve its success in HIV-PWID are necessary. The multidisciplinary and comprehensive care of HIV-1 intravenous drug users provided at an outpatient drug addiction center is able to reduce the incidence of NTI and improve cART effectiveness, and should be considered a useful strategy in the management of this type of HIV-patients.

However, patients who continue to inject drugs heavily and those who have interrupted cART prior to admission to a drug addiction center continue to be at higher risk for NTI. These patients require more intensive follow-up and additional medical support to remain engaged in cART at long term. In this respect, directly-observed therapy administered at the addiction center could be a valid option for this subgroup of HIV-PWID.

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