Should We Care About Plasmodium Vivax and HIV Coinfection? A Systematic Review and a Cases Series From the Brazilian Amazon

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Research

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Abstract

Background. Malaria and HIV are two important public health issues. However, data on HIV-Plasmodium vivax co-infection (HIV/PvCo) is scarce, with most of the available data related to Plasmodium falciparum in the African region. It is unclear whether HIV can change the clinical course of Plasmodium vivax (Pv) malaria, and thereby increase the risk of complications. In this study, a systematic review of the HIV/PvCo is presented, including new cases from the Brazilian Amazon.

Methods. Medical records from a tertiary care center in the Western Brazilian Amazon (2009 to 2018) were reviewed to identify HIV/PvCo hospitalized patients. Demographic, clinical and laboratory characteristics, and outcomes are reported. We also performed a systematic review of published studies on HIV/PvCo. Metadata, number of HIV/PvCo cases, demographic, clinical, and outcome data were extracted if available.

Results. A total of 1048 vivax malaria patients were hospitalized in the 10-year period; 21 (2.0%) were HIV/PvCo cases, of which nine (42.9%) had AIDS-defining illnesses. For eleven (52.4%) patients, this was their first malaria infection. Seven (33.3%) patients were unaware of their HIV status and were diagnosed at hospitalization. Severe malaria criteria were found in 5 (23.8%) patients. One patient died. The systematic review provided 17 articles (12 cross-sectional or longitudinal studies and 5 case report studies). A higher prevalence of studies involved cases in African and Asian countries (35.3% and 29.4%, respectively), and the prevalence of reported co-infections ranged from 0.1 to 60%. Cases of severe malaria-HIV coinfection were not reported.

Conclusion. Reports of HIV/PvCo are scarce in the literature, with only a few studies describing clinical and laboratory outcomes. Systematic screening for both co-infections are not performed, and therefore, a realistic prevalence of HIV/PvCo is absent. This study showed a low prevalence of HIV/PvCo, despite local malaria and HIV high prevalence. Even though relatively small, this is the largest case series to describe HIV/PvCo.

Background

Malaria and Human Immunodeficiency Virus (HIV) infections are two major public health problems. Given the considerable epidemiological overlap between malaria and HIV, a substantial number of co-infections may occur. In 2019, malaria accounted for 228 million cases and resulted in 405,000 deaths. Of the five Plasmodium species that can infect humans with malaria, Plasmodium vivax is the most geographically widespread, with a higher impact in endemic areas, and is responsible for 75% of malaria-related cases in the Latin American region. Currently, 37.9 million people are living with HIV worldwide, with 1.7 million newly infected; an estimated 770,000 deaths were due to AIDS-related diseases in 2018. Globally, these infections, together, claim the lives of about 2 million people each year.

Malaria and HIV infections can interact in a bidirectional and synergistic way with each other, leading to an exponential boost in their deleterious effects. HIV can impair immune responses to malaria parasites, leading to an inability to control the parasite clearance and resulting in high parasitic loads, which in turn can increase malaria transmission rates. Clinically, HIV has been shown to contribute to a higher incidence of falciparum malaria, including its severe form, which is characterized by anemia, cerebral malaria, and increased risk of congenital infections. The impact of HIV on the severity of malaria appears to be restricted to patients with CD4 cell counts < 350 cells/µl.

Malaria, meanwhile, is associated with strong CD4 + cell activation and increased levels of pro-inflammatory cytokines, which provides an ideal microenvironment for HIV viral replication and potentially worsens the clinical picture of the patients, increasing the rates of HIV transmission and progression to AIDS. The immunosuppression due to HIV infection can reduce plasmodium control. Moreover, HIV therapy can impair malaria treatment, with a significant increase in adverse events and selection of potential treatment-resistant parasites. Plasmodium infection has also been shown to increase HIV viral load, decrease CD4 + T-cell count, and consequently increase HIV progression to AIDS. However, these interactions are mostly described for Plasmodium falciparum.

Studies reporting HIV-Plasmodium vivax co-infection (HIV/PvCo) are scarce. As such, a clear understanding of both diseases and their interactions is necessary for more effective control measures, especially in co-endemic areas of vivax malaria and HIV. In this study, we describe clinical and laboratory outcomes in a case series of HIV/PvCo patients admitted to a tertiary care center in the Western Brazilian Amazon. We also describe evidence regarding HIV/PvCo, through a systematic review of current literature.

Methods

Case series

All cases of patients admitted to the Fundação de Medicina Tropical Dr. Heitor Vieira Dourado (FMT-HVD) for suspected Plasmodium vivax malaria infection, from March 4th, 2009 to December 31st, 2018, were screened for eligibility for this study. The FMT-HVD is a tertiary reference health care center for infectious diseases located in Manaus, Western Brazilian Amazon and receives patients seeking care and also those referred by public and private care networks. The FMT-HVD is part of the Brazilian public health system and adopts all Brazilian guidelines for the management of sexually transmitted infections, including HIV infection in adults, as well as malaria treatment. Diagnosis and treatment for both diseases are free of charge.

All patients are registered in the hospital’s electronic medical records (EMR), from which data for our study were collected after a thorough examination of the database. All data regarding the demographics, malaria symptoms, previous history of HIV infection, laboratory exams, and outcome status (survival or death) in an anonymized manner were retrieved from individual medical records. HIV infection was previously determined by two positive Rapid Diagnostic Tests (RDTs) and confirmed by an immunoassay test, as defined by the Brazil Ministry of Health, and the diagnosis was present in the EMR system. Plasmodium vivax
malaria infection was confirmed by a positive thick blood smear test, as defined by the Brazil Ministry of Health, and diagnostic information was subsequently recorded in the hospital’s EMR and/or the Malaria Epidemiological Surveillance Information System (Sivep-Malaria). Patients were diagnosed with severe malaria according to the World Health Organization (WHO) guidelines.

Systematic review

A systematic review regarding studies of HIV/PvCo was conducted in conformity with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies reporting HIV/PvCo were systematically identified through multiple electronic databases (Medline/PubMed, Lilacs and Scielo), using the following keywords as the search strategy: (HIV AND malaria) OR (AIDS AND malaria) OR (HIV AND vivax) OR (AIDS AND vivax) OR (HIV AND Plasmodium) OR (AIDS AND Plasmodium). The last search was performed in February of 2020. No date or language restrictions were applied. All types of study designs, with primary clinical data, were included (cross-sectional, longitudinal, case reports, and case series). All duplicates were removed. Additional studies were obtained by a search of the references in the included studies.

Titles and abstracts were reviewed to confirm the inclusion of data on HIV/PvCo and P. vivax mono-infections. Included studies were assessed for eligibility by a full-text review and excluded when an inconclusive diagnosis of Plasmodium species and/or doubtful HIV positive co-infection was reported. The systematic review process was conducted by two independent authors of the study. Disagreements were resolved by consensus.

For cross-sectional and longitudinal studies, the following data were retrieved: author, year of publication, country, total of malaria cases, total of vivax malaria cases, vivax malaria cases with prior HIV, mean age of population, comorbidities and co-infections, and clinical outcomes. From the reports and case series, demographic, clinical, and laboratory data were retrieved. Baseline patient characteristics were summarized as medians, with interquartile range (IQR) or means with standard deviation (SD).

Ethical considerations

This study was approved by the Ethics Review Board (ERB) at the FMT-HVD and followed the Guidelines and Standards for the regulating research on human subjects established in Resolution 466/12, of the National Health Council of the Brazilian Ministry of Health. A waiver of informed consent was obtained due to the retrospective design of the study. Patient anonymity was preserved throughout the analysis.

Results

Case series

A total of 1,144 patients (5.5% of all FMT-HVD hospitalizations) were admitted with a malaria diagnosis during the study period. Of these, 1,048 (91.6%) were diagnosed with P. vivax mono-infection, and out of these, 21 (2.0%) were positive for HIV (Fig. 1).

Table 1 shows a summary of the HIV/PvCo patients. Fourteen (66.7%) were men. The mean age was 33 (± 14.2 years), with the youngest patient being a 14-year-old boy (case 6). According to HIV status, twelve (57.1%) patients were living with HIV; nine (42.9%) presented an AIDS-defining disease; seven (33.3%) were diagnosed with HIV at hospital admission. Prior HIV viral load and CD4 T-cell counts were reported in twelve (57.1%) patients, with a mean of 32.188 (± 74,514) copies/mL and 386 (± 306.4) cells/µl, respectively. A CD4+ cell count of < 200 cells/µl was recorded in eight (42.1%) patients. The use of antiretroviral treatment (ART) was registered in fourteen (66.7%) patients; however, only three (14.3%) showed adherence to treatment in the six months prior to hospital admission.
| ID | Sex/Age | Viral load (copies/mL) | CD4 + cell count (cells/µL) | Primoinfection/ Semiquantitative Parasitemia (+) | Concomitant conditions/ co-morbidities | AIDS defining illness | ARV treatment/ adherence | Severe Malaria (WHO Criteria) |
|----|---------|------------------------|-----------------------------|-----------------------------------|---------------------------------|---------------------|-------------------------|-----------------------------|
| 1  | F,22    | 19,109                 | 130                         | Yes/++.                           | Pregnancy (22 weeks)            | No                  | No                      | No                          |
| 2  | M,51    | 0                      | 1,202                       | No/++.                            | None                            | No                  | No                      | No                          |
| 3  | F,27    | ND                     | 6***                        | No/+                              | OC, TB (5th month treatment)    | Yes                 | 3Tc + AZT + ATV/r        | No                          |
| 4  | M,52    | ND                     | ND                          | Yes/++                            | None                            | No                  | 3Tc + AZT + LPV/r.       | No                          |
| 5  | F,24    | 1,740                  | 536                         | No/++.                            | G6PD d                          | No                  | No                      | Significant bleeding (persistent brownish metrorrhagia) and respiratory distress |
| 6  | M,14    | 162                    | 325                         | Yes/++.                           | None                            | No                  | AZT + 3Tc + LPV/r + RAL/ | No                          |
| 7  | M,42    | ND                     | ND                          | No/++.                            | TB (2nd month treatment), NTX, SYP | Yes                 | TDF + 3Tc + EFV/        | No                          |
| 8  | M,27    | 58,825                 | 17                          | No/+                              | TB, NTX, PNM, OC                | Yes                 | 3Tc + 3Tc + LPV/r/      | No                          |
| 9  | M,31    | 21,271                 | 126                         | Yes/++                            | None                            | No                  | 3Tc + AZT + EFV/        | No                          |
| 10 | M,29    | 90,336***              | 23***                       | No/++                             | AIDs wasting syndrome, GTB, SYP | Yes                 | No                      | Anemia (6.7 g/dL), Pulmonary edema and respiratory distress |
| 11 | M,66    | 0                      | 542                         | No/1/2 +                          | None                            | No                  | 3Tc + AZT + RTV/        | No                          |

M – Male; F – Female; DM – Diabetes Mellitus; TB – Tuberculosis; ISSO – Isosporiasis; SAL – Salmonella; NTX – Neurotoxoplasmosis; CMV – Cytomegalovirus; ASC – Ascaris lumbricoides; GIA – Giardia spp; SAL – Salmonella spp; SYP – Syphilis, PNM – Pneumonia; OC – Oropharyngeal infection by Candida spp.; LLC – Lower limb cellulitis, GTB – Ganglionar Tuberculosis; PFP – Peripheral facial nerve paralysis; BC – Bowen’s disease; HCV – Hepatitis C virus; HeZ – Herpes Zoster virus; HSV – Herpes simplex virus; AKI – Acute Kidney Insufficiency; G6PD d – Glucose-6 phosphate dehydrogenase enzyme deficiency; 3Tc – Lamivudine; AZT – Zidovudine/Azidothymidine; ATV/r – Atazanavir/Ritonavir; TDF – Tenofovir; EFV – Efavirenz; DTG – Dolutegravir; LPV/r – Lopinavir/Ritonavir; RAL – Raltegravir; ** RDT positive at hospital admission; *** at hospital admission; ND – Not defined.
| ID | Sex/Age | Viral load (copies/mL) | CD4 count (cells/µL) | Primoinfection/Semiquantitative Parasitemia (+) | Concomitant conditions/co-morbidities | AIDS defining illness | ARV treatment/adherence | Severe Malaria (WHO Criteria) |
|----|---------|------------------------|---------------------|-----------------------------------------------|--------------------------------------|----------------------|-------------------------|-----------------------------|
| 12 | M, 26   | 14,763                 | 228                 | Yes/++                                        | TB (2nd month treatment)             | No                   | 3Tc + AZT + EFV/Started treatment at hospital. | No                          |
| 13 | M, 29   | 6,894                  | 266                 | Yes/+++                                       | Asthma                              | No                   | 3Tc + AZT + LPV/r/ Low adherence.             | No                          |
| 14 | F, 31   | 660                    | 308                 | No/++                                         | G6PD d                              | No                   | 3Tc + ATV + TDF/Yes Hyperbilirubinemia (total bilirubin = 12.09 mg/dL) + AST (81 IU/L), ALT (105 IU/L), GGT (609 IU/L) | No                          |
| 15 | F, 19   | 88,561***              | 195***              | Yes/+                                         | NTX                                 | Yes                  | 3Tc + TDF + DTG/ Yes                           | No                          |
| 16 | F, 49   | 56***                  | 180***              | Yes/+                                         | Hypertension, DM, Obesity, HCV, HerZ, AKI | Yes                   | 3Tc + TDF + DTG/ Yes                           | No                          |
| 17 | M, 13   | 230                    | 417                 | Yes/1/2 +                                     | None                                | No                   | 3Tc + AZT + LPV/r/ Low adherence.             | No                          |
| 18 | M, 51   | ND**                   | ND**                | No/++                                         | NTX                                 | Yes                  | AZT + 3TC + LPV/r/ Low adherence.             | No                          |
| 19 | M, 50   | 262,604                | 427                 | No/+                                          | TB, AKI, DM, LLC, ISSO, SAL          | Yes                  | No Respiratory distress                       | No                          |
| 20 | M, 39   | 0***                   | 145***              | Yes/+++                                       | None                                | No                   | AZT + 3TC + LPV/r/ Low adherence.             | No                          |
| 21 | F, 35   | ND**                   | ND**                | Yes/++                                        | TB, HIV associated wasting syndrome | Yes HIV status unknown until hospitalization. No treatment. | Hyperbilirubinemia (5.71 mg/dL) + AST (558 IU/L) and GGT (441 IU/L) associated to other organ dysfunction, AKI (Creatinine 4.5 mg/dL), Metabolic acidosis and Respiratory distress | No                          |

M – Male; F – Female; DM – Diabetes Mellitus; TB – Tuberculosis; ISSO – Isosporiasis; SAL – Salmonella; NTX – Neurotoxoplasmosis; CMV – Cytomegalovirus; ASC – Ascaris lumbricoides; GIA – Giardia spp; SAL – Salmonella spp; SYP – Syphilis; PNM – Pneumonia; DC – Gastroenteritis infection by *Candida spp*; LLC – Lower limb cellulitis, GTB – Ganglionar Tuberculosis; PFP – Peripheral facial nerve paralysis; BC – Bowen's disease; HCV – Hepatitis C virus; HerZ – Herpes Zoster virus; HSV – Herpes simplex virus; AKI – Acute Kidney Insufficiency; G6PD d – Glucose-6-phosphate dehydrogenase enzyme deficiency; 3Tc – Lamivudine; AZT – Zidovudine/Azidothymidine; ATV/r – Atazanavir/Ritonavir; TDF – Tenofovir; EFV – Efavirenz; DTG – Dolutegravir; LPV/r – Lopinavir/Ritonavir; RAL – Raltegravir; ** RDT positive at hospital admission; *** at hospital admission; ND – Not defined

Primary malaria infection was informed for 11 (52.4%) patients. A previous history of comorbidities and co-infections was present in 14 (66.7%) patients. Of these, seven (33.3%) reported a diagnosis of HIV, vivax malaria, and tuberculosis (TB) co-infection. One (4.8%) female patient was pregnant. She was treated solely with chloroquine for 3 days. According to WHO guidelines, severe malaria criteria (significant bleeding, respiratory distress, severe anemia, pulmonary edema, metabolic acidosis, and hyperbilirubinemia, associated with organ dysfunction) were present in 5 (23.8%) patients (cases 5, 10, 14, 19 and 21) (Table 1).

Two (9.5%) patients returned to the hospital with signs of hemolysis and were diagnosed with G6PD deficiency. In both cases primaquine was stopped. One (4.8%) patient with severe malaria was treated with intravenous artesunate, died on the next day (case 21). The remaining patients completed antimalarial treatment with chloroquine and primaquine. Malaria treatment was performed according to Brazilian Ministry of Health guidelines.

Anemia (hemoglobin level < 12 g/dL) was observed in 16 (76.2%) patients, one of whom was severely anaemic (Hb < 7 g/dL). Low platelet levels (< 150,000/mm³) were recorded in eighteen (85.7%) patients, while severe thrombocytopenia (< 50,000/mm³) was observed in ten (47.6%) patients, with a single subject presenting significant bleeding (case 5) (Table 1).

**Systematic review**
The original search yielded a total of 8,460 studies. After the exclusion of duplicates, screening, and use of predefined inclusion criteria, only 11 studies were included (Fig. 2). Subsequently, six other studies were added after reference search of the included studies. The selected studies were reviewed and then stratified into two main groups: a first group consisting of 12 cross-sectional or longitudinal studies (Table 2) and a second group composed of five case report studies (Table 3).

**Table 2. HIV-Plasmodium vivax co-infections according to the scientific literature.**

| Author, Year | Country (city) | Type of study/ study population | Total malaria cases | Total P. vivax malaria cases | Vivax malaria cases with prior HIV/AIDS | Mean age of population (±SD)/(IQR) |
|--------------|----------------|---------------------------------|---------------------|-----------------------------|----------------------------------------|----------------------------------|
| Volsky, 1986 | Venezuela (Tachira) | Cross-sectional/ Patients presenting to hospital for malaria diagnosis | 24 | 12 | 5*(20.8) | 10-60 |
| Lo, 1991 | Brazil (São Paulo) | Cross-sectional/ Selected patients seeking care for malaria, who had shared injectable drugs. HIV and vivax malaria were transmitted by needle sharing in most cases | 12 | 12 | 3(25.0) | 24 |
| Barata, 1993 | Brazil (São Paulo) | Cross-sectional/ Selected patients seeking care for malaria, who had shared injectable drugs. HIV and vivax malaria were transmitted by needle sharing needle sharing in most cases | 99 | 24 | Unknown | 23 (±6.3) |
| Erhabor, 2006 | Nigeria (Niger Delta) | Case-control within an ART program/ patients attending a health facility | 30 | 2 | 2 (6.7) | 35.2 (±1.29) |
| Ramirez, 2011 | Spain (Madrid) | Retrospective case-series/ patients diagnosed with malaria in a local hospital | 398 | 8 | 1 (0.25) | 36.5 (31-47) |
| Bharti, 2012 | India (Chennai) | Cross-sectional / subjects randomly selected from newly diagnosed HIV-1+ individuals seen at a Voluntary Counseling and Testing Center | 45 | 27 | 27 (60.0) ** | 40(±9) |
| Wondimeneh, 2013 | Ethiopia (Gondar) | Retrospective/ HIV+ adult individuals with febrile illness | 73 | 20 | 20 (27.4) ** | 33.5+9 |
| Douglas, 2014 | Indonesia (Papua province) | Retrospective/ all P. vivax individuals attending to a hospital | 3495 | 3495 | 5 (0.1) | 3.1 (1.8-24.5) |
| Ratanapunya, 2015 | Thailand (Tak province) | Cross-sectional/ malaria patients attending to clinic | 867 | 350 | 9(1.0) | ND |
| Mohapatra, 2017 | India (Manipur and Mizoram) | Prospective/ follow-up of HIV+ individuals | 333 | 22 | 3(0.9) ** | 28.9 (±6.3) (Manipur); 34.5 (±6.5) (Mizoram) |
| Sahle, 2017 | Ethiopia (Ethiopia) | Cross-sectional/ HIV+ adults | 86 | 3 | 3 (3.5) ** | 31.95 (±17.6) |
| Wondimeneh, 2018 | Ethiopia (Kolla-Diba) | Cross-sectional/ febrile patients attending to hospital | 91 | 35 | 4(11.4) | 28 (±15.7) Males; 28 (±14.7) Females |

SD= Standard Deviation, ND= Not defined, *= Recently HIV diagnosed; ART – antiretroviral therapy; ** study including only HIV+ patients;
| Author, Year                  | Sex/Age | Viral load (copies/mL) | CD4+ cell count (cells/μL) | Primoinfection/ Semiquantitative Parasitemia (+) | Concomitant conditions/ co-morbidities | AIDS defining illness | ARV treatment/ adherence | Severe Malaria (WHO Criteria) |
|------------------------------|---------|------------------------|----------------------------|-------------------------------------------------|-------------------------------------|----------------------|--------------------------|-----------------------------|
| Katongole-Mbidde, 1988        | F,37    | ND **                  | ND **                      | ND/ND                                           | PNM (Pneumocystis jirovecii)        | Yes                  | ND                       | No                          |
| McIver, 2010                 | M,57    | 0                      | 500                        | ND/++++                                          | PNM                                 | Yes                  | 3TC+AZT+ATV/Yes.           | No                          |
| Tano, 2014                   | M,50    | 2,352                  | 115                        | No/Patient was diagnosed by IFI.                 | ND                                  | No                   | ND/No                    | Anemia (5.6 g/dL)           |
| Ranaweera, 2018              | M,36    | ND                     | ND                         | No/++++                                          | TB/PNM (Pneumocystis jirovecii)     | Yes                  | ND                       | Hyperbilirubinemia (total bilirubin=5.03), Shock (Systolic BP < 80 mmHg) |
| Montenegro-Idrogo, 2019       | F,35    | 105,000 ***            | 350***                     | Yes/++                                           | ND                                  | No                   | No                       | Impaired consciousness (Glasgow coma score 6/15) |
|                              | M,43    | ND                     | ND                         | Yes/+***                                         | ND                                  | No                   | No                       | No                          |

M – Male; F – Female; BP – Blood pressure; TB – Tuberculosis; PNM – Pneumonia; 3Tc – Lamivudine; IFI – Indirect immunofluorescence; AZT – Zidovudine/Azidothymidine; ATV – Atazanavir; TDF – Tenofovir; ** RDT positive at hospital admission; *** at hospital admission; ND – Not defined

The highest prevalence of studies reporting HIV/PvCo was found in the African and Asian regions, with 35.3% and 29.4%, respectively. The prevalence of reported co-infections ranged from 0.1 to 60%; age ranged from 10 to 60 years. No cases of severe malaria, according to WHO guidelines, were reported. Data from the six case reports are presented in Table 3. The mean age of these patients was 51.6 (± 13.6 years). Prior and recent HIV viral load and CD4 T-cell count tests were reported in three (50.0%) patients and the use of ART was described in two (33.3%) cases, with one patient adhering to treatment.

Pneumocystis sp. pneumonia, and TB were reported in three cases (50.0%). Only two (33.3%) patients presented severe malaria, according to WHO guidelines.

Discussion

Both malaria and HIV are highly prevalent in tropical and subtropical regions, which may increase the prevalence of such co-infection. Although the prevalence of the co-infection of malaria, especially with *P. falciparum*, and HIV has been previously reported in Africa, only a few studies described cases of HIV/PvCo patients. In fact, from our initial search, only 2% of studies dealt with HIV/PvCo, which could be due to several factors, such as low co-infection rates, low prevalence of severe cases and therefore, lack of reporting, and most importantly, lack of systematic HIV screening in vivax malaria positive patients.

The prevalence of HIV co-infection in vivax malaria patients in this study was lower than in similar studies from other vivax endemic regions. However, since HIV/PvCo is not systematically screened in Brazil, its real burden is unknown. Furthermore, it is important to mention that HIV-positive cases have been increasing in recent years in the northern region of Brazil, which is where most malaria cases occur in the country. HIV, malaria, and TB are considered separately as the most common and severe infectious diseases in the world. Interestingly, a triple co-infection with these three agents was more prevalent in this study when compared with other studies from Africa, although this may be attributed to screening, as previously mentioned.

Two patients presented G6PD deficiency. The lower the activity of G6PD, the lower the individual’s ability to tolerate oxidative stress; in the face of oxidative stressors, such as certain foods, e.g., fava beans, and drugs, such as primaquine or sulfonamides, G6PD deficient individuals may develop acute life-threatening hemolysis. The prevalence of G6PD deficiency is relevant to both HIV and malaria. Despite HIV infection and antiretroviral therapy (ART) are both associated, separately and together, with increased oxidative stress, the impact of G6PD deficiency on the oxidative stress of people living with HIV (PLHIV) on ART is controversial. PLHIV have significantly lower levels of antioxidants, hematology parameters, and CD4 + cells in comparison to healthy subjects; nonetheless, PLHIV on ART have presented higher level of antioxidants compared to ART naïve subjects. Also, antioxidant status was significantly higher in PLHIV than in non-infected individuals.
higher in those with $\text{CD4} + \geq 200 \text{cells/mm}^3$. The prevalence of G6PD deficiency varies across Latin America and Caribbean countries, with the African variant presenting a wide range in these regions. Primarily, primaquine is a strong oxidative drug and may cause severe acute hemolysis in G6PD deficient individuals receiving malaria treatment. Currently, G6PD deficiency is not screened before treatment for either disease. Therefore, we could not determine whether G6PD deficiency in HIV/PvCo had an impact on clinical outcomes.

Separately, malaria and HIV cause relevant laboratory abnormalities; a co-infection scenario may intensify such alterations. Anemia, thrombocytopenia, and leukopenia, for both malaria and HIV separately, and in co-infected patients, have been reported to be strong and independent predictors of morbidity and mortality.

The Prevalence of anemia in our case series was high, with most patients presenting mild to moderate anemia, similar to other studies of HIV/PfCo. Nonetheless, this is higher when compared to $P.$ vivax mono-infected adults from the Amazonas. A high prevalence of thrombocytopenia (85.7%) was also observed in this study. Two studies conducted in patients with $P.$ vivax showed a similar prevalence (62.9% and 72%, respectively). In a systematic review, severe and fatal thrombocytopenia was observed in 10.1% of patients with vivax mono-infection malaria, while severe thrombocytopenia was more prevalent in this study. Anemia and thrombocytopenia in HIV-malaria co-infections have a multifactorial origin and are a frequent complication that may become clinically important in HIV infection.

The impact of HIV on the clinical severity of falciparum malaria seems to be primarily motivated by the inability of the immune system to control the parasitic burden. Severe malaria was observed in approximately 30% of adults with falciparum malaria and HIV in the urban area of Burkina Faso. Studies in areas of low malaria transmission in South Africa and India showed an association between severe malaria and HIV. For severe vivax malaria, the current study showed a higher prevalence compared to another study with vivax severe malaria in children and adult patients (23.8% versus 12.6%). Despite the low number of cases, HIV co-infection seems to act as a booster for the clinical worsening of vivax malaria, as it has a higher prevalence than that found in vivax malaria mono-infection patients treated at FMT-HVD (approximately 14%). Some studies have shown that the risk of malaria severity increases in HIV patients with a CD4 + T cell count < 200 x $10^6$ cells/L or < 350 cells/µl. In this study, 42.1% of patients with malaria infection had CD4 cell counts of less than 200 cells/µl, and one of them had severe malaria.

This study had several limitations. Regarding the systematic review, prevalence studies and those exploring severe clinical outcomes may underestimate the co-infection, as it is rarely screened systematically in vivax malaria-endemic regions. The comparison of clinical disease dynamics and important outcomes was not possible due to the absence of control groups, e.g., $P.$ vivax mono-infection and HIV mono-infection to address associations of laboratory and clinical outcomes to HIV/PvCo, this is mainly due to the fact that systematic screening for this co-infection is not routinely performed. Moreover, there is a low prevalence of severe cases of $P.$ vivax, especially when opportunistically diagnosed and treated, or in the absence of comorbidities. Furthermore, despite the analysis of the present results, we cannot assume that malaria increases anemia and thrombocytopenia in PLHIV, or vice-versa. Additionally, the accurate prevalence of HIV/PvCo, and roughly all other co-infections, is significantly hampered by the absence of a systematic screening, which in low- and middle-income countries is basically performed at medical discretion when there is clinical suspicion.

Conclusion

Malaria as a result of $P.$ vivax infection appears to have a low prevalence in HIV-infected individuals, with only a few studies describe clinical and laboratory outcomes. Our study showed a low prevalence of HIV/PvCo, despite important local prevalence of malaria and HIV separately. Even though relatively small, as yet, this is the largest case series to describe HIV/PvCo. The data described here indicates the need for further research on the interaction between HIV and vivax malaria infections, due to the potential worsening of both diseases in the co-infection scenario, the possible impact of G6PD deficiency and the possible epidemiological effects. Moreover, at present, with a potential increase of severe cases due to the increase of vivax malaria and new HIV diagnoses, prospective studies are needed to elucidate aspects related to pathogenesis of co-infection, concomitant treatment and drug interactions, severity outcomes, and the possible increase in $P.$ vivax relapses secondary to this co-infection. Also, future studies should address how $P.$ vivax malaria chronically impacts CD4 cells and how this is associated to HIV viral load dynamics.

Abbreviations

AIDS acquired immunodeficiency syndrome; ART: Antiretroviral Treatment for HIV/AIDS; CD4: CD4 + T-cells; EMR: electronic medical record; G6PD: glucose-6-phosphate dehydrogenase; FMT-HVD: Fundação de Medicina Tropical Doutor Heitor Vieira Dourado; HIV: human immunodeficiency virus; HIV/PfCo: HIV-Plasmodium falciparum co-infection; HIV/PvCo: HIV-Plasmodium vivax co-infection; PRISMA: preferred reporting items for systematic reviews and meta-analyses; RDT: rapid diagnostic tests; SIVEP: national epidemiological surveillance system for malaria; TB: tuberculosis; WHO: World Health Organization.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Review Board (ERB) at the FMT-HVD and followed the Guidelines and Standards for the regulating research on human subjects established in Resolution 466/12, of the National Health Council of the Brazilian Ministry of Health. A waiver of informed consent was obtained due to the retrospective design of the study. Patient anonymity was preserved throughout the analysis.

Consent for publication
All authors consent to publication.

**Availability of data and material**

All data generated from this study are included in the manuscript.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

PLDT, NCV, CCG and JV were responsible for the data collection from medical records. PLDT and NCV performed the systematic review. PLDT, BMS, DCC, VSS and FV performed the statistical analysis and wrote the first manuscript draft. PLDT, DCC, VSS, AMS, FEME, MVGL, WMM and FV participated in study design, coordination and elaborated the final version of manuscript. All authors read and approved the final manuscript.

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**Figures**

**Figure 1**

Study flowchart of hospitalized HIV-positive (cases) with *Plasmodium vivax* malaria.
Figure 2

Flow chart of inclusion of studies reporting HIV-Plasmodium vivax co-infection.