

Travel-related health events and their risk factors in HIV-infected sub-Saharan migrants living in France and visiting their native country: The ANRS VIHVO cohort study



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ABSTRACT

Background: Literature on health events in HIV-infected travellers is scarce, particularly in sub-Saharan African (SSA) migrants.

Methods: We investigated health events in HIV-infected SSA migrants living in France during and after travel to their native country. All had a pre-travel plasma viral load (pVL) below 200 copies/mL and were on stable

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combined antiretroviral therapy (cART). Logistic regression models were used to assess the risk factors for at least one adverse health event or febrile event.

Results: Among 264 HIV migrants, pre-travel median CD4 count was 439/mm³ and 27 migrants (6%) experienced a low-level viremia between 50 and 200 copies/mL. One hundred (38%) experienced at least one event (13 experienced two events). The most common events were gastrointestinal, including diarrhoea (n = 29, 26%), respiratory events (n = 20, 18%), and malaria (n = 17, 15%; 1 death). In multivariable analysis, a pre-travel low-level viremia and a lack of pre-travel medical advice significantly increased the risk for any event (OR 4.31, 95% CI, 1.41–13.1; and OR 3.62, 95% CI, 1.38–9.47; respectively). A lack of pre-travel advice significantly increased the risk for febrile event.

Conclusions: Early and tailored counselling on pre-travel medical advice regarding diarrhoea and vector-borne diseases prophylactic measures in HIV-infected SSA migrants should be emphasised before travel to Africa.

1. Introduction

There are approximately 5.8 million migrants (8.8% of the whole population) living in France; 670,000 of those migrants were born in sub-Saharan Africa (SSA) [1]. Furthermore, migrants originating from SSA constitute 23% of the 200,000 HIV-infected individuals in France [1–3]. Since the introduction of combined antiretroviral therapy (cART), the quality of life of HIV-infected individuals has markedly improved. As a result, HIV-infected SSA migrants travel more frequently to their native countries for long travel duration [3,4].

In comparison to the general population of travellers, HIV-infected SSA migrants are at greater risk of contracting infectious diseases, particularly malaria. This could be due to two factors. First, more severe malaria cases are associated with decreased CD4 cell counts [5–8]. Second, there is a perception of low risk of infection that limits pre-travel physician visits and prevention counselling [9–13].

Studies on the travel-related health problems of HIV-infected persons that visit tropical regions are scarce and often small and retrospective in nature [6,8,14–20]. Further, no such studies have specifically focused on HIV-infected SSA migrants living in a Western country who visit their native country of origin. The aim of our study was to describe travel-related health events and their risk factors in HIV-infected SSA migrants included in the ANRS VIHVO study.

2. Material and methods

2.1. Design and population

Between July 2006 and June 2009, the ANRS VIHVO study prospectively enrolled 268 HIV-infected migrants, who were SSA natives living in France, within 8 weeks of a visit to their native country for between 2 weeks and 6 months. We selected stays longer than 2 weeks in order to exclude touristic trips that do not address critical problems for HIV physicians in terms of care. The 6-month limit delay was chosen because it was not possible for pharmacies to dispense more than 6 months of ART on one occasion when authorized by the prescribing physician [21].

The aim of the ANRS VIHVO Study was to identify travel-related risk factors of adherence failure to cART [21] and potential interactions between cART and antimalarial drugs administration [22]. The inclusion criteria were as follows: aged at least 18 years, current HIV plasma viral load (pVL) < 200 copies (cp)/mL, and unchanged cART for at least 3 months prior to enrolment. Having a pVL < 200 cp/mL was defined as a controlled infection. This included an undetectable viral load if pVL was < 50 cp/mL and low-level viremia if pVL was ≥ 50 cp/mL. Participants were enrolled in 24 French university outpatient clinics.

Secondly, we performed an ancillary analysis including all the participants of ANRS VIHVO study while focusing on travel-related events.

Participant characteristics and travel data were collected at enrolment during the 8 weeks preceding the trip, as well as within the week following their return to France. Adherence to prophylactic measures and travel-related health events of migrants were recorded on a standardised form by physicians at two visits: during the week following their return to France and during another visit planned between 8 and 12 weeks after their return to France.

2.2. Pre-travel medical advice and prophylactic measures

Pre-travel medical advices were given and prophylactic measures prescribed either in the setting of an HIV outpatient clinic or in a specialized pre-travel clinic especially when participants were referred for yellow-fever vaccination. Thus, pre-travel advices were not systematically and uniformly provided. We considered that participants had received pre-travel medical advice on diarrhoea and vector-borne diseases when counselled on both faecal-oral illness prevention, including hand washing, water hygiene, food hygiene, and vector-borne disease prevention (including cutaneous repellents, clothing repellents and bed netting), during the pre-travel visit. Adherence to vector control measures was defined as the use of at least one of the following control measures during travel: cutaneous repellents, clothing repellents, or bed netting. Adherence to malaria chemoprophylaxis was defined as compliant use of any recommended drug, i.e. less than one missed dose per week. The exception was mefloquine compliance, for which one missed dose during the entire period of prophylaxis was considered non-compliance.

2.3. Travel-related health events

Travel-related health events were defined as all health events occurring during travel or within the month following their return, with the exception of malaria (which was included even if it occurred more than 1 month after returning). The events were categorised according to the Geosentinel network guidelines [12], as follows: malaria; diarrhoea and other gastrointestinal; upper and lower respiratory; oral and dental; cardiovascular; febrile unspecified; dermatologic; neurologic and sensorineural; injury and musculoskeletal; genitourinary and gynaecologic; ophthalmologic; or metabolic. Events were described according to their time of occurrence, i.e. during or after travel, and according to whether subsequent medical care (i.e. outpatient visit, hospitalisation, medical evacuation) was sought. All diagnoses of malaria, both confirmed (documentation of *Plasmodium*) and suspected (clinical signs including response to specific therapy), were considered.

2.4. Statistical analysis

Univariable and multivariable logistic regression models were used to examine factors associated with the occurrence of at least one travel-related health event during or after travel. Gender, age, AIDS stage,

Table 1

Participants and travel characteristics of 264 HIV-infected sub-Saharan migrants living in France and visiting their native country, the ANRS VIHVO study (2006–2009).

	N ^a	n	(%)
Gender, n (%)	264		
Male		107	(41)
Female		157	(59)
Age (years), Median (IQR)	264	41	(35–48)
Mean CD4 count (cells/mm³), Median (range)	263	439	(66–1,580)
Mean CD4 count (cells/mm³), Median (IQR)	263	439	(329–570)
Type of housing, n (%)	264		
Family		236	(89)
Friends		5	(2)
Hotel		8	(3)
Own home		6	(2)
Rented apartment		8	(3)
Other		1	(1)
Travel destination, n (%)	264		
Central Africa		129	(49)
Cameroon		64	
Congo		25	
Democratic Republic of Congo		19	
Central African Republic		10	
Other countries		11	
West Africa		122	(46)
Ivory Coast		42	
Mali		36	
Togo		8	
Other countries		36	
East and Southern Africa		10	(4)
Islands		3	(1)
Travel duration (weeks), Median (IQR)	261	5	(4–8)
Pre-travel advice (diarrhoea and vectors), n (%)	248		
No		21	(8)
Yes		227	(92)
Adherence to at least one vector control measure^b, n (%)	199		
No		88	(44)
Yes		111	(56)
Adherence to cutaneous repellent^b, n (%)	199		
No		120	(60)
Yes		79	(40)
Adherence to bed-nets^b, n (%)	199		
No		132	(66)
Yes		67	(34)
Adherence to clothes repellent^b, n (%)	199		
No		193	(97)
Yes		6	(3)
Malaria chemoprophylaxis prescribed, n (%)	241		
Chloroquine alone		1	(0)
Mefloquine		28	(12)
Atovaquone–Proguanil		23	(10)
Doxycycline		174	(72)
Chloroquine–Proguanil		10	(4)
No prophylaxis		5	(2)
Adherence to malaria chemoprophylaxis, n (%)	236		
Not collected		39	(17)
Not adherent		43	(18)
Adherent		154	(65)
Vaccination against yellow fever^c, n (%)	226		
Not up to date		20	(9)
Before travel advice visit		155	(69)
During travel advice visit		51	(22)
Vaccination against diphtheria–tetanus–poliomyelitis^c, n (%)	225		
Not up to date		65	(29)
Before travel advice visit		118	(52)
During travel advice visit		42	(19)
Vaccination against typhoid fever^c, n (%)	226		
Not up to date		157	(69)
Before travel advice visit		36	(16)
During travel advice visit		33	(15)

IQR, interquartile Range.

^a N = migrants with available information.

^b Adherence to vector-control measures was assessed only in the 227 patients who received pre-travel advice.

^c Vaccination analyses were conducted in the patients with available data for both previous vaccinations and vaccinations during the visit.

CD4 count, pVL, cotrimoxazole prophylaxis, cART regimen, duration of cART, travel duration, and pretravel advice were considered in the analysis. Variables with a p-value < 0.20 in the univariable analysis were included in the multivariable model. Factors associated with the occurrence of at least one febrile event (malaria or unspecified fever) were also assessed. The pVL variable was included in the framework of both multivariable models because we considered that viral replication which occurs previously to the travel reflecting adherence to cART could be associated with health events such as febrile illness, diarrhoea or HIV-related infections. The analysis was performed with SAS software (ver. 9.3; SAS Institute, Cary, NC, USA).

2.5. Ethics

This study was approved by the Institutional Ethics Committees of Direction Générale de la Santé and Comité de Protection des Personnes de la Pitié-Salpêtrière, during the session of 26/04/2006. All participants received written information, signed consent forms, and were informed of their right to prevent their personal data from being used.

3. Results

3.1. Study population and travel characteristics

Among the 268 migrants enrolled in the VIHVO ANRS study, 264 attended their post-travel visit and were included in this study. Migrant characteristics are summarised in Table 1. In total, 157 (59%) of the migrants were females, with a median age of 41 years (interquartile range [IQR]: 35–48 years). Pre-travel CD4 cell counts ranged from 66 to 1,580/mm³, with a median count of 439/mm³ (IQR: 329–570/mm³).

The main reason for travel was to visit friends or relatives (239 [89%] individuals). All participants travelled to their country of origin: 129 (49%) travelled to Central Africa, mainly Cameroon (n = 64), Congo (n = 25), the Democratic Republic of Congo (n = 19), and Central African Republic (n = 10). Additionally, 122 (46%) travelled to West Africa, mainly Ivory Coast (n = 42), Mali (n = 36), and Togo (n = 8). Further, 10 participants (4%) travelled to East Africa. The median travel duration was 5 weeks (IQR: 4–8 weeks).

3.2. Pre-travel medical advice and prophylactic measures

Pre-travel medical advice on diarrhoea and vector-borne diseases was provided to 227 (92%) of 248 migrants with available data. Among the 227 migrants who received pre-travel medical advice on diarrhoea and vector-borne diseases, 111/199 (56%) reported adherence to at least one of the vector control measures. Malaria chemoprophylaxis was prescribed to 236 (98%) of the 241 migrants with available data, and 154/236 (65%) reported adherence. Doxycycline was the main type of malaria chemoprophylaxis prescribed in 174/236 (74%) migrants. Among the 226 migrants with available data, 206 (91%) were vaccinated for yellow fever, 160 (71%) for diphtheria-tetanus-poliomyelitis, and 69 (31%) for typhoid fever, either previously or during the pre-travel advice visit.

3.3. Travel-related health events

At least one health event was reported in 100 (38%) migrants, among whom 13 had two events. Among the overall 113 events, 76 (67%) occurred during travel and 56 (50%) required medical care of which 38 (68%) were sought during the travel. These included 45 outpatient visits, 10 hospitalisations, and 1 medical evacuation (Figs. 1 and 2).

The 113 health events were categorised as follows (Table 2): 29

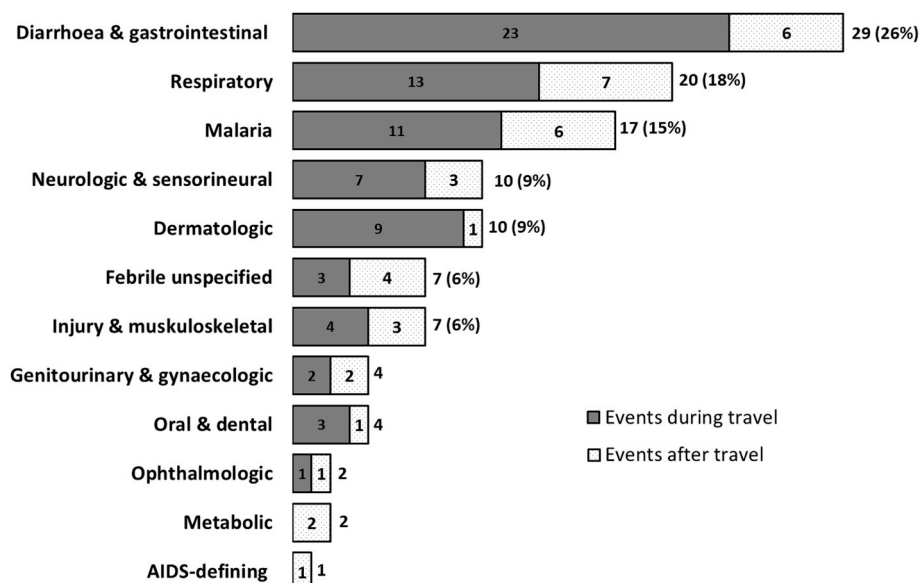


Fig. 1. Travel-related health events according to the timing of occurrence during or after travel in 264 HIV-infected sub-Saharan migrants living in France and visiting their native country, the ANRS VIHVO study (2006–2009).

(26%) diarrhoea and other gastrointestinal events, 20 (18%) upper and lower respiratory events, 17 (15%) malaria events, 10 (9%) neurologic and sensorineural events, 10 (9%) dermatologic events, 7 (6%) unspecified febrile events, 7 (6%) injury and musculoskeletal events, 4 oral and dental events, 4 genitourinary and gynaecologic events, 2 ophthalmologic events, 2 metabolic events, and 1 AIDS-related event.

The only fatal event that occurred during the study was severe malaria in a 26-year-old Nigerian woman with a pre-travel pVL < 50 cp/mL and a CD4 T cell count of 354/mm³. The participant also showed a lack of compliance to doxycycline prophylaxis and post-travel pVL < 50 cp/ml, CD4 T cell of 194/mm³ with concomitant *Plasmodium*

falciparum parasitaemia of 1.8% at admission. The participant was hospitalised in the intensive care unit and expired 2 months later due to refractory acute respiratory distress syndrome.

3.4. Risk factors for travel-related health events

The risk factors for at least one travel-related adverse health event are shown in Table 3. Pre-travel low-level viremia (pVL between 50 and 200 cp/mL) and lack of pre-travel medical advice regarding diarrhoea and vector-borne disease prevention were significantly associated with travel-related health events (adjusted odds ratio [aOR] 4.31 [95% CI,

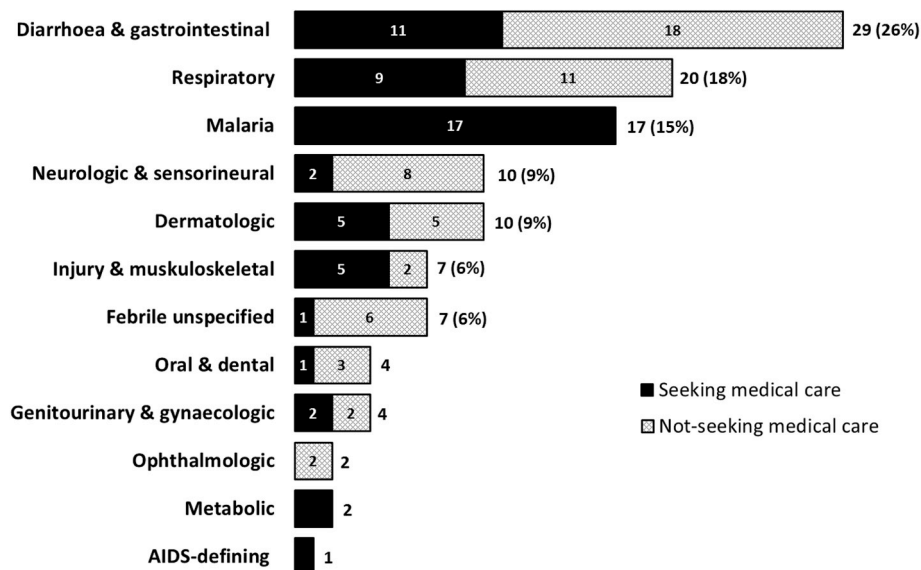


Fig. 2. Travel-related health events according to medical-care-seeking behaviour in 264 HIV-infected sub-Saharan migrants living in France and visiting their native country, the ANRS VIHVO study (2006–2009).

Table 2

Detailed description of travel-related health events in 264 HIV-infected sub-Saharan migrants living in France and visiting their native country, the ANRS VIHVO study (2006–2009).

Diarrhoea & gastrointestinal events	29
<i>Diarrhoea</i>	22
<i>Abdominal pain</i>	2
<i>Nausea/vomiting</i>	2
<i>Colic amoebiasis</i>	1
<i>Liver cytolysis</i>	1
<i>Constipation</i>	1
Respiratory events	20
<i>Flu-like</i>	4
<i>Pneumonia</i>	3
<i>Sinusitis</i>	3
<i>Rhinitis</i>	3
<i>Bronchitis</i>	2
<i>Otitis</i>	2
<i>Coughs</i>	2
<i>Pertussis</i>	1
Malaria events	17
<i>Confirmed</i>	6
<i>Suspected</i>	11
Neurologic & sensorineural events	10
<i>Headache</i>	2
<i>Fatigue</i>	2
<i>Cerebral ischemic attack</i>	2
<i>Dizziness</i>	1
<i>Lower limb paraesthesia</i>	1
<i>Lower limb myalgia</i>	1
<i>Tinnitus</i>	1
Dermatologic events	10
<i>Rash</i>	2
<i>Mycosis</i>	1
<i>Abscess</i>	1
<i>Loiasis</i>	1
<i>Leg wound</i>	1
<i>Lichen planus</i>	1
<i>Condyloma</i>	1
<i>Pruritus on limbs</i>	1
<i>Drug-induced photosensitivity</i>	1
Febrile unspecified events	7
Injury & musculoskeletal events	7
<i>Fracture</i>	2
<i>Sprain</i>	2
<i>Sciatic</i>	1
<i>Lumbago</i>	1
<i>Metacarpophalangeal pain</i>	1
Oral & dental events	4
<i>Pharyngitis</i>	3
<i>Dental pain</i>	1
Genitourinary & gynaecologic events	4
<i>Spontaneous miscarriage</i>	1
<i>Induced abortion</i>	1
<i>Pollakiuria</i>	1
<i>Vaginal fungal infection</i>	1
Ophthalmologic events	2
<i>Conjunctivitis</i>	2
Metabolic events	2
<i>Diabetes disorder</i>	2
AIDS-defining event	1
<i>Tuberculous arthritis</i>	1
TOTAL events	113

1.41–13.1] and 3.62 [95% CI, 1.38–9.47], respectively) after adjustment for the duration of cART.

The risk factors for the occurrence of at least one travel-related febrile event are shown in Table 4. A lack of pre-travel medical advice regarding diarrhoea and vector-borne disease prevention was significantly associated with a febrile event (aOR 4.60 [95% CI, 1.24–17.1]) after adjustment for age, pVL, cART duration and type of cART (protease inhibitor (PI)-based regimen vs. other).

4. Discussion

In this study, 100 (38%) of 264 HIV-infected sub-Saharan migrants living in France experienced at least one travel-related adverse health event during travel to their native country, among whom 13 had two events. Medical care was sought for 56 (50%) of the 113 events. Diarrhoea and other gastrointestinal disorders were the most common events, followed by respiratory symptoms and malaria-related events. Reported adherence rates to vector control measures and malaria chemoprophylaxis were low. Participants with low-level pre-travel viraemia, and those receiving no pre-travel medical advice on diarrhoea and vector-borne diseases, had about a four-fold higher risk of experiencing travel-related health events than those with undetectable pVL and pre-travel medical advice, respectively. Lack of pre-travel medical advice was also associated with the occurrence of a febrile event.

Because consultation conducted in a specialized pre-travel clinic was not systematically offered, some participants might have missed dedicated pre-travel medical advices possibly explaining suboptimal compliance to prophylactic measures. More, malaria prophylaxis and travel-related vaccinations are not refunded by the French Social Security and low awareness of health risks during the travel is clearly recognized among migrants visiting friends and relatives (VFRs) [10,23].

One third of our participants experienced at least one travel-related health event, which was lower than the 64–87% of health events reported in the general population of international travellers to resource-limited countries [11,24–27]. This was despite our focus on SSA where the risk for travel-related health events is particularly high compared to other parts of the world [8,9,11–13]. The low proportion of events in our study population could be partly explained by a lower burden of diarrhoea and other gastrointestinal events in migrants native to SSA compared to non-migrants. This could be explained by the controlled HIV infection in our cohort, the high proportion of participants who sought pre-travel medical advice, and the existence of local mucosal immune responses against feco-oral transmitted illnesses in migrants originating from SSA [28–30]. The single case of fatal malaria shows the potential severity of this disease [31], especially among HIV-infected immunocompromised individuals [5–8,32,33], and the need for careful anticipation of travel with tailored counselling to include relevant advice on malaria prophylaxis.

Studies on travel-related health problems in HIV-infected individuals visiting tropical regions are scarce, and most data available are from small samples that do not focus on migrant populations [6,8,14–20]. However, three observational studies that assessed travel-related health events among HIV-infected travellers had significantly large sample sizes [6,8,14]. Belgian (93 HIV-infected individuals) and Spanish (72 HIV-infected individuals) studies showed that infectious events and related hospitalisations were more frequent in HIV-infected travellers than in non-infected ones. Malaria was the most frequent event and occurred twice as frequently in HIV-infected travellers. Further, the second most frequent health events were respiratory tract infections and infections due to intestinal parasites, respectively in the Belgian and in the Spanish cohorts. Finally, a retrospective, cross-sectional study (763 individuals from the Danish HIV Cohort) did not focus on tropical regions but showed as in our study, that diarrhoea was the most frequent health problem during travels, followed by respiratory and dermatologic events. This significant frequency of respiratory events (including pneumonia) in the literature [6,14] and in our study are in accordance with a recent meta-analysis study showing a higher incidence of pneumococcal diseases in immunocompromised persons, especially in HIV-infected ones, than in healthy persons [34].

Our study focused specifically on HIV-infected SSA migrants living in a Western European country and visiting their country of origin. Our

Table 3

Risk factors for the occurrence of at least one travel-related health event in 264 HIV-infected Saharan migrants living in France and visiting their native country, the ANRS VIHVO study (2006–2009).

	All	n ^a (%)	Univariate analysis			Multivariate analysis		
	(n = 264)	(n = 100)	Odds Ratio	(95% CI)	p-value	Odds ratio	(95% CI)	p-value
Gender								
Female	157	56 (36%)	–	–	–	–	–	–
Male	107	44 (41%)	1.26	(0.76–2.09)	0.370	–	–	–
Age (years)								
< 45	169	60 (36%)	–	–	–	–	–	–
≥ 45	95	40 (42%)	1.32	(0.79–2.21)	0.289	–	–	–
Clinical stage								
Non-AIDS	183	66 (36%)	–	–	–	–	–	–
AIDS	81	34 (42%)	1.28	(0.75–2.19)	0.362	–	–	–
CD4 count (cells/mm ³)								
≥ 350	184	67 (36%)	–	–	–	–	–	–
< 350	79	33 (42%)	1.25	(0.73–2.15)	0.412	–	–	–
HIV plasma viral load (cp/mL)								
undetectable < 50	247	89 (36%)	–	–	–	–	–	–
low level viremia [50–200]	16	11 (69%)	3.91	(1.31–11.6)	0.014	4.31	(1.41–13.1)	0.010
Cotrimoxazole prophylaxis								
No	230	84 (37%)	–	–	–	–	–	–
Yes	34	16 (47%)	1.54	(0.75–3.19)	0.240	–	–	–
cART regimen								
non PI-based	100	37 (37%)	–	–	–	–	–	–
PI-based	164	63 (38%)	1.06	(0.64–1.77)	0.819	–	–	–
Duration of cART (years)								
≥ 5	113	37 (33%)	–	–	–	–	–	–
< 5	150	62 (41%)	1.45	(0.87–2.41)	0.155	1.61	(0.94–2.75)	0.083
Travel duration (days)								
< 30	89	31 (34%)	–	–	–	–	–	–
30–90	143	55 (38%)	1.17	(0.67–2.03)	0.578	–	–	–
≥ 90	29	13 (45%)	1.52	(0.65–3.56)	0.335	–	–	–
Pre-travel medical advice regarding diarrhoea and vectors								
Yes	227	80 (35%)	–	–	–	–	–	–
No	21	14 (67%)	3.68	(1.42–9.43)	0.007	3.62	(1.38–9.47)	0.009

CI, confidence interval; cART, combination antiretroviral therapy.

^a n = 100 migrants reporting at least one health event.

participants had high median CD4 cell counts and cotrimoxazole prophylaxis prescribed to people with low CD4 cell counts, lowers the risk of infectious events [35,36]. This could explain that immunosuppression was not associated with travel-related health events in our study even though the risk of infectious diseases and hospitalisation is higher in HIV-infected travellers than in uninfected ones [6,8], as most HIV-infected travellers to SSA are migrants VFRs combining a high risk of travel-related health events and low awareness of health risks [4,10,14].

Participants to the ANRS VIHVO study showed a 11.5% decrease in cART adherence during the travel, mainly associated with lower socioeconomic conditions, negative perception about ART effectiveness, a prolongation of the stay and unexpected traumatic events during the stay abroad [21]. Even more, PI-containing cART compared to other cART was associated with virological rebound after the travel [37]. In our sub-study, PI-based cART regimen and cART duration of less than 5 years were close to be statistically significant risk factors for travel-related febrile events. This is because a shorter cART duration might be associated with poorer immunologic status and lower likelihood of recovery [38]. Additionally, due to the potential digestive side effects of PI, and to the potential pharmacokinetic interaction between PI and some types of malaria chemoprophylaxis, the oral bioavailability of malaria chemoprophylaxis may be lower in participants on PI-based cART [22].

Our study has some limits. The ANRS VIHVO study was mainly designed to assess adherence to cART in HIV-infected migrants

traveling to their country of origin, and the travel-related health events were prospectively reported by the participants at the two post-travel visits. However, all health events were retrospectively validated by two physicians that are experienced in HIV care and travel medicine. The limited number of febrile events also limited the robustness of the conclusion. However, this ANRS VIHVO sub-study is currently the largest to prospectively assess travel-related health events in HIV-infected travellers, and the first to specifically study HIV-infected SSA migrants living in a Western country and visiting their native country.

5. Conclusion

Our results highlight the need to tailor counselling towards adherence to pre-travel medical advice regarding diarrhoea and vector-borne diseases prophylactic measures. If an earlier pre-travel counselling is tailored, HIV-infected migrants could maintain a sustainable undetectable HIV pVL and thus minimise the risk of travel-related health events, some of which could be fatal. A specific education program directed towards HIV-infected sub-Saharan migrants visiting their native country could help to achieve these goals.

Conflicts of interest

The authors declared having no conflict of interest.

Table 4

Risk factors for the occurrence at least one travel-related febrile event in 264 HIV-infected sub-Saharan migrants living in France and visiting their native country, the ANRS VIHVO study (2006–2009).

	All (n = 264)	n ^a (%) (n = 19)	Univariate analysis			Multivariate analysis		
			Odds ratio	(95% CI)	p-value	Odds ratio	(95% CI)	p-value
Gender								
Female	157	10 (6%)	–	–	–	–	–	–
Male	107	9 (8%)	1.35	(0.53–3.44)	0.530	–	–	–
Age (years)								
< 45	169	15 (9%)	–	–	–	–	–	–
≥ 45	95	4 (4%)	0.45	(0.15–1.40)	0.169	0.47	(0.14–1.52)	0.208
Clinical stage								
Non-AIDS	183	11 (6%)	–	–	–	–	–	–
AIDS	81	8 (10%)	1.71	(0.66–4.44)	0.267	–	–	–
CD4 count (cells/mm ³)								
≥ 350	184	14 (8%)	–	–	–	–	–	–
< 350	79	5 (6%)	0.82	(0.29–2.36)	0.714	–	–	–
HIV plasma viral load								
undetectable < 50 cp/mL	247	17 (7%)	–	–	–	–	–	–
low level viremia 50–200 cp/mL	16	2 (13%)	1.93	(0.41–9.21)	0.408	2.00	(0.73–5.46)	0.177
Cotrimoxazole prophylaxis								
No	230	16 (7%)	–	–	–	–	–	–
Yes	34	3 (9%)	1.29	(0.36–4.70)	0.695	–	–	–
cART regimen								
non PI-based	100	3 (3%)	–	–	–	–	–	–
PI-based	164	16 (10%)	3.50	(0.99–12.3)	0.051	3.53	(0.97–12.9)	0.055
Duration of cART (years)								
≥ 5	113	4 (4%)	–	–	–	–	–	–
< 5	150	15 (10%)	3.03	(0.98–9.38)	0.055	2.94	(0.91–9.51)	0.072
Travel duration (days)								
< 30	89	4 (4%)	–	–	–	–	–	–
30 to 90	143	12 (8%)	1.95	(0.61–6.23)	0.262	–	–	–
≥ 90	29	3 (10%)	2.45	(0.52–11.7)	0.260	–	–	–
Pre-travel medical advice regarding diarrhoea and vectors								
Yes	227	4 (19%)	–	–	–	–	–	–
No	21	13 (6%)	3.87	(1.14–13.2)	0.030	4.60	(1.24–17.1)	0.023

CI, confidence interval; cART, combination antiretroviral therapy.

^a n = 19 migrants reporting at least one febrile event.

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Appendix A. Supplementary data

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References

- [1] Brutel C. Les immigrés récemment arrivés en France 2014. INSEE; 28 November 2014 <https://www.insee.fr/fr/statistiques/1281393>, Accessed date: 29 September 2018.
- [2] Prevalence of HIV in France. 27 March 2018 <http://invs.santepubliquefrance.fr/fr./Dossiers-thematiques/Maladies-infectieuses/VIH-sida-IST/Infection-a-VIH-et-sida/Prevalence-du-VIH>, Accessed date: 29 September 2018.
- [3] Living with hiv: first results of the anrs-vespa2 study. Institut de Veille Sanitaire; 2 July 2013 BEH n°26-27 http://invs.santepubliquefrance.fr/beh/2013/27/pdf/2013_26-27.pdf, Accessed date: 29 September 2018.
- [4] van Aalst M, Verhoeven R, Omar F, Stijnis C, van Vugt M, de Bree GJ, et al. Pre-travel care for immunocompromised and chronically ill travellers: a retrospective study. *Trav Med Infect Dis* 2017;19:37–48. <https://doi.org/10.1016/j.tmaid.2017.07.006>.
- [5] Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M, Gilks CF. HIV infection as a cofactor for severe falciparum malaria in adults living in a region of unstable malaria transmission in South Africa. *AIDS Lond Engl* 2004;18:547–54.
- [6] Bottieau E, Florence E, Clerinx J, Vlieghe E, Vekemans M, Moerman F, et al. Fever after a stay in the tropics: clinical spectrum and outcome in HIV-infected travelers and migrants. *J Acquir Immune Defic Syndr* 2008;48:547–52. <https://doi.org/10.1097/QAI.0b013e31817bebc5>.
- [7] Mouala C, Guiguet M, Houze S, Damond F, Pialoux G, Viget N, et al. Impact of HIV infection on severity of imported malaria is restricted to patients with CD4 cell counts < 350 cells/microl. *AIDS Lond Engl* 2009;23:1997–2004. <https://doi.org/10.1097/QAD.0b013e31832832f4215>.
- [8] Perez-Molina JA, Martinez-Perez A, Serre N, Trevino B, Ruiz-Giardin JM, Torrus D, et al. Characteristics of HIV infected individuals traveling abroad. Results from the +REDIVI Collaborative Network. *Enfermedades Infecc Microbiol Clínica* 2016;34:108–13. <https://doi.org/10.1016/j.eimc.2015.03.023>.
- [9] Fenner L, Weber R, Steffen R, Schlagenhauf P. Imported infectious disease and purpose of travel, Switzerland. *Emerg Infect Dis* 2007;13:217–22. <https://doi.org/10.3201/eid1302.060847>.
- [10] Pistone T, Guibert P, Gay F, Malvy D, Ezzedine K, Receveur MC, et al. Malaria risk perception, knowledge and prophylaxis practices among travellers of African ethnicity living in Paris and visiting their country of origin in sub-Saharan Africa. *Trans R Soc Trop Med Hyg* 2007;101:990–5. <https://doi.org/10.1016/j.trstmh.2007.05.009>.
- [11] Dia A, Gautret P, Adheossi E, Bienaime A, Gaillard C, Simon F, et al. Illness in French travelers to Senegal: prospective cohort follow-up and sentinel surveillance data. *J Travel Med* 2010;17:296–302. <https://doi.org/10.1111/j.1708-8305.2010.00439.x>.
- [12] Marks M, Armstrong M, Whitty CJM, Doherty JF. Geographical and temporal trends in imported infections from the tropics requiring inpatient care at the Hospital for Tropical Diseases, London - a 15 year study. *Trans R Soc Trop Med Hyg* 2016;110:456–63. <https://doi.org/10.1093/trstmh/trw053>.
- [13] Harvey K, Esposito DH, Han P, Kozarsky P, Freedman DO, Plier DA, et al. Surveillance for travel-related disease—geosentinel surveillance system, United States, 1997–2011. *Morb Mortal Wkly Rep Surveill Summ Wash DC* 2002;62:1–23. 2013.
- [14] Nielsen US, Jensen-Fangel S, Pedersen G, Lohse N, Pedersen C, Kronborg G, et al. Travelling with HIV: a cross sectional analysis of Danish HIV-infected patients. *Trav Med Infect Dis* 2014;12:72–8. <https://doi.org/10.1016/j.tmaid.2013.10.006>.
- [15] Wieten RW, Leenstra T, Goorhuis A, van Vugt M, Grobusch MP. Health risks of travelers with medical conditions—a retrospective analysis. *J Travel Med* 2012;19:104–10. <https://doi.org/10.1111/j.1708-8305.2011.00594.x>.
- [16] Simons FM, Cobelens FG, Danner SA. Common health problems in HIV-infected travelers to the (sub)tropics. *J Travel Med* 1999;6:71–5.
- [17] Cathcart S, Boyle J, Sabin C, Johnson M, Zuckerman JN. Pre-travel preparation and

- outcome of HIV-infected travellers from a UK clinic. *Trav Med Infect Dis* 2003;1:114–8. [https://doi.org/10.1016/S1477-8939\(03\)00024-3](https://doi.org/10.1016/S1477-8939(03)00024-3).
- [18] Dekkiche S, de Valliere S, D'Acremont V, Genton B. Travel-related health risks in moderately and severely immunocompromised patients: a case-control study. *J Travel Med* 2016;23. <https://doi.org/10.1093/jtm/taw001>.
- [19] Wasilczuk K, Korzeniewski K. Immunocompromised travellers. *Int Marit Health* 2017;68:229–37. <https://doi.org/10.5603/IMH.2017.0041>.
- [20] van Aalst M, van Ruisen MCE, Verhoeven R, de Bree GJ, Goorhuis A, Grobusch MP. Travel-related health problems in the immunocompromised traveller: an exploratory study. *Trav Med Infect Dis* 2018;25:50–7. <https://doi.org/10.1016/j.tmaid.2018.05.005>.
- [21] Abgrall S, Fugon L, Lele N, Carde E, Bentata M, Patey O, et al. Visiting one's native country: the risks of nonadherence in HIV-infected sub-Saharan migrants—ANRS VIHVO study. *J Int Assoc Phys AIDS Care* 2013;12:407–13. <https://doi.org/10.1177/2325957413488181>.
- [22] Abgrall S, Le Bel J, Lele N, Laouenan C, Eychehen N, Mentre F, et al. Lack of effect of doxycycline on trough concentrations of protease inhibitors or non-nucleoside reverse transcriptase inhibitors in HIV-infected patients. *HIV Clin Trials* 2013;14:313–8. <https://doi.org/10.1310/hct1406-313>.
- [23] Pistone T, Schwarzing M, Chauvin P, Ezzedine K, Receveur M-C, Djossou F, et al. Reimbursement of malaria chemoprophylaxis for travellers from Europe to Sub-Saharan Africa: cost-effectiveness analysis from the perspective of the French national health insurance system. *Health Policy Amst Neth* 2008;88:186–99. <https://doi.org/10.1016/j.healthpol.2008.03.002>.
- [24] Hill DR. Health problems in a large cohort of Americans traveling to developing countries. *J Travel Med* 2000;7:259–66.
- [25] Chen LH, Han PV, Wilson ME, Stoney RJ, Jentes ES, Benoit C, et al. Self-reported illness among Boston-area international travelers: a prospective study. *Trav Med Infect Dis* 2016;14:604–13. <https://doi.org/10.1016/j.tmaid.2016.09.009>.
- [26] Vilkmán K, Pakkanen SH, Laaveri T, Siikamaki H, Kantele A. Travelers' health problems and behavior: prospective study with post-travel follow-up. *BMC Infect Dis* 2016;16:328. <https://doi.org/10.1186/s12879-016-1682-0>.
- [27] Angelo KM, Kozarsky PE, Ryan ET, Chen LH, Sotir MJ. What proportion of international travellers acquire a travel-related illness? A review of the literature. *J Travel Med* 2017;24. <https://doi.org/10.1093/jtm/tax046>.
- [28] Leder K, Tong S, Weld L, Kain KC, Wilder-Smith A, von Sonnenburg F, et al. Illness in travelers visiting friends and relatives: a review of the GeoSentinel Surveillance network. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2006;43:1185–93. <https://doi.org/10.1086/507893>.
- [29] O'Brien DP, Leder K, Matchett E, Brown GV, Torresi J. Illness in returned travelers and immigrants/refugees: the 6-year experience of two Australian infectious diseases units. *J Travel Med* 2006;13:145–52. <https://doi.org/10.1111/j.1708-8305.2006.00033.x>.
- [30] Martin PM, Mathiot J, Ipero J, Kirimat M, Georges AJ, Georges-Courbot MC. Immune response to *Campylobacter jejuni* and *Campylobacter coli* in a cohort of children from birth to 2 years of age. *Infect Immun* 1989;57:2542–6.
- [31] Rapport d'activités 2017 de l'année d'exercice 2016. Centre National de Référence du Paludisme pour la France métropolitaine (CNRP); 2016. http://cnrpaludisme-france.org/docs/rapport_activites_cnr_paludisme_2016.pdf, Accessed date: 4 February 2018.
- [32] Mouala C, Houze S, Guiguet M, Abboud P, Pialoux G, Viget N, et al. Imported malaria in HIV-infected patients enrolled in the ANRS CO4 FHDH study. *J Acquir Immune Defic Syndr* 1999;49:55–60. <https://doi.org/10.1097/QAI.0b013e31817e635b>. 2008.
- [33] Whitworth J, Morgan D, Quigley M, Smith A, Mayanja B, Eotu H, et al. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. *Lancet Lond Engl* 2000;356:1051–6. [https://doi.org/10.1016/S0140-6736\(00\)02727-6](https://doi.org/10.1016/S0140-6736(00)02727-6).
- [34] van Aalst M, Lotsch F, Spijker R, van der Meer JTM, Langendam MW, Goorhuis A, et al. Incidence of invasive pneumococcal disease in immunocompromised patients: a systematic review and meta-analysis. *Trav Med Infect Dis* 2018;24:89–100. <https://doi.org/10.1016/j.tmaid.2018.05.016>.
- [35] Campbell JD, Moore D, Degerman R, Kaharuzza F, Were W, Muramuzi E, et al. HIV-infected ugandan adults taking antiretroviral therapy with CD4 counts > 200 cells/μl who discontinue cotrimoxazole prophylaxis have increased risk of malaria and diarrhea. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2012;54:1204–11. <https://doi.org/10.1093/cid/cis013>.
- [36] Anglaret X, Chene G, Attia A, Toure S, Lafont S, Combe P, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. *Cotrimo-CI study group. Lancet Lond Engl* 1999;353:1463–8.
- [37] Kankou JM, Bouchaud O, Lele N, Guiguet M, Spire B, Carrieri MP, et al. Factors associated with virological rebound in HIV-positive sub-Saharan migrants living in France after traveling back to their native country: ANRS-VIHVO. *J Immigr Minor Health* 2019. <https://doi.org/10.1007/s10903-019-00864-y>.
- [38] Ndumbi P, Gillis J, Raboud J, Cooper C, Hogg RS, Montaner JSG, et al. Characteristics and determinants of T-cell phenotype normalization in HIV-1-infected individuals receiving long-term antiretroviral therapy. *HIV Med* 2014;15:153–64. <https://doi.org/10.1111/hiv.12096>.