Heterogeneous response to HAART across a diverse population of HIV-infected individuals – Results from the ANRS-EN12-VESPA Study

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Abstract

Objectives: Benefits from HAART may be heterogeneous across HIV-infected individuals. We measured the differences in the rate of HAART failure across the various subgroups represented at the level of a country.

Design: We used data from a national representative sample of people living with HIV and followed at hospital in France (ANRS-EN12-VESPA survey).

Methods: Analyses were restricted to the 896 participants on HAART for ≥6 months and antiretroviral-naïve at HAART initiation. Different indicators of treatment failure were defined: immunologic failure (absence of increase of ≥100 CD4 cell/mm^3); immuno-virologic failure (CD4 cell count≤200/mm^3 and detectable HIV-RNA); clinical failure (occurrence of an AIDS-defining illness >3 months after HAART initiation). Differences in the frequency of treatment failure across the various subgroups were measured using logistic regression models adjusted for major established determinants of response to HAART

Results: Overall, 19.6% of the study participants experienced immunologic failure, 3.4% immuno-virologic failure, and 3.0% clinical failure, with substantial variations across the various subgroups. Compared to homo/bisexual males, migrants had higher rates of immunologic failure (respectively, adjusted odds-ratio 2.27, 95% confidence interval [1.14-4.56] for migrant males and 2.19 [1.17-4.08] for migrant females), of immuno-virologic failure (respectively, 8.23 [1.77-38.33] and 6.91 [1.03-46.32]), and of clinical failure (respectively, 4.60 [1.01-20.86] and 4.22 [0.84-21.17]).

Conclusions: In France, migrants consistently appear to be at increased risk of immunologic, immuno-virologic and clinical treatment failure compared to the other HIV-infected individuals. Understanding the reasons underlying such heterogeneity in terms of living conditions and educational/cultural background appears to be important.

Introduction

In the era of highly active antiretroviral therapies (HAART), the magnitude of immunological and virological responses to treatment constitute strong predictors of disease progression and death among HIV-1-infected patients [1, 2]. Response to HAART has been shown to be influenced by various factors including characteristics at the time of HAART initiation (HIV disease advancement [2]; history of suboptimal antiviral treatment [3]), treatment characteristics (HAART duration [4]; level of adherence [5]; experience of treatment discontinuation [6]), sociodemographics (age [7]; gender [8]), comorbidity (depression [9]; HCV coinfection [10]) and ongoing drug use [11].

In Western countries, the HIV-infected population is made up of diverse subgroups characterized by highly contrasted socioeconomic and cultural backgrounds [12]. Longitudinal studies have suggested that after accounting for major established risk factors of treatment failure, benefits from HAART may be heterogeneous across these different subgroups. A lower beneficial impact of HAART on the risk of disease progression and/or death has been reported among persons with a history of injecting drug use (IDU) [4] and among migrants [13], while homosexual men may have benefited from HAART more than the others [14].

However, such differences have not been reported consistently across studies. This may be due to methodological concerns including the exclusion of some categories of individuals from the study samples, or the inadequate accounting for acknowledged determinants of treatment failure.

The present study aimed at measuring the differences in the rate of failure to HAART across the various subgroups of HIV-infected persons represented at the level of a country, accounting for subgroups differences in major established determinants of response to HAART. We used data from a French national representative sample of people living with

HIV and followed at hospital. In France, access to care for HIV infection is universal and, since antiretroviral treatments are provided exclusively through hospital physicians' prescription, HIV infection is almost exclusively managed through hospital outpatient clinics, regardless of disease severity [15]. The sample we used has been constituted specifically with the concern for reflecting the diversity of the HIV epidemic in terms both of individuals' and disease management characteristics, thus allowing us to account for the great heterogeneity in situations encountered at the country level.

Material and Methods

Study design

We used data from the ANRS-EN12-VESPA study, a large survey aimed at studying the social situation and living conditions of HIV-infected persons in France. The study design has been detailed elsewhere [16]. Data were collected between December 2002 and September 2003 among a random stratified sample of 4,963 HIV-infected outpatients recruited in 102 French hospital departments delivering HIV care. The stratification criteria were departments' geographic location and size of HIV caseload. Eligible individuals were those diagnosed as being HIV1-infected for at least six months, aged 18 or older, and, for non-French citizens, living in France for at least six months. In the participating departments, physicians invited a sample of HIV-infected outpatients, randomized according to the order in which they were received, to participate in the study. Those with very poor understanding of the French language were excluded.

Individuals who agreed to participate signed an informed consent and answered a face-to-face standardized questionnaire administered by a trained interviewer, using the CAPI system (Computer Assisted Personal Interview). Detailed information was collected on individuals' sociodemographic characteristics and on the different aspects of their life with HIV including access to and use of the healthcare system, health behaviors, occupational status, income, housing, social support, HIV disclosure, HIV-related discriminations, sexual activity and reproductive life. This information concerned both the situation at the time of the study and that at the time of HIV diagnosis; major changes occurred during the course of the disease were collected, providing retrospective information on participants' social trajectory during the course of the disease. Median length of interview was 40 minutes. After interview completion, participants received a 15€ voucher and were asked to fill in an additional self-administered questionnaire including psychometric scales. Information on health status,

including characteristics of HIV infection and its management at the time of the study and retrospectively since diagnosis and HCV serostatus was documented from medical records.

The study reached the ethical requirements of the French "Commission Nationale Informatique et Libertés".

Data collected

Among 4,963 eligible individuals, 2,932 participants were included in the study. Two hundred and sixty four were not solicited because of major cognitive impairment or health problems, while 1,767 declined to participate. Individuals who refused most frequently cited a lack of time; compared to participants, they were more likely to have been HIV-infected through a way other than homo/bisexual contacts and to be employed at the time of the study.

Weighting procedure

Non participation was 41% of the randomized individuals overall, with substantial differences according to HIV transmission category, employment status and immunological status. Major socio-demographic and health-related characteristics were collected both among respondents and non-respondents, allowing for a weighting procedure to take into account this participation bias. This weighting procedure included two steps: first, considering the unequal probability of enrolment related to the heterogeneous frequency of hospital visits, a weight was attributed to each individual corresponding to the inverse number of hospital visits he(she) had reported for the preceding year; second, to account for non-response, an additional weight was computed, using a method of calibration adjustment [17], in such a way that the weighted distribution of the participants regarding transmission group, employment status and immunological status was comparable to that of the entire eligible population.

Variables of interest

Different indicators of treatment failure were defined using data from the medical records. Immunologic failure was defined as the absence of increase of ≥100 CD4 cell/mm^3 between HAART initiation and the time of data collection. Immuno-virologic failure was defined as the combination of a CD4 cell count≤200/mm^3 and a detectable HIV-RNA at the time of data collection. Participants who had developed a first AIDS-defining illness after a period of >3 months on HAART were considered to be in clinical failure. HAART was defined as the concomitant receipt of at least 3 antiretrovirals.

Based on the characteristics of the HIV epidemic in western Europe [12], participants were divided in seven subgroups corresponding to the most significant groups of persons living with HIV infection in France: homo/bisexual males, IDU heterosexual males, IDU females, French-native heterosexual males without history of IDU, French-native females without history of IDU, migrant heterosexual males without history of IDU, and migrant females without history of IDU. Non French-natives who did not have French nationality at birth were classified as migrants. These seven subgroups constitute homogeneous epidemiological entities regarding HIV transmission [12] and show marked differences in socioeconomic characteristics and living conditions [18].

Data also included information on the following established determinants of response to HAART: 1) data from medical records, i.e. CD4 cell count, HIV-RNA and AIDS at HAART initiation; time since first HAART initiation and HAART regimen prescribed at the time of data collection; date of HIV diagnosis; and HCV coinfection; 2) depressive symptoms at the time of interview as measured by the Hospital Anxiety and Depression Scale (HADS) [19] included in the self-administered questionnaire and 3) participant-reported age and level of treatment adherence at the time of data collection, active drug use in the year preceding interview, and history of interruption of ≥6 months in HIV care since diagnosis. Adherence was assessed using a dichotomous indicator ("highly" versus "poorly" adherent) validated in

previous cohort studies [20], summarizing four questions dealing with dose taking during the prior week [21].

Statistical analyses

Analyses were restricted to participants on HAART for at least 6 months at the time of data collection and antiretroviral-naïve at the time of HAART initiation. Differences in the frequency of each indicator of treatment failure across the various subgroups were measured using logistic regression models accounting for weighted data and adjusted for the major established determinants of response to HAART described above. Homo/bisexual males were used as the reference group. All statistical analyses were performed using Stata 9.0® (Stata Corporation, College Station, TX).

Results

Study population

Overall, 1939 participants had been on HAART for at least 6 months at the time of the study, among whom 896 were antiretroviral-naïve at HAART initiation. Of these 896, 38.4% were homo/bisexual men, 27.3% were French-native heterosexuals (16.9% males, 10.4% females), 22.3% were migrant heterosexuals (11.0% males, 11.3% females) and 12.0% were IDU (8.7% males, 3.3% females). The majority of the heterosexual migrants originated from Sub-Saharan Africa (76.3% of the males and 82.3% of the females).

As shown in Table 1, these various subgroups showed marked differences on established determinants of response to HAART. Migrant heterosexual females (median age 33 years), were younger than the other groups while French-native heterosexual males were the oldest (median age 47 years). The majority (73.3%) of the IDU participants had been diagnosed as being HIV-infected in the pre-HAART era, while this was the case for only one third of the homo/bisexual males and French-native heterosexuals and 13.3% of the migrants. Similarly, individuals with a history of IDU had spent the longest time on HAART at the time of data collection (57 months in median) and migrants the shortest time (32 months). At the time of data collection, 25.2% of the participants were prescribed a regimen including a protease inhibitor and 46.4% a non-nucleoside reverse transcriptase inhibitor, without difference across subgroups. At HAART initiation, French-native heterosexuals males, IDU and migrants were more likely than homo/bisexual males and French-native heterosexuals females to have a marked immunodeficiency (CD4<200/mm^3); French-native heterosexuals males were also more likely to have reached the AIDS stage. Compared to the other subgroups, IDU participants more frequently reported a history of interruption in HIV care (33.8% vs. 6.3%) and current drug use at the time of the study (27.2% vs. 0.3%); they were also more likely to be HCV-coinfected (88.0% vs. 6.4%) and to present symptoms of depression (22.1% vs.

12.5%). Migrants reported suboptimal adherence more frequently than the other participants in this study (56.1% vs. 34.6%).

Differences in treatment failure rates across subgroups

Overall, 19.6% of the study participants experienced immunologic failure, 3.4% immuno-virologic failure, and 3.0% clinical failure. As shown in Table 2, these rates showed substantial variations across the various subgroups: immunologic failure rate ranged from 10.6% among French-native heterosexual males to 37.5% among migrant females; immuno-virologic failure rate from 0% among IDU females to 9.2% among IDU males; and clinical failure rate from 0.6% among French-native heterosexual females to 9.1% among IDU males.

Multivariate analysis accounting for subgroups differences in major established determinants of response to HAART suggested that compared to homo/bisexual males, migrants had higher rates of immunologic failure (respectively, adjusted odds-ratio 2.27, 95% confidence interval [1.14-4.56] for migrant males and 2.19 [1.17-4.08] for migrant females), of immuno-virologic failure (respectively, 8.23 [1.77-38.33] and 6.91 [1.03-46.32]), and of clinical failure (respectively, 4.60 [1.01-20.86] and 4.22 [0.84-21.17]). For the other subgroups, the rate of HAART failure did not differ from that of the homo/bisexual males in multivariate analysis. The other characteristics associated with an increased rate of treatment failure in multivariate analysis included age≥50, time on HAART<24 months, baseline CD4 cell count≤200/mm^3, baseline HIV-RNA ≥100,000 copies/ml, AIDS at baseline, history of interruption in HIV care, suboptimal adherence, HCV coinfection and current drug use.

Discussion

Our results suggest that at the level of a country, here France, long-term benefits from antiretroviral multitherapies are not homogeneous across subgroups of the HIV-infected population. Heterosexual migrants consistently appear to be at increased risk of immunologic, immuno-virologic and clinical treatment failure compared to the other HIV-infected individuals, even after accounting for differences in established determinants of response to treatment. Considering that access to care and treatment for HIV infection is universal in France (as reflected in our data by the absence of difference in the type of HAART regimen prescribed across subgroups) and that analyses have taken into account differences in baseline characteristics at HAART initiation, our findings are likely to reflect a heterogeneous response to HAART rather than differences in access to healthcare; the latter, if they exist, may further increase such heterogeneity.

The ANRS-EN12-VESPA survey, with its large randomized sample of persons living with HIV and followed at hospital all over France, provides a unique dataset to study the diversity of HIV-infected population at a national level. The retrospective design of our study has probably allowed for the inclusion of individuals who are likely to be underrepresented in studies assessing treatment outcomes prospectively. Indeed, prospective follow-up is likely to lead to the exclusion of the individuals with the most precarious socioeconomic conditions [22], implying a reduced heterogeneity across individuals with regard to these characteristics in the study sample compared to the diversity existing within the source population. Thus, prospective studies may sometimes fail to detect differences across subgroups that are characterized by marked differences in socioeconomic status and the contribution of other types of studies to the question of inequalities across subgroups appears of importance. Our results suggest that the significant role of major determinants of response to HAART on treatment failure reported in prospective studies is found as well at the population level, and

that additional characteristics related to foreign-nativity may also play a role, beyond that of the established factors.

The interpretation of our results must remain cautious due to concerns related to the retrospective nature of the study. First, individuals who died between HAART initiation and the study were excluded from the sample. Although this point may have led to an underestimation of treatment failure rates in our study, it is unlikely to have influenced the differences we report since analyses have been adjusted for acknowledged predictors of treatment failure and death. Second, only few points of laboratory measures were available to define immuno/virologic failure. To ensure accurate indicators of response to treatment despite this limitation, we gave precedence to CD4 cell count measurement rather than HIV-RNA which is highly subject to acute changes over time. Lastly, using a single cross-sectional measure of time-dependent phenomenons such as depressive symptoms, adherence to treatment and ongoing drug use has probably led us to underestimate their association with treatment failure. However, the established predictive role of these factors has been effectively found and accounted for in our analyses. Although information on the different regimens prescribed over time was also lacking, we took into account the duration of HAART treatment as a proxy for this sequencing.

Heterosexual migrants without history of IDU account for the great majority of the non-French native population living with HIV infection in France (85.4% in our sample) as in other western European countries [12]; they mostly include individuals originating from sub-Saharan Africa (79.3%) or other non-European countries (14.0%) and are characterized by a recent immigration in France (median: 6 years at the time of the study). Non-heterosexual migrants constitute a marginal part of the HIV-infected population (homo/bisexual migrants account for 2.2% of our sample and IDU migrants for 1.6%); moreover, they differ from heterosexual migrants in that they mainly come from other European countries (respectively, 59.4% and 52.7%) and have been settled in France for a long time (respectively, median of 13

and 24 years at the time of the study). For all these reasons, homo/bisexual and IDU migrants have not been analyzed as separate subgroups and have been classified together with French-native homo/bisexuals and IDU, respectively, rather than with heterosexual migrants.

Our finding of an increased risk of treatment failure among heterosexual migrants in France is consistent with data from the Netherlands suggesting that migrants followed in a clinic in Amsterdam have poorer virologic and clinical responses to HAART compared to the non-migrants [13]. On the other hand, migrants were not found to have an impaired response to HAART neither in Denmark [23] nor in London [24]. These two latter studies included individuals regardless of history of antiretroviral treatment prior to HAART initiation; since history of pre-HAART treatment, a strong predictor of response to HAART, is likely to be distributed differentially among migrants and non migrants, differences may have been underestimated in these studies.

There can be various explanations for our findings. Racial differences in viral subtypes, drug metabolism and levels of CD4 cell count and HIV-RNA have been shown, with a potential role on the magnitude and/or the measure of therapeutic response. However, studies have found that race does not constitute an independent predictor of HAART failure [25, 26] and that immuno-virologic response to HAART is comparable between persons from low- and high-income parts of the world [27], suggesting that racial differences are unlikely to explain our findings.

Alternatively, the heterogeneity we report may result from differences in living conditions and educational/cultural background. HIV-infected migrants in western countries encounter particularly adverse socioeconomic conditions. Among participants of the ANRS-EN12-VESPA study, precarious housing conditions and lone parenthood at the time of the study were more frequent among migrants than among French-natives [18]. Moreover, over half (53%) of the heterosexual migrants reported financial difficulties and 33% reported food

privation through lack of money in the preceding month, compared to 21% and 7% of the other participants, respectively; social isolation, as defined by <1 weekly contact with family members/friends, concerned 20% of the heterosexual migrants versus 12% of the others (data available on request). Such adverse living conditions may have indirect effects on response to treatment through various pathways including poor adherence, high comorbidity (e.g., depression, tuberculosis, bacterial coinfections), inadequate healthcare, low social support, life event stress, or maladaptive coping [21, 28-31]. The low level of literacy of HIV-infected migrants [18] may further constitute a barrier to adequate access to care and HIV treatment adherence and knowledge, with consequences on health status [32, 33]. Furthermore, cultural factors as well as the stigmas of HIV, race and ethnicity probably also influence treatment adherence and healthcare providers' attitudes and interactions with their patients [34]; HIV stigmatization in migrants' community may additionally result in low rates of HIV disclosure, with consequent low social support. Among participants of the ANRS-EN12-VESPA study, 17% of the heterosexual migrants versus 4% of the others had kept their HIV status secret from their social circle.

Our findings have important public health implications since the proportion of heterosexual migrants coming from countries with high HIV prevalence, especially sub-Saharan Africa, and living in precarious socioeconomic conditions has been rising drastically in the last few years [12]. Understanding the reasons underlying a poorer response to treatment in this population appears to be important. Although the present study precludes from drawing any conclusion in terms of causality, our results suggest that living conditions and educational/cultural background may play a major role on therapeutic failure. Further studies should prospectively assess the different pathways involved in such heterogeneity.

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Table 1. Characteristics* of the 896 participants on HAART for ≥6 months and antiretroviral-naïve at HAART initiation, overall and according to subgroup. ANRS-EN12-VESPA Study.

		Homo/bisexual males	French-native heterosexual males	French-native heterosexual females	Migrant heterosexual males	Migrant heterosexual females	IDU males	IDU females	Total
Overall		38.4	16.9	10.4	11.0	11.3	8.7	3.3	100.0
Age (years)	Median	42	47	41	41	33	41	40	41
	<30	6.6	0.4	11.6	6.3	23.2	-	-	7.1
	30-39	32.6	26.3	32.2	31.6	50.8	38.3	37.4	34.1
	40-49	35.8	31.2	31.6	44.2	15.2	55.6	56.8	35.6
	≥50	25.0	42.0	24.5	17.9	10.8	6.1	5.7	23.2
Period of HIV diagnosis	Median	1998	1998	1997	2000	2000	1991	1989	1998
	<1996	34.3	28.9	37.4	13.6	13.0	66.7	90.6	33.7
	≥1996	65.7	71.1	62.6	86.4	87.0	33.3	9.4	66.3
Time spent on HAART (months)	Median	48	43	52	33	27	57	62	44
	6-12	7.1	4.9	6.2	13.1	21.5	1.3	9.0	8.5
	12-24	13.7	17.8	8.5	13.7	21.9	8.6	3.8	14.0
	24-60	45.3	54.8	49.1	52.2	52.4	48.9	35.2	48.8
	>60	33.9	22.5	36.2	21.1	4.2	41.1	51.9	28.7
CD4 cell count at start of HAART ($/mm^3$)	>350	35.0	17.7	23.8	17.5	12.1	23.6	23.4	25.0
	201-350	26.7	31.8	35.5	29.6	38.5	14.3	27.6	29.1
	51-200	23.1	28.6	21.8	28.5	39.7	42.7	33.3	28.4
	≤50	15.2	21.4	18.9	24.4	9.7	19.4	15.6	17.4
HIV RNA at start of HAART (copies/ml)	<10 000	13.9	11.2	12.7	5.6	22.9	19.4	18.0	14.0
	10 000-29 999	10.5	9.1	13.5	11.7	24.5	4.8	11.8	11.8
	30 000-100 000	23.1	25.9	24.3	26.6	14.7	17.7	23.5	22.7
	≥100 000	47.5	50.3	43.9	54.2	34.8	54.6	34.5	47.1
	Unknown	5.0	3.5	5.6	1.8	3.1	3.5	12.1	4.3
AIDS at start of HAART	No	76.8	66.1	78.7	69.8	81.7	78.3	79.6	75.2
	Yes	23.0	33.9	19.7	25.7	18.3	20.4	20.4	23.9
	Unknown	0.3	-	1.6	4.5	-	1.3	-	0.9
History of interruption in HIV care	No	92.8	92.6	90.5	94.0	98.0	63.9	66.0	89.8
	Yes	7.2	7.4	9.1	3.7	2.0	34.4	32.1	9.7
	Unknown	-	-	0.4	2.3	-	1.7	1.8	0.5
Adherence to HAART	High	61.7	76.8	75.6	46.1	41.7	49.6	59.7	60.6

	Poor	38.3	23.2	24.4	53.9	58.3	50.4	40.3	39.4
HCV coinfection	No	93.7	97.0	91.7	92.0	91.7	9.7	18.0	83.8
	Yes	6.3	3.0	8.3	8.0	8.3	90.3	82.0	16.2
Depressive symptoms	No	71.2	72.7	70.7	45.7	40.2	48.6	55.7	62.6
	Mild	10.3	6.3	9.1	4.2	7.7	14.0	17.7	9.1
	Moderate/severe	3.7	5.0	4.8	2.6	5.5	8.1	4.5	4.5
	Unknown	14.7	15.9	15.4	47.5	46.6	29.3	22.1	23.7
Current drug use	No	99.3	100.0	100.0	100.0	100.0	73.3	71.5	96.4
	Yes	0.7	-	-	-	-	26.7	28.5	3.6

* weighted %

IDU: intravenous drug users

Table 2: Characteristics associated with treatment failure in multivariate analysis among the 896 participants on HAART for ≥6 months in 2003 and antiretroviral-naïve at HAART initiation. ANRS-EN12-VESPA Study.

		Immunologic failure		Immuno-virologic failure		Clinical failure	
		%	OR [95%CI]	%	OR [95%CI]	%	OR [95%CI]
Overall		19.6		3.4		3.0	
Group	Homo/bisexual males	16.4	1	1.4	1	1.8	1
	French-native heterosexual males	10.6	0.73 [0.39-1.33]	4.1	2.75 [0.68-11.08]	1.8	1.23 [0.22-6.84]
	French-native heterosexual females	13.4	0.93 [0.45-1.91]	0.9	0.63 [0.07-6.09]	0.6	0.36 [0.02-5.96]
	Migrant heterosexual males	27.4	2.27 [1.14-4.56] *	6.7	8.23 [1.77-38.33] *	5.6	4.60 [1.01-20.86] *
	Migrant heterosexual females	37.5	2.19 [1.17-4.08] *	4.1	6.91 [1.03-46.32] *	3.1	4.22 [0.84-21.17] ¶
	IDU males	27.6	0.95 [0.33-2.73]	9.2	2.78 [0.32-24.08]	9.1	9.53 [0.32-284.21]
	IDU females	17.3	0.41 [0.09-1.79]	0	-	4.4	3.23 [0.07-150.78]
Age (years)	<30	29.5	1.02 [0.48-2.18]	0	-	2.9	4.75 [0.40-56.29]
	30-39	22.1	1	4.2	1	1.4	1
	40-49	17.3	0.82 [0.51-1.32]	3.0	0.69 [0.21-2.22]	3.6	1.69 [0.45-6.39]
	≥50	16.8	1.10 [0.65-1.88]	4.0	1.88 [0.48-7.31]	4.5	5.09 [1.03-25.21] *
Period of HIV diagnosis	<1996	19.9	1	5.1	1	5.0	1
	≥1996	19.5	0.90 [0.52-1.55]	2.7	0.37 [0.09-1.60]	1.9	076 [0.20-2.91]
Time spent on HAART	6-12 months	34.2	2.97 [1.39-6.34] *	5.7	2.16 [0.53-8.74]	0	-
	12-24 months	28.3	2.50 [1.28-4.86] *	4.0	1.35 [0.36-5.07]	2.3	0.20 [0.03-1.45]
	24-60 months	17.1	1.15 [0.66-2.02]	2.9	1.15 [0.40-3.32]	2.0	0.26 [0.09-0.79] *
	>60 months	16.5	1	3.5	1	5.6	1
CD4 cell count at start of HAART ($/mm^3$)	>350	25.7	1	1.6	1	0.8	1
	201-350	20.1	0.61 [0.36-1.02] ¶	1.2	0.73 [0.12-4.62]	0.7	0.96 [0.09-9.72]
	51-200	19.3	0.67 [0.39-1.14]	5.1	3.19 [0.61-16.78]	7.1	6.18 [1.54-24.76] *
	≤50	10.4	0.44 [0.19-0.99] *	7.1	7.88 [1.50-41.51] *	9.7	11.49 [1.87-70.66] *
HIV RNA at start of HAART (copies/ml)	<10 000	29.1	1	3.4	1	1.2	1
	10 000-29 999	28.7	1.00 [0.50-2.01]	1.8	0.82 [0.09-7.52]	1.3	1.88 [0.18-20.10]
	30 000-100 000	18.0	0.60 [0.32-1.09] ¶	1.2	0.23 [0.04-1.47]	4.1	2.60 [0.35-19.13]
	≥100 000	15.2	0.53 [0.30-0.94] *	5.1	1.64 [0.37-7.26]	3.6	2.06 [0.32-13.37]
	Unknown	22.3	1.09 [0.41-2.90]	1.4	0.76 [0.05-11.88]	0	-
AIDS at start of HAART	No	22.3	1	3.2	1		
	Yes	11.0	0.60 [0.34-1.07] ¶	4.2	0.45 [0.17-1.18]		
	Unknown	20.2	0.32 [0.02-6.21]	0	-		
History of interruption in HIV care	No	18.8	1	2.8	1	2.3	1

	Yes	27.5	1.82 [0.86-3.84]	10.8	3.11 [0.54-17.96]	10.1	5.45 [1.26-23.60] *
	Unknown	41.6	2.92 [0.05-170.94]	23.2	19.95 [1.00-399.16] *	0	-
Adherence to HAART	High	14.0	1	2.5	1	2.0	1
	Poor	28.1	1.87 [1.27-2.76] *	4.8	2.01 [0.89-4.52] ¶	4.4	2.60 [0.88-7.62] ¶
HCV coinfection	No	17.8	1	3.1	1	2.5	1
	Yes	28.4	2.13 [1.04-4.38] *	5.2	0.39 [0.11-1.42]	5.1	0.42 [0.02-7.57]
Depressive symptoms	No	18.0	1	3.4	1	2.3	1
	Mild	21.0	0.92 [0.45-1.91]	2.9	0.35 [0.08-1.57]	7.2	2.95 [0.73-11.86]
	Moderate or severe	23.0	1.00 [0.42-2.41]	9.8	3.55 [0.75-16.96]	6.0	4.33 [0.53-35.29]
	Unknown	22.9	1.05 [0.65-1.69]	2.7	0.43 [0.14-1.33]	2.6	0.74 [0.20-2.75]
Current drug use	No	19.2	1	3.0	1	2.9	1
	Yes	31.1	1.26 [0.43-3.73]	20.0	13.36 [1.38-129.66] *	4.7	0.28 [0.03-3.00]

OR: odds-ratio CI: confidence interval
IDU: intravenous drug users
* $p<0.05$ ¶ $p<0.10$