Malaria in HIV-infected patients in a nonendemic setting

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Background: The impact of HIV infection on malaria is unclear in nonendemic areas. In endemic territories, HIV has been reported to be a risk factor for higher morbidity. Nowadays, as HIV-infected patients travel more, it is important to assess the impact of HIV at the individual level on imported malaria.

Material and methods: This retrospective case–control study collected data on HIV-infected patients diagnosed with malaria (2000–2017) and matched them with two controls based on age, sex and ethnicity. Clinical and biological parameters were collected and compared.

Results: We identified 47 cases and matched them with 94 controls. Comparing each of the WHO 2014 severity criteria, hyperparasitemia above 10% ($P = 0.006$; 12.8 versus 1.1%), icterus ($P = 0.042$; 14.9 versus 4.3%), acute renal failure ($P = 0.022$; 25.5 versus 9.6%) and bacteraemia ($P = 0.014$; 6.4 versus 0%) were significantly more present in HIV-infected patients with a trend to more cerebral malaria (12.8 versus 6.4%). HIV-infected patients were hospitalized more frequently and for longer periods. We observed a higher number of severity criteria when $CD4^+$ T-cell count was lower, especially below 200 cells/μl. The difference in occurrence of severe malaria disappeared when patients with $CD4^+$ T-cell count more than 500 cells/μl and undetectable viral load ($n = 9$) were compared with controls. De-novo HIV diagnosis was made during the malaria episode in 17% of cases.

Conclusion: HIV infection has an impact on the imported malaria profile, although it is unclear whether well controlled HIV-infected patients have a higher risk of severe malaria. HIV-infected patients should be particularly targeted for pretravel advice.

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Introduction

Malaria and HIV are two major global health issues with high morbidity and mortality. There were approximately 37.9 million people living with HIV worldwide at the end of 2018 [1]. Malaria currently remains one of the deadliest infectious diseases in the world while being one of the most common tropical infection with tuberculosis. Up to 99.7% of malaria cases were caused by *Plasmodium falciparum (P. falciparum)* in 2017 [2,3] amongst the 219 million malaria cases reported and the estimated 435 000 attributed deaths [4]. Despite worldwide efforts to eradicate malaria, the number of imported malaria cases increased in nonendemic areas between 2000 and 2015 as well as severe malaria cases from 6.4 to 12.4% of total imported malaria cases [5].

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Most studies on the impact of HIV infection on malaria have been conducted in malaria endemic countries and suggest that HIV patients are at a greater risk of contracting malaria, developing more severe forms of the disease, presenting higher parasitemia, presenting severe anaemia, responding poorly to antimalarial treatments and dying, than HIV-negative individuals [6–8]. Indeed, studies have shown that malaria (inducing a defect of inflammatory cytokines) and HIV (via, among others, the defect of effective $CD4^+$ T cells) act synergistically on the immune system, disturbing the immunological balance between pro- and anti-inflammatory responses to *Plasmodium* spp., thus causing a more severe pattern of both diseases with increased rate of complications. Furthermore, *Plasmodium* spp. activates $CD4^+$ T cells leading to increased HIV replication and higher HIV viral burden impacting the progression of HIV disease and HIV transmission [9].

The single study evaluating the impact of HIV infection on imported malaria, conducted in a nonendemic country, was a retrospective nonmatched study on 265 patients identified from National French Databases between 2000 and 2003. This study showed that malaria was more severe in HIV-infected patients with a $CD4^+$ cell count below 350 cells/μl [10]. Since then, progress has been made in both HIV and malaria treatment. A new class of antiretroviral drugs, integrase inhibitors, became available resulting in changes in the recommended European first-line treatment regimens for HIV infection with better tolerance and efficacy [11]. EACS also recommends HIV to be treated as soon as the diagnosis is made regardless of $CD4^+$ cell count. Consequently, the majority of HIV-infected patients in industrialized countries have today a better health and quality of life [12,13]. As a result, these patients travel more frequently than in the past [14]. A significant proportion of these patients travel as Visiting Friends and Relatives (VFR): this particular population is known to represent an important proportion of imported malaria cases [15]. This is explained by several factors including socioeconomic factors such as reduced access to healthcare, longer duration of travel, the housing and geographical placement of the family and friends visited and the risk perception as some consider themselves to be immune [15,16]. Progress has also been made in malaria treatment since 2003. In chloroquine-resistant areas, atovaquone-proguanil or quinine in combination with doxycycline were used [17]. Since 2001, artemisinin-based combination therapies (ACTs) are considered as the first-line therapy by WHO and became gradually available in our country several years later.

Taking into consideration the recent changes in HIV and malaria management, as well as the changing epidemiology in imported malaria cases, the question remains: does HIV infection impact on malaria presentation and outcome in nonendemic countries today? The aim of our study was to assess the impact of HIV infection on imported malaria *on an individual level* in a single medical centre in Belgium, an industrialized nonendemic country.

Materials and methods

We conducted a retrospective matched case–control study at CHU Saint-Pierre, a 582-bed public hospital in the centre of Brussels, Belgium. Patients were selected from our laboratory database if they presented a positive blood smear for *P. falciparum* from 2000 to 2017. They were excluded if they were infected with a species of *Plasmodium* other than *P. falciparum* knowing that other species are rarely deadly, were younger than 18 years or if clinical or laboratory data were missing. PCR for malaria diagnosis was not used in this study. The selected patients were then cross-checked with our HIV database. Finally, two controls (malaria in HIV-negative patients) were matched for each case (malaria in a HIV-infected patient) based on sex, ethnicity (white or African) and age (using three age categories: 18–25, 26–65, >65 years old).

Data collected for cases and controls were demographic characteristics, latest travel destination, use of malarial prophylaxis, pregnancy, duration of symptoms before medical contact, clinical and biological parameters, duration of hospitalization, malaria treatment received, ICU hospitalization (and duration) and mortality. For HIV-infected patients, we also collected closest $CD4^+$ cell count (categorized as <200, 200–500, >500 cells/μl), nadir $CD4^+$ cell count (categorized as <200 and >200 cells/μl), closest HIV viral load, use of antiretroviral therapy (ART) and identified de-novo diagnosed HIV patients during malaria episode. Closest $CD4^+$ cell counts and viral load were ones measured within a range of 6 months prior to and after the malaria episode. If there was a value during malaria episode, it was not collected. Undetectable viral load was defined as less than 50 copies/ml.

The severity of malaria was assessed for every patient using clinical and biological parameters as well as different scores and definitions (detailed in Appendix 1, http://links.lww.com/QAD/B734) [18]: the latest WHO definition [2014], the modified WHO's 2014 definition, the strict and broad definition from the French Recommendations, and the Malaria Score of Adults (MSA). According to the WHO 2014 definition, severe malaria is defined as having at least one of the following criteria: hyperparasitemia (>10%), acidosis, hypoglycaemia, severe anaemia (<7 g/dl), renal impairment, icterus, pulmonary oedema, shock, significant bleeding, impaired consciousness, prostration or convulsions (Appendix 1, http://links.lww.com/QAD/B734). As tenofovir is known to cause kidney injury including acute kidney

injury (AKI) and atazanavir icterus, we checked these potential biases by considering those patients with AKI and comparing those who received tenofovir to those who did not, and by considering those patients with icterus and comparing those who received atazanavir to those who did not. None of the HIV-infected patients were treated with cotrimoxazole. As bacteraemia is a known complication of malaria and as presence of a neurological symptom is a clinical indication for intravenous treatment, presentation with any abnormal neurological symptom and/or bacteraemia were also recorded.

We broadened cerebral malaria's definition and defined it as any abnormal neurological symptom as it is used in clinical practice. Consequently, we modified the WHO's 2014 definition of severe malaria to 'having one or more of the WHO 2014 criteria and/or presence of any abnormal neurological symptom'.

The French Recommendations 2017 adapted the WHO definition of severe malaria to imported malaria cases. The broad definition is similar to WHO's except that hyperparasitemia is defined as a parasitemia above 4% (see appendix 1, http://links.lww.com/QAD/B734).

The MSA score takes into account the presence of cerebral malaria, haemoglobin (Hb) level less than 5 g/dl, a serum creatinine level greater than 3 mg/dl and respiratory distress [19]. MSA ranges from 0 to 10; when the score is above 5, there is a greater than 90% predicted mortality.

We divided our data into two periods (2000–2008 and 2009–2017) arbitrarily because the management of malaria and HIV evolved in the last 18 years, and even more drastically in the recent years. The number of imported malaria and severe malaria cases in HIV-positive individuals were compared between these two periods. We compared HIV-positive individuals with HIV-negative controls for the following characteristics: number of cases of severe malaria according to the modified WHO 2014 definition, number of cases of severe malaria according to the strict and broad definitions from the French recommendations, scores obtained from MSA, presence of a positive modified WHO criteria for severe malaria, malaria treatments delivered and outcomes. We also compared parasitemia with the number of severity criteria present.

We then compared the presence of a positive modified WHO criteria for severe malaria in controls to cases, stratified into three groups according to their closest $CD4^+$ cell count (<200, 200–500, >500 cells/μl). Finally, we also identified risk factors for severe malaria. Sex, age and parasitemia of patients with severe malaria were compared with those with nonsevere malaria according to our modified WHO definition. In the subgroup of cases (HIV-positive patients), current $CD4^+$ cell count, nadir $CD4^+$ cell count, viral load and ART in patients with severe malaria were compared with those with nonsevere malaria.

Simple descriptive statistics were used to summarize the data using the median and interquartile ranges (IQRs) ranges for continuous data and the total number and percentages for categorical data. Hypothesis testing for differences between groups were performed with the Wilcoxon test for continuous data and the Fisher's exact test for categorical data. All reported *P*-values were two-sided. *P*-values less than 0.05 were considered statistically significant. Statistical analysis was produced using SAS statistical software (version 9.4; SAS Institute, Cary, North Carolina, USA).

The study was approved by the CHU Saint-Pierre's ethics committee.

Results

We identified 47 cases infected with HIV and malaria and 94 HIV-negative controls (*N* total = 141) from the 1809 malaria patients' database between 2000 and 2017. When comparing the two consecutive periods (2000–2008 and 2009–2017), there were significantly more imported malaria cases during the second period [cases: 30/47 (63.8%) versus 17/47 (36.1%)]. However, no difference was observed in rates of severe malaria in cases [10/30 (33.3%) versus 6/17 (35.2%); $P = 1$] between the two periods.

Patient demographic and clinical characteristics are summarized in Table 1. Almost all patients were of African ethnicity (97.9%) and most were male (61.7%). Median age was 40 years (IQR: 31–53). There was one pregnant woman (in controls). Among our 141 patients, more than 99% acquired *P. falciparum* while travelling to sub-Saharan Africa, and 97.9% of them travelled as VFR. Use of malaria prophylaxis was generally poor [5/47 (10,6%) versus 11/94 (11,7%); $P = 0.966$], and median delay before medical contact was 4 days [IQR: (2–7)], with no significant differences between cases and controls.

Eight patients were diagnosed de-novo with HIV infection during their malaria episode, with a median $CD4^+$ cell count of 100 cells/μl and median viral load of 236 000 copies/ml.

In the remaining HIV-positive patients, median $CD4^+$ cell count was 450 cells/μl [IQR: (294–576)] and median HIV viral load was 50 copies/ml [IQR: (20–7775)], with 35 out of 39 (89.7%) patients on ART, but only 23 (66%) with undetectable viral load (Table 1).

Table 1. Population characteristics.

	Cases HIV-positive patients	Controls HIV-negative patients
All, $N=141$	$N=47$	$N=94$
Sex		
Female	18 (38.3%)	36 (38.3%)
Male	29 (61.7%)	58 (61.7%)
Median age (years)	42 [33–53]	38.5 [31–50]
African ethnicity	46 (97.9%)	92 (97.9%)
Prophylaxis, *N* (%)	5 (10.6%)	11 (11.7%)
Delay before medical contact	4 [2–6]	4 [3–7]
$CD4^+$ cell count (cells/μl)	424 [229–539]	/
HIV viral load $N=43$ (copies/ml)	115 [20–100 000]	/
Undetectable HIV VL (<50 copies/ml) in patients under ART: $N=23$ (65.7%)		/
ART, *N* (%) NB: HIV patients diagnosed *de novo* not included	35 (89.7%)	/
Nadir $CD4^+$ cell count (cells/μl)	197 [22–295]	/
HIV acquisition mode		
Blood products	1 (2.1%)	/
Heterosexual	35 (74.5%)	
Homo/bisexual	1 (2.1%)	
Vertical transmission	1 (2.1%)	
Unknown	9 (19.1%)	

Data was expressed in total numbers (%), or median (IQR). Univariate Fisher's exact test was used to calculate *P*-values for sex, ethnicity and prophylaxis. Univariate Wilcoxon test was used to calculate *P*-values for median age and delay before medical contact. A *P*-value <0.05 was considered statistically significant.

Significantly more cases of severe malaria were observed in HIV-positive patients according to our modified WHO 2014 definition (16/47 cases versus 15/94 controls; $P=0.018$) (Table 2) and according to the strict ($P=0.004$) and broad ($P=0.001$) definitions of the French recommendations 2017. Two cases had a MSA score above 5, while all of controls' scores were below 5. Despite a high predicted mortality, both patients survived.

When comparing each WHO 2014 criteria for severe malaria, AKI (25.5 versus 9.6%; $P=0.022$), icterus (14.9 versus 4.3%; $P=0.042$) and hyperparasitemia above 10% (12.8 versus 1.1%; $P=0.006$) were significantly more frequent in HIV-positive patients than in HIV-negative patients. Parasitemia was found to be directly proportional to the number of severity criteria present in both cases and controls. Despite higher rates of hyperparasitemia in HIV-positive patients, median parasitemia *per*

Table 2. Malaria severity criteria: WHO 2014, cerebral malaria; Comparisons of cases and controls and HIV-positive patients according to their $CD4^+$ cell counts; and definitions.

					HIV-positive patients $N=47$			
Malaria severity criteria	Cases	Controls	*P*	HIV-negative patients $N=95$	$CD4^+$ cell count <200 cells/μl $N=12$	$CD4^+$ cell count 200–500 cells/μl $N=22$	$CD4^+$ cell count > 500 cells/μl $N=13$	*P*
Bacteraemia	6.4% ($N=3$)	0	0.014	0	2 (20%)	1 (4.3%)	0	0.002
				47 (50.5%)	6 (60%)	7 (30.4%)	3 (21.4%)	
Cerebral malaria	12.8% ($N=6$)	6.4% ($N=6$)	0.214	6 (6.4%)	0	5 (21.74%)	1 (7.1%)	0.108
Hyperparasitemia								0.006
>10%[a]	12.8% ($N=6$)	1.1% ($N=1$)	0.006	1 (1.1%)	2 (20%)	3 (13.04%)	1 (7.1%)	0.007
>4%[b]	23.4% ($N=11$)	7.4% ($N=7$)	0.014	7 (7.4%)	3 (30%)	7 (30.4%)	1 (7.1%)	
Impaired consciousness[a]	8.5% ($N=4$)	7.4% ($N=7$)	1	7 (7.4%)	0	3 (13.04%)	1 (7.1%)	0.727
Prostration[a]	2.1% ($N=1$)	0	0.333	0	0	1 (4.3%)	0	0.333
Convulsion[a]	2.1% ($N=1$)	0	0.333	0	0	1 (4.3%)	0	0.333
Shock[a]	2.1% ($N=1$)	2.1% ($N=2$)	1	2 (2.1%)	0	1 (4.3%)	0	0.707
Severe bleeding[a]	0	0	-	0	0	0	0	/
Acidosis[a]	0	1.1% ($N=1$)	1	1 (1.1%)	0	0	0	1
Hypoglycaemia[a]	2.1% ($N=1$)	0	0.333	0	0	1 (4.3%)	0	0.333
Anaemia[a]	2.1% ($N=1$)	0	0.333	0	1 (10%)	0	0	0.071
Acute renal failure[a]	25.5% ($N=12$)	9.6% ($N=9$)	0.022	9 (9.4%)	3 (30%)	7 (30.4%)	2 (14.3%)	0.03
Icterus[a]	14.9% ($N=7$)	4.3% ($N=4$)	0.042	4 (4.3%)	2 (20%)	4 (17.39%)	1 (7.1%)	0.042
Pulmonary oedema[a]	4.3% ($N=2$)	1.1% ($N=1$)	0.257	1 (1.1%)	1 (10%)	1 (4.3%)	0	0.139
Severe malaria WHO 2014				15 (15.96%)	5 (50%)	8 (34.8%)	3 (21.4%)	0.031

Univariate Fisher's exact test was used to calculate *P*-values. A *P*-value <0.05 was considered statistically significant. Data were expressed in total numbers (%).
[a]WHO 2014 criteria.
[b]WHO 2000 criteria.

Table 3. Outcome in cases and controls.

Outcome	Cases	Controls	*P*
Hospitalization ($N=78$)	80.8% ($N=38$)	35.1% ($N=33$)	<0.0001
Total length of hospitalization (days)	6 [4–11]	5 [3–5]	0.027
Admission in ICU ($N=17$)	19.1% ($N=9$)	10.6% ($N=10$)	0.193
ICU hospitalization length (Median days)	5 [3–6]	3 [1–3]	0.127
Death rates	2.1% ($N=1$)	0	0.333

Univariate Fisher's exact test was used for hospitalizations, ICU and death rates *P*-values. A *P*-value <0.05 was considered statistically significant. Data were expressed in total numbers (%), or median (IQR). The lengths of total hospitalization and in ICU *P*-values were performed with univariate Wilcoxon rank test.

se was not significantly higher in cases than in controls (0.8 versus 0.9% in controls). There were more cases of cerebral malaria in HIV-positive patients (12.8 versus 6.4%), but the difference was not significant ($P=0.214$) (Table 2). Three cases (6.4%) were diagnosed with concomitant bacteraemia, all three with *Salmonella spp*, and none in the controls ($P=0.014$). Two patients with bacteraemia had a $CD4^+$ cell count below 200 cells/μl. Anaemia (defined as Hb <7 g/dl) was not significantly more present in cases than controls, but cases did present significantly lower Hb levels than controls (median Hb level: 12.8 versus 13.3 g/dl; $P=0.023$). Platelets count was similar in both groups.

Malaria treatments were not significantly different in cases or controls. First oral use of Artemisinin derivates was reported in 2008 and intravenous use in 2011. The most frequent treatment administered was oral Atovaquone/Proguanil (administered to almost half of the patients), followed by Dihydroartemisinin/Piperaquine and intravenous quinine. Ten patients received intravenous Artesunate [6/47 (12.7%) cases versus 4/94 (4.2%) controls; $P=0.08$].

Cases were hospitalised more frequently [38/47 (80.8%) versus 33/94 (35.1%); $P<0.0001$)] and for longer periods than controls (median length of hospitalization: 6 [IQR: (4–11)] versus 5 [IQR: (3–5)] days; $P=0.027$. There was a trend to more ICU hospitalizations for cases [9/47 (19.1%) versus 10/94 (10.6%); $P=0.193$] with no difference in duration of ICU stay compared with controls. One case died of cerebral malaria (*status epilepticus*) followed by shock and multiple organ failure despite intravenous artesunate administration. No deaths occurred in the controls.

Age and sex were not identified as risk factors for severe malaria. HIV-positive patients with severe malaria had a lower current median $CD4^+$ cell count (302 versus 455 cells/μl; $P=0.028$) and a lower nadir $CD4^+$ cell count (17 versus 225 cells/μl; $P=0.04$) than HIV-positive patients without severe malaria. Current HIV viral load was not different in patients with severe malaria (see Appendix 2, http://links.lww.com/QAD/B734).

Comparing controls to HIV-positive patients stratified according to closest $CD4^+$ cell counts (<200, 200–500, >500 cells/μl) for each WHO 2014 criteria for severe malaria: bacteraemia ($P=0.002$), parasitemia above 10% ($P=0.006$), AKI ($P=0.03$) and icterus (0.042) were observed significantly more frequently in patients with $CD4^+$ cell counts less than 200 cells/μl (Table 2). Differences in severe malaria occurrence disappeared when patients with $CD4^+$ cell counts more than 500 cells/μl and undetectable viral load were compared with controls (Appendix 2, http://links.lww.com/QAD/B734).

Discussion

This case–control study showed an increased rate of severe imported malaria in HIV-positive patients compared with non-HIV patients according to at least two international definitions. We also observed a higher rate of AKI, icterus, hyperparasitemia, bacteraemia and longer hospital stay in cases than controls. A lower $CD4^+$ cell count and lower nadir $CD4^+$ cell count were risk factors for severe malaria. No differences in terms of complications or severity of malaria were observed when comparing well controlled HIV-positive patients with $CD4^+$ cell counts more than 500 cells/μl and undetectable viral load, with controls. We showed also an almost two-fold increase in imported malaria amongst HIV-positive patients from 2000–2008 to 2009–2017.

The study was carried out in a public, downtown hospital in Brussels. All cases except one were of African ethnicity, and almost all travelled to visit friends and relatives in sub-Saharan Africa. Our observations may therefore not apply to white patients travelling as tourists. The study showed a significant increase in imported malaria in HIV-positive patients from 2000–2008 to 2009–2017. This concords with epidemiological data showing that despite a worldwide decrease in malaria incidence by 18% between 2010 and 2016 [4], imported malaria increased in several industrialized countries [5,20].

The rate of severe imported malaria in the general population varies between 2 and 16% [20,21], which is consistent with the rate observed in our controls (15.9%), although our HIV population had a remarkably higher rate (34%). AKI, icterus, hyperparasitemia and bacteraemia were more frequent and a worse outcome in terms of (duration of) hospitalization was observed. This

is consistent with several studies in endemic areas [22–25]. For instance, a 2014 prospective study in Maputo, Mozambique, described an increased malaria severity in HIV-positive adults ($n = 70$) compared with HIV-negative patients ($n = 61$) with more frequent respiratory distress, bleeding disturbances and/or haemolysis, icterus, low serum glucose levels and renal failure. Malaria parasitemia and mortality were higher in HIV-positive patients [25]. Both innate and adaptive immunity are part of immune response to malaria. $CD4^+$-T lymphocytes coordinate innate and adaptive response by inducing the production of TH1 cytokines (e.g. interferon, IL-1) and immunoglobulins via B lymphocytes. An in-vitro interferon production defect occurs in HIV-positive patients that persists through 6 months of ART [26]. Several studies have reported that HIV-positive patients are at risk of having higher parasite densities than HIV-negative patients [27,28]. Cytokine defects may partially contribute to higher parasite burdens in HIV patients who are moreover already known to have fewer effective antimalarial antibodies, thus leading to less effective neutralization and opsonisation capabilities [26].

In our study, lower current $CD4^+$ cell count and lower nadir $CD4^+$ were risk factors for severe malaria, but detectable viral load seemed to have no influence. Immune restoration and past immunodeficiency seem therefore of major importance in developing a severe malaria, which has already been demonstrated for cardiovascular and neoplasic complications in HIV-positive patients [29–32]. Profoundly immunosuppressed patients ($CD4^+$ cell count <200 cells/μl) were more prone to complications, including bacteraemia and AKI. On the contrary, well controlled patients with $CD4^+$ cell count more than 500 cells/μl and undetectable viral load showed no difference in terms of complications or severity of malaria to controls. This is in line with the only other study on the impact of HIV on imported malaria in a nonendemic country (France), a cross-sectional study (2000–2003) comparing 104 HIV-positive patients with nonmatched 161 HIV-negative patients, showing significantly more severe malaria (using WHO 2000's definition) in HIV-positive patients with $CD4^+$ cell count less than 350 cells/μl. Despite a different type and period of study, the most frequent complications were similar to ours: HIV patients with $CD4^+$ cell count less than 350 cells/μl were more likely to develop hyperparasitemia, consciousness impairment, icterus and AKI [10].

Almost 20% ($n = 8$) of cases were diagnosed *de novo* with HIV during their malaria episode; among them, four had severe malaria. De-novo HIV-diagnosed patients were all late presenters according to the European definition (Late presentation with advanced disease= diagnosed with HIV with a $CD4^+$ cell count below 350 cells/μl or an AIDS defining event, regardless of $CD4^+$ cell count, in the six months following HIV diagnosis) with a median $CD4^+$ cells count of 100 cells/μl. The French study did not mention any de-novo HIV diagnosis during malaria episodes. HIV testing should thus be recommended whenever encountering a case of (severe) malaria. Moreover, patients from sub-Saharan Africa are one of the known risk groups to target for HIV testing. All opportunities to offer this screening are to be seized, including pretravel consultation.

Anaemia was not frequently observed and is probably a more useful criteria of severity in endemic areas. Platelet count in our study was not lower in HIV-positive patients than in controls. More severe malaria in HIV-positive patients has resulted in an increase in the number and duration of hospitalizations, with a trend towards more admissions to ICU and increased use of intravenous artesunate when available. To our knowledge, BHIVA recommendations are the only existing specific guidelines to address management of imported malaria in HIV-positive patients [33].

To our knowledge, this is the first matched case–control study on HIV-positive patients with malaria in a nonendemic setting. The study has several limitations. Due to its retrospective design, information on malaria prophylaxis (use and proper use) was missing for a large number of patients. The results may not be generalized to other patient populations than Africans visiting friends and family, but this appears to be an important patient population to study.

Being a retrospective study, we did not have precise data apart from ethnicity as a proxy to try to evaluate premunition, so we cannot estimate the exact role of premunition on the severity of malaria.

In conclusion, we confirm that HIV-positive patients are more at risk of developing severe imported malaria. It is thus crucial to increase the awareness of both physicians and patients about this risk by targeted tools, especially before travel for VFR. Further studies in well controlled patients should be conducted to clarify the exact role of HIV *per se* (without immunosuppression) in malaria severity.

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Conflicts of interest

The authors report no conflict of interest in this work.

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