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ABSTRACT

Background: In France, around 25% of the estimated number of people living with HIV are migrants, of whom three quarters are from sub-Saharan Africa (SSA). Our objective was to determine factors associated with virological rebound (VR) at the occasion of a transient stay to the country of origin.

Methods: HIV-positive migrants from SSA participating to the ANRS-VIHVO adherence study between 2006-2009, on effective ART with controlled pre-travel HIV-1 plasma viral load (VL), were included. Outcome was VR, defined as VL≥50 copies/mL at the post-travel visit during the week following the return to France.

Results: Among 237 persons (61.6% female, median age 41 years (IQR, 35-47), median time on ART 4.2 years (IQR, 2.2-7.1), 27 (11.4%) experienced VR. The main purpose of the travel was to visit family and median time spent abroad was 5.3 weeks (IQR, 4.1-8.8). The travel was extended longer than anticipated by at least one week in 42 individuals (17.7%). In multivariable logistic model, risk factors for VR were male sex (adjusted OR (aOR) 5.1; 95%CI 1.6-16.2)), no employment in France (aOR 2.0; 1.2-3.5), self-reported non-adherence during the trip (aOR 14.9; 4.9-45.9) and PI-containing regimen (aOR 4.6; 1.2-17.6). In another analysis not including self-reported adherence, traveling during Ramadan while respecting the fast (aOR 3.3; 1.2-9.6) and extension of the stay (aOR 3.0; 1.1-7.8) were associated with VR.

Conclusions: Virological rebound was partly explained by structural barriers to adherence such as extension of the travel and inadequate management of Ramadan fasting. Individuals' journeys should be carefully planned with health care providers.

Keywords: HIV, antiretroviral therapy, virological rebound, migrant, travel, sub-Saharan Africa.

INTRODUCTION:

In France, around 35 000 migrants were thought to live with HIV in France in 2010, of whom 76% of female and 69% of male were actually diagnosed, representing 25% of the 148 900 estimated number of people living with HIV [1]. Migrants from sub-Saharan Africa represented three quarters of migrants living with HIV [2]. HIV-positive migrants living in France who travel back to their native country are more exposed to health difficulties in relation to their trip, i.e. infectious tropical diseases [3-5] or decreased adherence [6-10]. Many reasons have been mentioned to explain decreased adherence in HIV-positive people traveling to tropical countries to visit friends and relatives: nondisclosure and fear of stigmatization [7-9], lack of enough treatment during the stay because of lack of enough medications supply before departure when travel is not anticipated or is unexpectedly lengthened [9], impaired intake because of digestive intolerance if a tropical disease occurs [3]. On the other hand, there is a need to maintain virological suppression to prevent sexually transmission of HIV to the spouse during the travel. A previous analysis of the ANRS-VIHVO cohort showed 11.5% of reduced reported adherence to ART in HIV-positive sub-Saharan migrants previously adherent to their antiretroviral therapy who travelled to their country of origin [9]. The impact of this self-reported lack of adherence on viral suppression was still to be investigated as well as the role of barriers to adherence. We aimed to assess factors associated with virological rebound in individuals included in the ANRS-VIHVO study who had an undetectable viral load before the trip.

MATERIALS AND METHODS

Design & Population

Between 2006 and 2009, the ANRS-VIHVO study enrolled, in 24 French university participating centers, 268 HIV-1-positive native sub-Saharan African persons living in France, aged at least 18 years, who planned to visit their native country for a period between two weeks and six months within the next 8 weeks. All had a plasma viral load (pVL) below 200 copies/ml and were on ART combination, containing at least three antiretroviral drugs with at least a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI), unchanged for at least three months prior to enrollment. For the present study, we selected individuals who were enrolled while their pVL was below 50 copies/ml: 237 individuals were included.

Medical and social data were collected at enrollment, at a post travel visit during the week following the return to France and at a third visit 8 to 12 weeks after the return to France. Demographic, social, clinical, and immuno-virological data were retrieved from the participants' medical records. Self-administered questionnaires, previously validated among migrants in France [11], administered at enrollment and during the week following the return to France, collected information about adherence to cART in the 4 days and in the 4 weeks preceding enrollment while in France or the day back to France while travelling [9]. At each assessment, people were classified into two categories: adherent group (with high or moderate adherence, i.e. 80-100% of prescribed tablets taken) and non adherent group (<80% of prescribed tablets taken), as described elsewhere [9]. Because of the 6 months limit for the travel duration and the French rules for drug delivery, participants had the possibility to leave France with the whole antiretroviral stock required for the full duration of their trip.

Statistical analyses

Virological rebound was defined by pVL ≥ 50 copies/ml at the post-travel visit during the week following the return to France [12-13]. Potential correlates of virological rebound considered for the study were gender (male vs female), age, CD4 cell count before the travel (≥ 350 vs < 350), AIDS status, time since ART initiation, ART regimen (PI vs. NNRTI), literacy level (can read and/or write French vs. cannot read or write French), employment (unemployed vs. employed either in the formal or in the informal sector), lodging during the trip (with the steady partner vs. other), trip extension for at least one week, unexpected traumatic troubles during the stay, including political, natural, accidental (road injury, theft), familial ones (bereavement, moral pressure, conflicts), period of traveling (during the Ramadan fasting while respecting the fast), self-reported adherence during the trip (adherence vs. non-adherence). Quantitative variables were dichotomized according to the median value except for CD4 cell count which was dichotomized according to the threshold value recommended in national and international guidelines for ART initiation at the time of the study [14-15].

Statistical differences between people who remained with pVL<50 copies/ml and people with a virological rebound after their travel were evaluated using Fisher's exact test for categorical variables and Wilcoxon-Mann-Whitney test for quantitative variables. Multivariable logistic regression models were used to assess potential factors associated with virological rebound including all variables possibly associated with the outcome of interest in the univariable analyses ($p < 0.15$). A backward stepwise selection was used to select the final multivariable

model. All variables possibly associated ($p<0.15$) with virological rebound in the univariable analyses were first included. Then variables with the highest Type III p-value were iteratively removed until no variable was left. The final model was the model with the lowest Akaike Information Criterion (AIC). Two multivariable analyses were separately investigated, one with and one without self-reported adherence status during the trip. Stata statistical software version 12 was used to perform the analyses.

Ethics

This study was approved by the institutional ethics committees, Direction Générale de la Santé and Comité de Protection des Personnes de la Pitié- Salpêtrière, at the session of 26/04/2006. All individuals received written information, provided signed consent to participate in the cohort study and were informed of their right to prevent their personal data from being used.

RESULTS

Of the 268 participants enrolled in the VIHVO study, 237 individuals (88.4%) with pVL below 50 copies/ml at the enrollment visit were included in the present study. Characteristics of the study population are summarized in table 1. Almost two thirds of the participants were female. Median age was 41 years (interquartile range (IQR), 35-47). Median time since HIV diagnosis was 5.3 years (IQR, 3.0-8.2), since ART initiation 4.2 years (IQR, 2.2-7.1) and since the first date with durable undetectable VL, i.e. last period of follow-up with no VL $\geq$ 200 copies/ml before the pre-travel visit, 2.2 years (IQR, 1.2-3.8). Median CD4 cell count before the travel was 440/mm3 (IQR, 336-575) and 70% of the participants had more than 350 CD4 cells/mm3. Social characteristics in France were as follows: 164 (69%) reported being owners or renters of their home in France, 147 (62%) were employed, 114 (50%) were married or living in a stable relationship.

One hundred and fifteen (49%) participants traveled to Central Africa, 109 (46%) to West Africa and 13 (5%) to East Africa. The main purpose of the trip was to meet their family for the vast majority (232 participants, 98%), and accommodation while abroad was at their spouse's for 32 (14%), at their family's house for 144 (60%) or in their own personal housing (owned or long-term rented accommodation) where their family usually lives for 29 (12%), friends or other for 32 (14%). Participants who lived at their spouse's were more frequently men (21/32, 66%) and participants who lived at their family's or friends' house were more

frequently women (135/205, 66%) (p = 0.004). Median number of people living in the same house was 5 (IQR, 4-8).

The median time spent abroad was 5.3 weeks (IQR, 4.1 - 8.8). However, 42 participants (17%) extended their stay at least one week longer than originally planned, median duration of extension 2.3 weeks (IQR, 1.7 - 5.4). Three individuals extended their stay for more than 6 months (11, 14 and 15 months). There was no difference in extending the stay between people with an employment and people with no employment (24/147 vs 18/90, p=0,49). During the stay, 82 individuals (34.6%) reported at least one medical event during the trip, ie. malaria, digestive disorders, respiratory disorders, skin disorders, isolated fever, neurological disorders, miscellaneous, 56 individuals (23.6%) reported at least one traumatic event during the trip and 10 individuals (4.7%) used traditional medicine (herbal preparations, marabouts, traditional healers).

Virological rebound:

Among the 237 participants, 27 (11,4%) had pVL ≥ 50 copies/ml when they returned to France with a median pVL of 755 copies/ml (IQR, 169 - 72 106), among whom 12 participants still had VL > 50 copies/ml (median 205 copies/ml, IQR, 94 - 2 599) at the subsequent study visit between 8 and 12 weeks after the return to France. Median (IQR) pVL during the week following the return to France was 13 375 copies/ml (550-107 360) for these 12 participants and 269 copies/ml (IQR, 76-52 460) for the 15 participants who subsequently had pVL < 50 Copies/ml (p<0.001). Subsequent undetectable pVL occurred in 9 among 14 individuals with pVL < 1000 copies/ml during the week following the return to France and in 6 among 13 individuals with pVL ≥ 1000 copies/ml (p=0.45). Antiretroviral therapy was unchanged for all individuals.

Results of univariate and multivariable analyses are shown in table 2. Virological rebound occurred in 8/32 (25.0%) individuals who were hosted by their spouse, 12/144 (8.3%) individuals hosted by their family, 3/29 (10.3%) individuals living in their own personal housing, 4/32 (12.5%) individuals living at friend's or other. In the multivariable logistic model, male sex (adjusted OR (aOR) 5.1; 95%CI 1.6-16.2), being unemployed (aOR 2.0; 95%CI 1.2-3.5), PI-containing regimen (aOR 4.6; 95%CI, 1.2-17.6 for PI versus NNRTI) and self-reported non-adherence during the trip (aOR 14.9; 95%CI 4.9-45.9) were associated with virological rebound. When self-reported adherence was removed from the model, traveling during the Ramadan period while respecting the fast (aOR 3.3; 95%CI 1.2-9.6) and extension

of the stay (aOR 3.0; 95%CI 1.1-7.8) were the trip determinants associated with virological rebound.

DISCUSSION

Factors associated with virological rebound after travel were assessed among HIV-positive individuals originating from sub-Saharan Africa, living in France and successfully treated with ART for a median of 4 years. Among the 237 individuals included in the study, 11% had pVL ≥ 50 copies/ml when they returned to France of whom about half had a controlled viral load at a subsequent visit 8 to 12 weeks after the return. Risk factors for virological rebound were male sex, no employment in France, PI-containing regimen and self-reported non-adherence during the stay abroad. In models not including self-reported adherence, unexpected extension of the stay and travelling during Ramadan while respecting the fast were associated with virological rebound.

Our study had some limitations. First, virological rebound, defined using a single viral load measurement at the time of the post-travel visit, included both individuals with a sustained virological rebound and individuals with a blip of viral replication. Indeed, 9 individuals among 14 with pVL < 1000 copies/ml during the week following the return to France who had a subsequent undetectable pVL could be considered to have a simple blip, ie single detectable viral load < 1000 copies/ml not confirmed at the subsequent sample [13]. However, even low-level viraemia episodes have been shown to be associated with increased risk of antiretroviral drug resistance and virological failure [16,17,18]. Second, we did not have data to assess viral replication during the travel. No resistance tests were systematically performed but half of the participants with a virological rebound after the travel had a controlled viral load without a change in their antiretroviral therapy within the next two to three months. Last, we assessed only HIV-positive people originating from sub-Saharan Africa who had an undetectable viral load before the travel. However, in France in 2015, 89% of men and 89% of women originating from Sub-Saharan Africa on ART had an undetectable viral load, close to the numbers of 92% and 93% for men and women born in France respectively (FHDH-ANRS CO4 cohort, personal communication). Some studies have described adherence outcome associated with travel to the tropics [6-9,19-20], few have focused on migrants originating from SSA traveling back to their country of origin [7,9] and none assessed risk factors for virological rebound after their travel.

A recent study has shown that region of origin but not travel *per se* was associated with a higher risk of virological rebound [10]. In this study, travel was a significant additional risk factor for virological rebound only in individuals originating from SSA but not in people from other origin, Western countries or other non-SSA countries. People visiting friends and relatives were at a higher risk for virological rebound but not frequent travelers, suggesting that the conditions of the travel rather than the travel per se affect the virological outcome during the travel [10]. Reasons for viral rebound were assessed in people living in Nigeria traveling for Hajj with antiretroviral interruption being mainly because of stigma in a congregational setting or failure to pass airport of departure or arrival with medications [19]. None of our study individuals reported having experienced difficulty when crossing the airports with their treatment. However, we did not question the experience of stigma in the community.

In our study, decreased self-reported adherence during the travel was associated with viral rebound. Although initial high levels of adherence during the first months of ART, ie > 95%, are necessary to achieve viral suppression after ART initiation [21,22], long-term moderate adherence has a less negative impact in the current context of potent therapy after a previous long duration of continuous HIV suppression, ie for more than 12 months [21,23-25]. Severe deviations to adherence during the travel probably explained viral replication after the travel as indicated by the association with unexpected extension of stay or travel during Ramadan. Despite a low number of events, we found an association between PI-regimen and virological rebound compared to regimen containing NNRTI or NNRTI plus PI as previously shown, one hypothesis being a higher level of intolerance associated with PIs in tropical countries [24-25]. It cannot be excluded that some ART regimens were more compatible with schedule modifications and food consumption during the Ramadan fasting [26].

Other factors of virological rebound during the travel were to be a male, and to be unemployed in France, a proxy of social condition. In our study, men had a three to five times higher aOR of virological rebound than women, contrary to other studies which also included men having sex with men [10,24,27]. Reasons for traveling back to the country of origin might have been different between men and women with men traveling more frequently to join their spouse or get married and women traveling more often to visit their relatives. Fear of stigma and HIV non disclosure could be risk factors, but as we were not able to differentiate disclosure in France and in the country of the travel we did not assess association between HIV non disclosure and post travel viral replication in our study [28].

In conclusion, although post travel viral rebound occurred in up to 11% of sub-Saharan HIV-positive migrants traveling to their native country, return to undetectability was rapid without any antiretroviral change for at least half of the individuals, probably because rate of resistance mutations acquisition is low after PI-containing cART interruptions [29]. Viral rebound was partly explained by structural barriers to adherence during travel such as extension of the stay and inadequate management of the Ramadan fasting. Individuals' journeys should be anticipated and carefully planned with health care providers, ensuring that they travel with enough medication so that any extension of their stay can be adequately managed. Ramadan fasting should also be anticipated with prescription of *ad hoc* drug combinations such as once daily dose and forgiving regimens.

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Table 1. Baseline characteristics of 237 HIV-positive migrants before traveling to sub-Saharan Africa

	N (%) or Median [IQR]
Male sex	91 (38.4)
Age (years)	41.0 [35.4- 47.4]
Region of birth	
Central Africa	117 (49.4)
West Africa	106 (44.7)
East Africa	14 (5.9)
Region of care	
Paris area	191 (80.6)
Other metropolitan area	46 (19.4)
Literacy level	
Unable to read or write French	31 (13.1)
Able to read and/or write French	206 (86.9)
Educational level*	
< Secondary school	130 (54.9)
≥ secondary school	107 (45.1)
Employment	
Yes (formal/informal)	147 (62.0)
Marital status	
Married/living together	114 (50.2)
Divorced	32 (14.1)
Single	81 (35.7)
CD4 cell count (/mm^3)	440 [336- 575]
Previous AIDS	68 (28.7)
Time since ART initiation (years)	4.2 [2.2- 7.1]
ART regimen	
NNRTI containing**	94 (39.7)
PI containing	143 (60.3)

ART, antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; IQR, interquartile range.

* Secondary school is for people aged 11 and over

** Nine individuals with NNRTI + PI (for example, boosted darunavir + etravirine)

Table 2. Factors associated with virological rebound (VL ≥ 50 copies/mL) in 237 HIV-positive migrants after their travel to sub-Saharan Africa

	All (N = 237)	VL≥50 cp/ml (n = 27)*	p	Model 1 aOR (95%CI)	Model 2 aOR (95%CI)
At enrollment, before travel:					
Sex Female	146	12 (8.2)	0.051	1.00	1.00
Male	91	15 (16.5)		5.06 (1.58-16.21)	2.98 (1.15-7.75)
Age < 42 years	120	13 (10.8)	0.784	-	-
≥ 42 years	117	14 (12.0)			
Literacy level					
No reading or writing French	31	8 (25.8)	0.013	NR	NR
Reading and/or writing French	206	19 (14.6)			
Employment**					
Yes (formal/informal)	147	11 (7.5)	0.015	1.00	1.00
No	90	16 (17.8)		2.01 (1.15-3.52)	2.17 (1.32-3.58)
CD4 cell count (/mm^3)					
< 350	70	11 (15.7)	0.141	NR	NR
≥ 350	167	16 (9.6)			
AIDS Status					
No	169	15 (8.9)	0.055	NR	NR
Yes	68	12 (17.6)			
Time since ART initiation (years)					
< 5	138	18 (13.0)	0.359	-	-
≥ 5	98	9 (9.2)			
ART					
NNRTI***	94	4 (4.3)	0.015	1.00	1.00
PI	143	23 (16.1)		4.63 (1.22-17.64)	3.87(1.24-12.06)
During the trip:					
Lodging					
Family, friends, other	205	19 (9.3)	0.016	NR	NR
Steady partner	32	8 (25.0)			
Extension of stay					
No	195	17 (8.7)	0.013	NR	1.00
Yes	42	10 (23.8)			3.00 (1.14-7.79)
Traumatic troubles during stay****					
No	181	17 (9.4)	0.081	NR	NR
Yes	56	10 (17.9)			
Medical events during stay					
No	155	15 (9.7)	0.253	-	-
Yes	82	12 (14.6)			
Traveling during the Ramadan period while respecting the fast					
Not concerned/out of period	198	18 (9.1)	0.023	NR	1.00
Concerned	39	9 (23.1)			3.32 (1.15-9.59)
Self-reported adherence					
Yes	187	10 (5.4)	<0.01	1.00	-
No	30	13 (43.3)		14.91 (4.85-45.86)	

ART, antiretroviral therapy; NNRTI, non nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; IQR, interquartile range; OR, odds ratio; NR, not retained in the final model.

* Values in the column are numbers (percentages)

** either part-time or full-time

*** Nine individuals with NNRTI + PI, one of these nine had a virological rebound
**** Troubles included political, natural, accidental (road injury, theft) and familial (bereavement, moral pressures, conflicts)