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# Immunogenicity and reactogenicity of yellow fever vaccine in people with HIV

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**Objective:** To evaluate immunogenicity and reactogenicity of yellow fever (YF) vaccine in people with HIV (PWH) compared to HIV-uninfected controls.

**Design:** In this longitudinal interventional trial (NCT03132311), PWH with $CD4^+$ cell count $\geq$200 cells/μl and controls, aged 18–59, without a previous history of YF vaccination received a single standard dose of YF vaccine (17DD) and were followed at Days 5, 30 and Year 1.

**Methods:** YF-neutralization titers were measured at Days 0, 30 and Year 1 and geometric mean titers (GMT) were calculated. Adverse events (AE) and YF virus detection were measured at Days 5 and 30. Linear regression evaluated factors associated with YF-neutralization titers.

**Results:** Two hundred and eighteen PWH and 82 controls were included. At baseline, all PWH were using antiretroviral therapy; 92.6% had undetectable HIV viral load (VL) and median $CD4^+$ cell count was 630 cells/μl [interquartile range (IQR) 463–888]. YF vaccine was safe and there were no serious AEs. At Day 30, seroconversion was observed in 98.6% of PWH [95% confidence interval (CI): 95.6–99.6] and in 100% of controls (95% CI: 93.9–100); at Year 1, 94.0% of PWH (95% CI: 89.6–96.7) and 98.4% of controls (95% CI 90.3–99.9) were seropositive. PWH had lower GMTs than controls at Day 30 and Year 1. Baseline VL >1000 copies/ml, low $CD4^+$ cell count and low $CD4^+/CD8^+$ ratio were associated with lower YF-neutralization titers.

**Conclusions:** YF vaccine is safe in PWH with $CD4^+$ cell count $\geq$200 cells/μl. YF vaccine immunogenicity is impaired in PWH, particularly among those with high VL, low $CD4^+$ cell count and low $CD4^+/CD8^+$ ratio at vaccination and YF-neutralization titers decays over time.



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## Introduction

Yellow fever (YF) is a mosquito-borne disease caused by a Flavivirus [1] and may vary from self-limiting febrile illness to severe hemorrhage and death [2]. YF is endemic in tropical regions of Africa and South America, where sporadic outbreaks have occurred [1]. In 2016–2018, Brazil faced a YF outbreak outside the endemic Amazon region that reached the country's most populous states in the South and Southeast regions, previously considered at low risk for the disease [3]. In response, a mass vaccination campaign was implemented and YF routine vaccination was recommended countrywide for individuals aged nine months or older [4].

The YF vaccine (17D or 17DD substrains [5]) is a live attenuated viral vaccine and a single dose induces seroconversion in more than 95% of healthy adults [6,7]. Presently, there are 37.7 million people with HIV (PWH) worldwide, most of them living in YF endemic areas [8]. Nonetheless, data on immunogenicity and safety of the YF vaccine in PWH are limited to few observational studies, most of them conducted in high-income, nonendemic settings [9–12].

YF vaccine is safe and severe adverse events (AE) are rare. In Brazil, the estimated incidences of YF vaccine-associated neurologic disease (YEL-AND) and YF vaccine-associated viscerotropic disease (YEL-AVD) were 0.84 and 0.19 cases per million doses, respectively [13]. In PWH, the incidence of YEL-AND and YEL-AVD remains unknown [14]; and a single case of YEL-AND (fatal meningoencephalitis) was reported [15].

We conducted a study to assess immunogenicity and reactogenicity of the YF vaccine in PWH, investigating a possible lower immune response as well as higher incidence of severe AE compared to HIV-uninfected people [HIV(−) controls].

## Methods

### Study design

This prospective longitudinal study enrolled PWH and HIV(−) controls to receive a single standard dose of YF vaccine (17DD, 0.5 ml, Bio-Manguinhos, Fiocruz) [16] from May 2017 through May 2018 at the Instituto Nacional de Infectologia Evandro Chagas/Fiocruz (Rio de Janeiro, Brazil). Participants aged 18–59 with no history of prior YF vaccination or disease were eligible for the study. Additional eligibility criteria were: no contraindication to the vaccine (i.e. pregnancy or breastfeeding, allergies [egg, poultry proteins, erythromycin, kanamycin, hereditary fructose intolerance]); having received immunoglobulins or blood products in the past 6 months; having received any live attenuated virus vaccine in the past month; history of thymus dysfunction; being on antagonist of the Chemokine Receptor type 5 (CCR5) antiretroviral medication; current symptoms of severe acute illness or fever $\geq$38°C. Among PWH, a documented $CD4^+$ cell count $\geq$200 cells/μl in the past 6 months was required. For HIV(−) controls, a nonreactive HIV rapid test at enrollment was required, and all women of reproductive age underwent pregnancy test before vaccine administration.

At enrollment, medical history and blood samples were obtained before vaccine administration. Follow-up visits were scheduled at Day 5, Day 30 and Year 1 after enrollment (visit windows were 3–10 days, 25–60 days and 275–455 days, respectively).

A sample size consisting of 300 PWH with $CD4^+$ cell count $\geq$200 cells/μl (100 participants in each of the following groups: $CD4^+$ 200–350; $CD4^+$ 351–499; and $\geq$500 cells/μl) and 100 HIV(−) controls were estimated considering 98% seroconversion 30–45 days after vaccination and to show a minimal, clinically relevant difference of 10% in seroconversion between PWH and HIV(−) controls (one-tailed 5% significance level and power of 90%). Sample size calculation was performed in WINPEPI (version 11.65) [17].

This study was approved by INI/Fiocruz Ethics Committee (CAAE: #67136517.9.0000.5262) and registered at Clinicaltrials.gov (NCT03132311). All participants provided written informed consent.

### Yellow fever vaccine immunogenicity

YF-neutralization titers were measured using the micro Plaque Reduction Neutralization – Horseradish Peroxidase (μPRN) at baseline and at Day 30 and Year 1 visits to assess vaccine immunogenicity, at the Laboratory of Virological Technology, Bio-Manguinhos (LATEV/Fiocruz) [18]. The μPRN test has shown great accuracy and agreement with the standard PRNT test [19]. Results were expressed as the reciprocal of the highest serum dilution capable of neutralizing the challenge virus by 50%, with maximum neutralization titer as 1 : 1458. Samples with titers $\geq$100 (3.15 $\log_{10}$ mIU/ml) were considered reactive (and defined seroconversion among those seronegative prior to vaccination), and those $\leq$70 were defined as nonreactive, considered non-protective. Results greater than 70 and less than 100 were considered inconclusive and were repeated [18].

## Yellow fever vaccine safety

Unsolicited and solicited clinical AEs were ascertained up to 30 days after vaccination. Solicited AEs were captured using a structured interviewer-applied questionnaire of signs/symptoms (injection site reactions [pain/tenderness, erythema/redness, induration/swelling], fever, drowsiness, headache, myalgia, nausea, vomits, malaise, rash, stridor, swollen lips, swollen eyelid, mental confusion, seizure, jaundice) that were asked to all participants during their Day 5 and Day 30 visits. Unsolicited AEs were any sign/symptom, not included in the solicited events questionnaire, reported by the participant during these visits. Laboratory tests to detect variations in complete blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin were collected at baseline, Day 5 and Day 30 visits. AEs of interest were new or deteriorated diseases or illnesses, or any clinically significant deterioration in laboratory tests. In this study, only vaccine-related AEs graded at least two [20] were considered, and serious adverse event (SAE) was defined as hospitalization or death following study enrollment.

YF virus detection at Day 5 and Day 30 was performed using qualitative real-time polymerase chain reaction (*in-house* real-time PCR [rt-PCR] at the Laboratory of Flavivirus (LABFLA/Fiocruz) [21]) in serum and urine samples; and plaque-forming unit (PFU) assay for quantification of viable YF viral particles ($\log_{10}$ PFU/ml) in serum (LATEV/Fiocruz) [22]. For analysis purposes, YF detection results were categorized as positive and negative. Post-vaccination YF detection was evaluated as both an outcome (YF safety profile description) and as an exposure variable that could be associated with vaccine immunogenicity and the occurrence of clinical and laboratory AEs (see details below).

Increases in HIV viral load (VL) following YF vaccination were assessed at Day 5 and Day 30 in a sub-analysis that include a convenience sample of 83 PWH (Supplementary material, http://links.lww.com/QAD/C962).

## Independent variables

Sociodemographic variables were age at enrollment and sex at birth. For all participants, baseline laboratory tests included Dengue (DENV) and Zika (ZKV) immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies (TR DPP ZDC IgM/IgG, Bio-Manguinhos). Among PWH, baseline HIV-VL (copies/ml, Abbot Park, Illinois, USA); $CD4^+$ cell count (cells/μl, BD Biosciences, California, USA) and $CD4^+/CD8^+$ ratio were measured. Use and duration of antiretroviral therapy (ART), time since HIV diagnosis and $CD4^+$ nadir (lowest $CD4^+$ recorded value prior to enrollment) were ascertained at baseline.

## Statistical analysis

Study participants were enrolled and analyzed in four groups according to their HIV status and baseline $CD4^+$ cell count: HIV(−) controls; and PWH with $CD4^+$ 200–350, 351–499 and ≥500 cells/μl. Demographic and clinical characteristics, and laboratory results of the study population were compared using Kruskal–Wallis test for continuous variables and Fisher's exact test or chi-square test for categorical variables.

Geometric mean titers (GMT) of YF-neutralizing antibodies were calculated at Day 30 and Year 1 for each group and results were compared using Kruskal–Wallis test. Additional exploratory analyses compared GMT in HIV(−) controls and PWH grouped according to HIV-VL and $CD4^+/CD8^+$ ratio, at baseline (Supplementary material, http://links.lww.com/QAD/C962). We further estimated the proportion and 95% confidence interval (95% CI) of participants who seroconverted at Day 30 and Year 1 visits, overall and by HIV status. Linear regression models with generalized estimating equations (GEE) to account for repeated measures within the same participant (i.e., at Day 30 and Year 1 visits) were used to evaluate factors associated with YF-neutralization titers ($\log_{10}$-transformed). For the regression models, HIV-related covariates (i.e. baseline $CD4^+$ cell count, $CD4^+/CD8^+$ ratio and HIV-VL) were categorized and the reference category for all of them was 'HIV(−) controls'. Unadjusted regression models tested the association of the covariates and the YF-neutralization titers. Stepwise backward statistical modeling included covariates with *P*-value <0.20. The final adjusted model kept age, sex and covariates with $P < 0.05$. Three final adjusted models were fitted: model 1 included a four-level variable combining HIV status and baseline $CD4^+$ cell count (HIV(−) controls [reference], PWH with $CD4^+$ 200–350, 351–499, and ≥500 cells/μl); model 2 included a five-level variable combining HIV status and baseline $CD4^+/CD8^+$ ratio (HIV(−) controls [reference], PWH with $CD4^+/CD8^+$ ratio <40, 0.40–0.69, 0.70–0.99, ≥1.0); and model 3 included a four-level variable combining HIV status and baseline HIV-VL (HIV(−) controls [reference], PWH with HIV-VL <40, 40–999 and ≥1000 copies/ml). $CD4^+$ cell count, $CD4^+/CD8^+$ ratio and HIV-VL could not be considered in the same model because of collinearity. Additional analyses that evaluated YF-neutralization titers only in PWH were performed, including models evaluated the association between continuous baseline $CD4^+$ cell count (square root transformed) and $CD4^+/CD8^+$ ratios and YF-neutralization titers (Supplementary material, http://links.lww.com/QAD/C962). As regression coefficients estimated the difference in $\log_{10}$ of YF-neutralization titers across categories of the explanatory covariates, the antilog measures the fold-variation in YF-neutralization levels compared to the reference category.

Frequencies of clinical and laboratory AEs were calculated for each group: HIV(−) controls; and PWH with $CD4^+$ cell count 200–350, 351–499 and ≥500 cells/μl. Logistic regression models with GEE to account for repeated measures within the same participant (i.e., at Day 5 and Day 30 visits) were used to evaluate factors associated with the odds of having an AE. Unadjusted regression models tested the association between each covariate with AE occurrence. Covariates with *P*-value <0.20 were included in an initial adjusted model and were removed one by one until the final adjusted model kept only covariates with $P < 0.05$; age and sex were kept in the final model. All analyses were performed in R (Version 4.3.0) [23].

## Results

Of 300 participants enrolled in the study, 218 were PWH and 82 HIV(−) controls (Figure 1, Supplemental Digital Content, http://links.lww.com/QAD/C962). Thirty percent of PWH had a $CD4^+$ cell count <500 cells/μl, with only 17 PWH in the 200–350 cells/μl subgroup. The PWH were older and had higher proportion of males than HIV(−) controls. At baseline, 81.9% of the participants had DENV IgG antibodies and 38.4% had ZKV IgG antibodies, with no difference seen between PWH and HIV(−) controls. At baseline, PWH were using ART for a median duration of 5.8 years, 92.6% had undetectable HIV-VL and had a median $CD4^+$ cell count of 630 cells/μl. PWH with lower $CD4^+$ cell count also had lower $CD4^+$ nadirs, lower $CD4^+$/ $CD8^+$ ratios, shorter time since HIV diagnosis and shorter ART duration, characterizing them as late presenters (Table 1).

### Yellow fever vaccine immunogenicity

Among the 300 participants enrolled, 12 (4%) participants (8 PWH and 4 HIV(−) controls) had baseline YF-neutralization titers ≥100 (seropositive at baseline) and were not excluded from the following analyses (Table 1, Supplemental Digital Content, http://links.lww.com/QAD/C962).

Post-vaccination YF-neutralization titers at Day 30 and Year 1 were related to the baseline $CD4^+$ cell count (Fig. 1). Compared to Day 30, a marked reduction in YF-neutralization titers was observed at Year 1 for all groups. In both time points, lowest neutralization titers were seen in PWH with baseline $CD4^+$ of 200–350 cells/μl (Fig. 1 and Table 2). YF-neutralization levels according to baseline HIV-VL and $CD4^+/CD8^+$ ratio are shown in Figure 2, Supplemental Digital Content, http://links.lww.com/QAD/C962 and Figure 3, Supplemental Digital Content, http://links.lww.com/QAD/C962.

The proportion of seroconversions at Day 30 was similar in PWH (98.6%, 95% CI 95.6–99.6) and HIV(−) controls (100%, 95% CI 93.9–100) (Table 2). One year after vaccination, those proportions decreased to 94.0% (95% CI 89.6–96.7) in PWH and 98.4% (95% CI 90.3–99.9) in HIV(−) controls. Proportion of seroconversion was lowest in PWH with baseline $CD4^+$ cell count of 200–350 cells/μl.

Linear regression modeling (Table 3) showed that YF-neutralization titers were 6.0-fold lower at Year 1 than at Day 30 (model 1, antilog [adjusted coefficient: −0.78]). In the adjusted models, controlled for age and sex, YF-neutralization titers were higher when YF virus was detected (rt-PCR) in serum and urine. Conversely, low $CD4^+$ cell count, low $CD4^+$/ $CD8^+$ ratio and high HIV-VL at baseline were independently associated with lower YF-neutralization titers. Additional analyses that included only PWH are shown in Figure 4, Supplemental Digital Content, http://links.lww.com/QAD/C962 and Table 2, Supplemental Digital Content, http://links.lww.com/QAD/C962. In the final adjusted model, YF-neutralization titers were higher among those with baseline $CD4^+$/ $CD8^+$ ratio ≥1.0 (adjusted coefficient: 0.45; 95% CI: 0.14–0.77) relative to those with $CD4^+/CD8^+$ ratio <0.40, whereas those with HIV-VL ≥1000 copies/ml (adjusted coefficient: 1.51; 95%CI: 3.13–0.11) had lower titers compared to PWH with HIV-VL <40 copies/ml. The association between baseline $CD4^+$ cell count and YF-neutralization titers was not significant and the effect of the other covariates (i.e. study visit and YF virus detection in serum and urine) were similar to the results seen in the main regression models.

### Yellow fever vaccine safety

A greater proportion of PWH had a positive YF rt-PCR in serum compared to HIV(−) controls (17.9 versus 6.8%, *P*-value 0.035). This was most marked at Day 5 (Table 3, Supplemental Digital Content, http://links.lww.com/QAD/C962). The proportion of participants with positive YF PFU was smaller in both comparison groups (5.8% in PWH versus 5.4% in HIV(−) controls, *P*-value 1.000). In urine samples, YF rt-PCR positivity was 3.4% in PWH versus 1.4% in HIV(−) controls (*P*-value 0.453). Persistence of positive YF rt-PCR in serum at Day 30 was observed in one participant, a PWH with $CD4^+$ cell count of 774 cells/μl and HIV-VL <40 copies/ml at baseline.

Eighty-three AEs were reported up to 30 days after YF vaccination; 22 were grade ≥2 and deemed related to the YF vaccine (in 18 participants). They were reported more frequently among HIV(−) controls than by PWH (12.2 and 5.5%, respectively) (described at Table 4, Supplemental Digital Content, http://links.lww.com/QAD/C962). Most AEs occurred up to Day 5 visit (16/22) and all participants fully recovered without the need of medical intervention. The most frequent

**Table 1. Age, sex, serological status for dengue and zika and HIV-related baseline data in PWH CD4$^+$ cell count categories and HIV(−) controls.**

| | PWH stratified by baseline CD4$^+$ (cells/μl) | | | Study population according to HIV status | | |
|---|---|---|---|---|---|---|
| | 200–350 *N* = 17 | 351–499 *N* = 50 | ≥500 *N* = 151 | PWH *N* = 218 | HIV(−) controls *N* = 82 | *P*-value |
| Age | | | | | | |
| Median (IQR) | 45.6 (37.4–49.5) | 46.5 (34.2–51.9) | 42.7 (36.7–50.4) | 43.9 (36.1–51.4) | 36.2 (27.9–46.3) | |
| Categories, *n* (%) | | | | | | <0.001[a] |
| 18–29 years | 3 (17.7) | 6 (12.0) | 17 (11.2) | 26 (11.9) | 28 (34.2) | |
| 30–39 years | 2 (11.7) | 11 (22.0) | 46 (30.5) | 59 (27.1) | 21 (25.6) | |
| 40–49 years | 8 (47.1) | 16 (32.0) | 46 (30.5) | 70 (32.1) | 22 (26.8) | |
| 50–59 years | 4 (23.5) | 17 (34.0) | 42 (27.8) | 63 (28.9) | 11 (13.4) | |
| Sex | | | | | | 0.1603[a] |
| Female | 4 (23.5) | 14 (28.0) | 50 (33.1) | 68 (31.2) | 36 (43.9) | |
| Male | 13 (76.5) | 36 (72.0) | 101 (66.9) | 150 (68.8) | 46 (56.1) | |
| DENV IgG Ab[c] | | | | | | 0.4518[a] |
| Negative | 6 (42.9) | 9 (20.0) | 27 (18.0) | 42 (19.44) | 12 (14.81) | |
| Positive | 10 (62.50) | 40 (81.63) | 124 (82.12) | 174 (80.56) | 69 (85.19) | |
| DENV IgM Ab[c] | | | | | | 0.7556[a] |
| Negative | 16 (100.00) | 48 (97.96) | 143 (94.70) | 207 (95.83) | 77 (95.06) | |
| Positive | 0 (0.00) | 1 (2.04) | 8 (5.30) | 9 (4.17) | 4 (4.94) | |
| ZKV IgG Ab[c] | | | | | | 0.3611[a] |
| Negative | 12 (85.7) | 27 (60.0) | 95 (63.3) | 137 (63.43) | 46 (56.79) | |
| Positive | 2 (14.3) | 18 (40.0) | 55 (36.7) | 79 (36.57) | 35 (43.21) | |
| ZKV IgM Ab[c] | | | | | | 0.5649[a] |
| Negative | 15 (93.75) | 49 (100.00) | 149 (98.68) | 213 (98.61) | 81 (100.00) | |
| Positive | 1 (6.25) | 0 (0.00) | 2 (1.32) | 3 (1.39) | 0 (0.00) | |
| Nadir CD4$^+$ (cells/μl)[c] | | | | | | |
| Median (IQR) | 79 (59.0–171.0) | 72 (32.0–183.0) | 268 (149.0–381.5) | 199 (71.0–344.0) | – | – |
| Categories, *n* (%) | | | | | | <0.001[b] |
| <50 | 4 (23.5) | 18 (36.0) | 21 (13.9) | 43 (19.7) | – | |
| 50–199 | 11 (64.7) | 19 (38.0) | 36 (23.8) | 66 (30.3) | – | |
| 200–349 | 2 (11.8) | 9 (18.0) | 43 (28.5) | 54 (24.8) | – | |
| ≥350 | 0 (0) | 4 (8.0) | 51 (33.8) | 55 (25.2) | – | |
| CD4$^+$/CD8$^+$ ratio[c] | | | | | | |
| Median (IQR) | 0.34 (0.2–0.4) | 0.56 (0.4–0.8) | 0.97 (0.7–1.3) | 0.8 (0.6–1.1) | – | – |
| Categories, *n* (%) | | | | | | <0.001[b] |
| <0.40 | 9 (52.9) | 15 (30.0) | 8 (5.3) | 32 (14.7) | – | |
| 0.40–0.69 | 7 (41.2) | 16 (32.0) | 28 (18.5) | 51 (23.4) | – | |
| 0.70–0.99 | 1 (5.9) | 16 (32.0) | 46 (30.5) | 63 (28.9) | – | |
| ≥1.0 | 0 (0) | 3 (6.0) | 69 (45.7) | 72 (33.0) | – | |
| HIV-VL (copies/ml), *n* (%)[c] | | | | | 0.281[b] | |
| <40 | 13 (81.3) | 46 (93.9) | 141 (93.4) | 200 (92.6) | – | |
| 40–999 | 2 (12.5) | 2 (4.1) | 8 (5.3) | 12 (5.6) | – | |
| ≥1000 | 1 (6.2) | 1 (2.0) | 2 (1.3) | 4 (1.8) | – | |
| Years since HIV diagnosis[c] | | | | | | |
| Median (IQR) | 2.55 (1.3–18.5) | 7.11 (4.0–11.1) | 8.70 (4.5–14.5) | 8.2 (4.0–14.0) | – | |
| Categories, *n* (%) | | | | | | 0.158[b] |
| <1 | 0 | 3 (6.0) | 5 (3.3) | 8 (3.7) | – | |
| 1–4.99 | 10 (58.8) | 16 (32.0) | 40 (26.5) | 66 (30.3) | – | |
| 5–9.99 | 2 (11.8) | 16 (32.0) | 46 (30.5) | 64 (29.4) | – | |
| ≥10 | 5 (29.4) | 15 (30.0) | 60 (39.7) | 80 (36.7) | – | |
| Years since ART initiation[c] | | | | | | |
| Median (IQR) | 2.4 (1.2–18.1) | 5.1 (2.6–10.3) | 6.2 (3.6–10.2) | 5.8 (2.6–10.2) | – | |
| Categories, *n* (%) | | | | | | 0.405[b] |
| <1 | 2 (11.8) | 4 (8.0) | 11 (7.3) | 17 (7.8) | – | |
| 1–4.99 | 8 (47.1) | 20 (40.0) | 53 (35.1) | 81 (37.2) | – | |
| 5–9.99 | 2 (11.8) | 13 (26.0) | 47 (31.1) | 62 (28.4) | – | |
| ≥10 | 5 (29.4) | 13 (26.0) | 40 (26.5) | 58 (26.6) | – | |

ART, antiretroviral therapy; DENV IgG Ab, dengue IgG antibody; DENV IgM Ab, dengue IgM antibody; HIV(−), controls for HIV-uninfected people; HIV-VL, HIV viral load; IQR, interquartile range; PWH, people with HIV; ZKV IgG Ab, zika IgG antibody; ZKV IgM Ab, zika IgM antibody.
[a]*P*-value for comparison among PWH and HIV(−) controls (chi-square and Fisher's test for categorical variables).
[b]*P*-value for comparison among PWH stratified by CD4$^+$ and HIV(−) controls (Kruskal–Wallis test for continuous variables and chi-square test for categorical variables).
[c]At baseline.

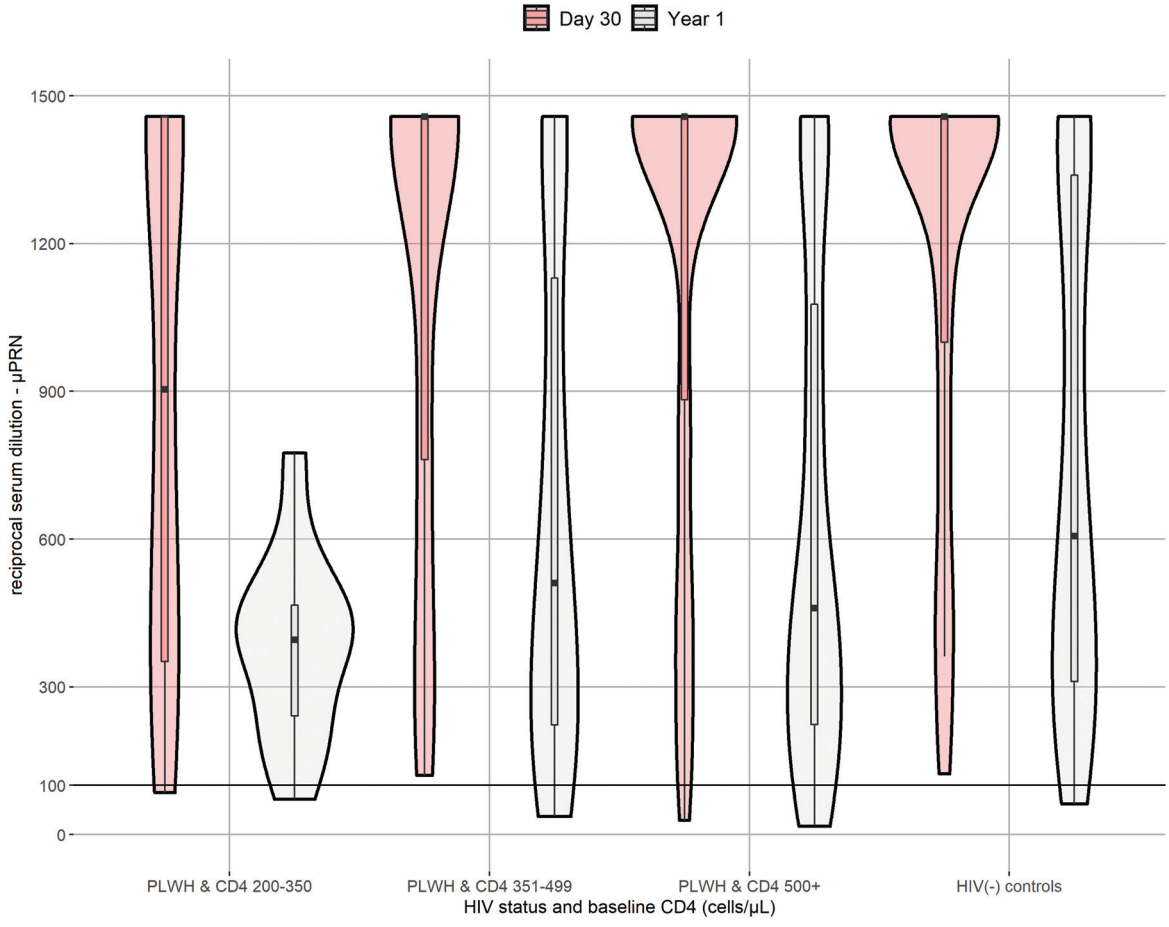


**Fig. 1. YF neutralization titers at Day 30 and Year 1 after YF vaccination in PWH CD4$^+$ cell count categories and HIV(−) controls.** Violin plot and a boxplot showing the density distribution, median (in bold), first and third quartiles of YF neutralizing antibody titers by study visit and baseline CD4$^+$ strata. HIV(−) controls, HIV-uninfected controls; PWH, people with HIV.

laboratory AE were neutropenia ($n = 5$) and elevated AST ($n = 5$). Headache was the most frequent clinical AE ($n = 6$), followed by fever ($n = 2$) and myalgia ($n = 2$). Six AEs were grade 3 (three neutropenia events occurred in two PWH; three elevated AST events occurred in two PWH). No vaccine-related SAE was observed.

In the final logistic regression model, participants with positive YF detection in urine (rt-PCR at Day 5) were more likely to have an AE (adjusted odds ratio [aOR] 18.55, $P$-value = 0.002). There was no clear pattern of association between 'HIV status and baseline CD4$^+$' and AE occurrence (Table 4).

A sub-analysis assessed increases in HIV-VL after YF vaccination, at Day 5 and Day 30, in a subset of 83 PWH. At baseline, 77 of 83 PWH (92.5%) had HIV-VL <40 copies/ml. After vaccination, 92.5% (74/80) and

**Table 2. Geometric means (95% CI) of YF-neutralization titers and proportion of seropositivity (95% CI), at Day 30 and Year 1 following vaccination, in PWH CD4$^+$ cell count categories and HIV(−) controls.**

| | Day 30 | | Year 1 | |
|---|---|---|---|---|
| | GMT (95% CI) | Seropositivity, % (95% CI) | GMT (95% CI) | Seropositivity, % (95% CI) |
| PWH & CD4$^+$ 200–350 | 711 (454–1115) | 94.1 (69.2–99.7) | 329 (219–493) | 91.7 (59.8–99.6) |
| PWH & CD4$^+$ 351–499 | 918 (742–1136) | 100 (91.1–100) | 451 (339–600) | 95.7 (84.3–99.3) |
| PWH & CD4$^+$ ≥500 | 978 (865–1107) | 98.6 (94.7–99.8) | 430 (363–510) | 93.7 (88.0–96.9) |
| HIV(−) controls | 1039 (904–1194) | 100 (93.9–100) | 583 (474–717) | 98.4 (90.3–99.9) |

CI, confidence interval; GMT, geometric means titer; HIV(−) controls, HIV-uninfected controls; PWH, people with HIV.

**Table 3. Multiple linear regression models of the association between YF-neutralization titers with age, sex, serological status for dengue and zika, YF vaccine virus detection and HIV-related laboratory indicators.**

| $Log_{10}$ μPRN | Unadjusted model | | Adjusted model 1 | | Adjusted model 2 | | Adjusted model 3 | |
|---|---|---|---|---|---|---|---|---|
| | Coef | 95% CI | Coef | 95% CI | Coef | 95% CI | Coef | 95% CI |
| Age (years) | | | | | | | | |
| 18–29 | Ref | | Ref | | Ref | | Ref | |
| 30–39 (ref 18–29 years) | −0.27 | −0.51, −0.03 | −0.19 | −0.44, 0.06 | −0.19 | −0.44, 0.05 | −0.20 | −0.43, 0.03 |
| 40–49 (ref 18–29 years) | −0.08 | −0.29, 0.13 | 0.03 | −0.19, 0.25 | 0.03 | −0.19, 0.25 | −0.02 | −0.23, 0.20 |
| 50–59 (ref 18–29 years) | −0.14 | −0.37, 0.10 | 0.03 | −0.22, 0.28 | 0.04 | −0.22, 0.29 | 0.02 | −0.23, 0.27 |
| Sex | | | | | | | | |
| Male | Ref | | Ref | | Ref | | Ref | |
| Female | 0.04 | −0.14, 0.22 | 0.06 | −0.12, 0.24 | 0.03 | −0.16, 0.21 | 0.05 | −0.13, 0.23 |
| Study visit | | | | | | | | |
| Day 30 | Ref | | Ref | | Ref | | Ref | |
| Year 1 | −0.76 | −0.86, −0.66 | −0.78 | −0.87, −0.68 | −0.77 | −0.87, −0.67 | −0.77 | −0.87, −0.67 |
| DENV IgG Ab[a] | | | | | | | | |
| Negative | Ref | | | | | | | |
| Positive | −0.08 | −0.29, 0.14 | | | | | | |
| ZKV IgG Ab[a] | | | | | | | | |
| Negative | Ref | | | | | | | |
| Positive | 0.02 | −0.16, 0.20 | | | | | | |
| YF virus detection in serum (rt-PCR) | | | | | | | | |
| No | Ref | | Ref | | Ref | | Ref | |
| Yes | 0.45 | 0.31, 0.60 | 0.49 | 0.33, 0.65 | 0.51 | 0.36, 0.67 | 0.48 | 0.32, 0.63 |
| YF virus detection in urine (rt-PCR) | | | | | | | | |
| No | Ref | | Ref | | Ref | | Ref | |
| Yes | 0.28 | −0.05, 0.62 | 0.39 | 0.07, 0.71 | 0.39 | 0.14, 0.65 | 0.40 | 0.07, 0.72 |
| YF virus detection in serum (PFU) | | | | | | | | |
| No | Ref | | | | | | | |
| Yes | 0.45 | 0.27, 0.62 | | | | | | |
| HIV status and nadir $CD4^+$ (cells/μl)[a] | | | | | | | | |
| HIV(−) controls | Ref | | | | | | | |
| PWH & <50 | −0.24 | −0.49, 0.01 | | | | | | |
| PWH & 50–199 | −0.18 | −0.40, 0.04 | | | | | | |
| PWH & 200–349 | −0.15 | −0.38, 0.09 | | | | | | |
| PWH & 350+ | −0.35 | −0.64, −0.05 | | | | | | |
| HIV status and $CD4^+$ (cells/μl)[a] | | | | | | | | |
| HIV(−) controls | Ref | | Ref | | | | | |
| PWH & $CD4^+$ 200–350 | −0.44 | −0.76, −0.11 | −0.50 | −0.85, −0.15 | | | | |
| PWH & 351–499 | −0.21 | −0.46, 0.03 | −0.26 | −0.52, 0.01 | | | | |
| PWH & 500+ | −0.20 | −0.39, −0.01 | −0.24 | −0.44, −0.03 | | | | |
| HIV status and $CD4^+/CD8^{++}$ ratio[a] | | | | | | | | |
| HIV(−) controls | Ref | | | | Ref | | | |
| PWH & <0.40 | −0.41 | −0.68, −0.13 | | | −0.56 | −0.88, −0.25 | | |
| PWH & 0.40–0.69 | −0.31 | −0.60, −0.03 | | | −0.32 | −0.62, −0.03 | | |
| PWH & 0.70–0.99 | −0.20 | −0.42, 0.03 | | | −0.27 | −0.51, −0.03 | | |
| PWH & 1.00+ | −0.10 | −0.32, 0.12 | | | −0.12 | −0.35, 0.11 | | |
| HIV status and HIV viral load (copies/ml)[a] | | | | | | | | |
| HIV(−) controls | Ref | | | | | | Ref | |
| PWH & VL <40 | −0.20 | −0.38, −0.03 | | | | | −0.25 | −0.44, −0.06 |
| PWH & VL 40-999 | −0.13 | −0.36, 0.10 | | | | | −0.08 | −0.36, 0.21 |
| PWH & VL 1000+ | −1.69 | −3.06, −0.32 | | | | | −1.83 | −3.51, −0.16 |

ART, antiretroviral therapyt; CI, confidence interval; Coef, linear coefficient; DENV IgG Ab, dengue IgG antibody; HIV(−) controls, HIV-uninfected controls; HIV-VL, HIV viral load; PFU, plaque forming units' assay, Ref: reference; PWH, people with HIV; rt-PCR, real time polymerase chain reaction; ZKV IgG Ab, Zika IgG antibody. Adjusted model 1 included a four-level variable that categorized study participants according to HIV status and baseline $CD4^+$ cell count (HIV(−) controls [reference]), PWH with $CD4^+$ 200–350, 351–499, and ≥ 500 cells/μl. Adjusted model 2 included a five-level variable that categorized study participants according to HIV status and baseline $CD4^+/CD8^+$ ratio (HIV(−) controls [reference]), PWH with $CD4^+/CD8^+$ ratio <40, 0.40–0.69, 0.70–0.99 and ≥1.0. Adjusted model 3 included a four-level variable that categorized study participants according to HIV status and baseline HIV-VL (HIV(−) controls [reference]), PWH with <40 copies/ml, 40–999 and ≥1000 copies/ml.
[a]At baseline.

92.6% (75/81) had HIV-VL <40 copies/ml at Day 5 and Day 30, respectively. Relative to baseline, HIV-VL increased in six participants, and the maximum VL was 311 copies/ml (measured at Day 30) (Table 5, Supplemental Digital Content, http://links.lww.com/QAD/C962).

## Discussion

In this prospective study, we showed that YF vaccine was immunogenic, safe and well tolerated in PWH with $CD4^+$ cell count ≥200 cells/μl. Nonetheless,

**Table 4. Association (crude and adjusted odds ratio) between adverse events (grade ≥2) with age, sex, serological status for dengue and zika, YF vaccine virus detection and HIV-related laboratory indicators.**

| | Adverse events | | | |
|---|---|---|---|---|
| | Unadjusted model | | Adjusted model | |
| | cOR | 95% CI | aOR | 95% CI |
| Age | | | | |
| 18–29 years | Ref | | Ref | |
| 30–39 years | 1.93 | 0.37, 10.03 | 2.71 | 0.45, 16.27 |
| 40–49 years | 1.14 | 0.21, 6.11 | 1.28 | 0.24, 6.96 |
| 50–59 years | 0.44 | 0.06, 3.32 | 0.75 | 0.09, 6.47 |
| Sex | | | | |
| Male | Ref | | Ref | |
| Female | 1.26 | 0.47, 3.40 | 1.29 | 0.42, 3.98 |
| Study visits when the AE was observed | | | | |
| Day 5 visit | 2.46 | 1.01, 5.98 | | |
| Day 30 visit | Ref | | | |
| DENV IgG Ab[a] | | | | |
| Negative | Ref | | | |
| Positive | 4.17 | 0.55, 31.50 | | |
| DENV IgM Ab[a] | NA | | | |
| Negative | | | | |
| Positive | | | | |
| ZKV IgG Ab[a] | | | | |
| Negative | Ref | | | |
| Positive | 1.04 | 0.39, 2.82 | | |
| ZKV IgM Ab[a] | NA | | | |
| Negative | | | | |
| Positive | | | | |
| YF virus detection in serum (rt-PCR) | | | | |
| No | Ref | | | |
| Yes | 2.34 | 0.65, 8.41 | | |
| YF virus detection in urine (rt-PCR) | | | | |
| No | Ref | | | |
| Yes | 10.97 | 2.20, 54.79 | 18.55 | 2.98, 115.3 |
| HIV status and $CD4^{+a}$ (cells/μl) | | | | |
| HIV(−) controls | Ref | | Ref | |
| PWH & $CD4^{+}$ 200–350 | 1.51 | 0.40, 5.79 | 2.41 | 0.53, 10.99 |
| PWH & 351–499 | 0.16 | 0.02, 1.31 | 0.17 | 0.02, 1.48 |
| PWH & 500+ | 0.38 | 0.13, 1.17 | 0.33 | 0.10, 1.09 |
| HIV status and nadir $CD4^{+}$ (cells/μl) | | | | |
| HIV(−) controls | Ref | | | |
| PWH & <50 | 0.39 | 0.08, 1.86 | | |
| PWH & 50–199 | 0.36 | 0.09, 1.39 | | |
| PWH & 200–349 | 0.15 | 0.02, 1.23 | | |
| PWH & 350+ | 0.80 | 0.22, 2.88 | | |
| HIV status and $CD4^{+}$ /$CD8^{+}$ ratio[a] | | | | |
| HIV(−) controls | Ref | | | |
| <0.40 | 0.51 | 0.11, 2.45 | | |
| 0.40–0.69 | 0.32 | 0.07, 1.55 | | |
| 0.70–0.99 | 0.39 | 0.10, 1.50 | | |
| 1.00+ | 0.47 | 0.11, 1.92 | | |
| HIV status and HIV-VL[a,b] (copies/ml) | | | | |
| HIV(−) controls | Ref | | | |
| PWH & HIV-VL <40 | 0.41 | 0.15, 1.12 | | |
| PWH & HIV-VL ≥40 | 0.52 | 0.06, 4.19 | | |

aOR, adjusted odds ratio adjusted; CI, confidence interval; cOR, odds ratio crude; DENV IgG Ab, dengue IgG antibody; HIV(−) controls, HIV-uninfected controls; HIV-VL, HIV viral load; PFU, plaque forming units' assay; PWH, people with HIV; Ref, reference; rt-PCR, real time polymerase chain reaction; ZKV IgG Ab, Zika IgG antibody. YF virus detection in serum (PFU) was not included in the model because there was at least one group had zero participants.

[a]At baseline.

[b]PWH was stratified only in two groups since there was no AE among those with VL >1000 copies/ml.

immunogenicity was impaired in PWH. A low $CD4^{+}$ cell count, low $CD4^{+}$/$CD8^{+}$ ratio and high HIV-VL at baseline were associated with lower YF-neutralization titers. Moreover, YF-neutralization titers decayed over time (up to one year after vaccination), potentially affecting the long-term protection of YF vaccine in PWH.

The standard dose of 17DD vaccine resulted in high seroconversion levels in PWH (99 and 94%) and HIV(−)

controls (100 and 98%) at Day 30 and Year 1 after vaccination, respectively. These levels are similar to those previously reported for healthy adults [6] and PWH [9,11,12]. In a recent Brazilian study [9] that included 12 PWH (median baseline $CD4^+$ cell count of 772 cells/μl) and 45 controls, authors found 100% seroconversion in both groups 30 days after vaccination and 92% in PWH 1 year after vaccination (17DD vaccine). Similar to our study, they also found an association between high $CD4^+/CD8^+$ ratio and higher YF-neutralization titers, while detectable HIV-VL was associated with lower YF-neutralization titers [24]. In France [11], a prospective study with 40 PWH (median $CD4^+$ cell count 702 cells/μl and all with undetectable HIV-VL) and 31 controls found 100% seropositivity at 28 days and one year after vaccination (using 17D vaccine). A similar seropositivity level, 95% within the first year after vaccination (17D vaccine), was reported in a retrospective study of the HIV Swiss Cohort [12] that used stored samples of 247 PWH (median $CD4^+$ cell count at vaccination of 536 cells/μl). In their study, detectable HIV-VL was associated with lower YF-neutralization titers. In consonance, a systematic review that evaluated YF immunogenicity among 561 PWH concluded that high $CD4^+$ cell count and suppressed HIV-VL at vaccination are associated with higher neutralizing antibody levels [25]. Finally, we found that post-vaccination YF virus detection (rt-PCR) was associated with higher YF-neutralization titers; a similar finding was reported in a Brazilian study that evaluated 17DD vaccine immunogenicity in adults with autoimmune rheumatic diseases [26].

Evidence suggests that the YF vaccine immune response wanes over time, and a booster dose might be advisable for PWH [9,11,12]. Our study showed that YF-neutralization titers did decay over time (up to one year after vaccination) in all participants. This was particularly concerning for PWH with low $CD4^+$ cell count, low $CD4^+/CD8^+$ ratio and high HIV-VL at baseline, for whom YF neutralizing antibody titers' peak at Day 30 had relatively lower values than HIV(−) controls. In 2014, the World Health Organization withdrew their recommendation for a booster dose of YF vaccine [27]. However, they recognized the possibility of a booster dose in specific populations, such as immunocompromised individuals and PWH. The marked decrease in YF-neutralization levels observed in our study, after only one year after a single standard dose of the YF vaccine, suggests that a substantial proportion of vaccinated PWH may become YF-seronegative (and unprotected) in the long term. In fact, data from the Swiss cohort retrospective study showed levels of seropositivity in PWH decreased from 95% within one year to 86% at five years and 75% at ten years after YF vaccination [12]. This is particularly relevant for YF endemic countries where HIV and YF burdens overlap, since routine verification of HIV serological status before vaccination cannot be implemented, the reintroduction of a booster dose should be considered. On the other hand, for nonendemic countries, the results of our study may help guide the best timing for YF vaccine recommendation for PWH. In nonurgent situations, delaying YF vaccination in PWH until ART initiation and HIV viral suppression improves vaccine immunogenicity [12].

The 17DD vaccine was safe and well tolerated in PWH and HIV(−) controls. Almost 80% of the observed AEs were mild, all AEs resolved without medical intervention, and there were no SAEs. Neutropenia and elevated AST were the most frequent laboratory grade $\geq$2 AEs and occurred more commonly in PWH than in HIV(−) controls. Neutropenia is relatively common in PWH and may result from direct HIV viral toxicity, opportunistic infections and drug toxicity [28]. Transient and benign post-vaccination neutropenia has been described for different vaccines [29] and is more likely to occur in individuals with lower baseline neutrophil count. A study that followed 1729 women living with HIV found that almost 80% presented neutrophil counts below 2000 cells/μl at some point, with 31% below 1000 cells/μl [30]. The elevated AST events observed in our study were not accompanied by ALT or total bilirubin elevations or signs and symptoms. AST is less specific than ALT as a biomarker of liver damage and inflammation [31]. It can be associated with muscle damage or even hemolysis [32]. In our study, post-vaccination YF virus detection (rt-PCR) was almost three times more frequent in PWH than in HIV(−) controls, and it was associated with higher odds of having a grade two or more AEs. Higher frequency and prolonged post-vaccination YF viremia have been described among elders [33] and in a case report of a bone marrow-suppressed individual [34]. Impaired innate immune response may explain the higher frequency of post-vaccination YF viremia in PWH, elders and other immune-compromised individuals [35].

Our study has limitations. First, we experienced difficulties in including healthy PWH with low $CD4^+$ cell count (200–350 cells/μl), mainly because of the Brazilian 'test and treat' recommendation for HIV care. Moreover, availability of highly potent first-line antiretroviral regimens (i.e. dolutegravir-based and efavirenz-based single pill) decreased the number of AIDS cases, increased $CD4^+$ cell count at ART initiation [36] and resulted in rapid $CD4^+$ recovery after ART initiation [37]. Often, participants would have a pre-enrollment $CD4^+$ cell count between 200 and 350 cells/μl, but at enrollment, $CD4^+$ cell count was already above 350 cells/μl. Nonetheless, though smaller than initially planned, our study is the only prospective study to vaccinate and follow PWH with $CD4^+$ cell count $<$350 cells/μl. Second, although not listed as an eligibility criterion, all PWH included in our study were using ART prior to vaccination, precluding us from studying the effect of ART use in YF vaccine outcomes. Third, over 90% of our

study population had undetectable HIV-VL at enrollment, underpowering the evaluation of the effect of baseline HIV-VL levels on YF vaccine outcomes. Nevertheless, we observed with reasonable confidence that HIV-VL $\geq$1000 copies/ml was associated with lower YF vaccine immunogenicity. Finally, our study was not powered enough to evaluate the incidence of rare vaccine-related SAE. In endemic countries, routine YF vaccination is not contingent on HIV testing, so individuals unaware of or who do not disclose their serological HIV status may receive the vaccine. Our study provides evidence to support current recommendations, but pharmacovigilance should target PWH and other immunocompromised individuals for uncommon AEs.

A major strength of our study was enrolling individuals with no prior YF vaccination/disease, and only 4% of our study population had pre-vaccination seropositivity (versus 33% observed in another Brazilian study [9] and 46% in the Swiss Cohort study [12]). Moreover, most of the initial seropositive participants had low YF-neutralization titers (<300) [38], which may suggest nonspecific reactions (i.e. sera cross-reactivity with DENV and ZKV antibodies). In addition, our regression model accounted for the potential effect of baseline DENV and ZKV antibodies on YF-neutralization titers, based on the hypothesis that antibodies against other flaviviruses could potentially impair YF vaccine immunogenicity [38]. Finally, we considered that "booster" from natural infection was unlikely in this study population, given the current epidemiological setting of YF in Brazil [39].

## Conclusion

YF vaccine immunogenicity is impaired in PWH using ART, particularly among those with high HIV-VL, low $CD4^+$/ $CD8^+$ ratio and low $CD4^+$ cell count at vaccination. Moreover, YF-neutralizing antibodies wane over time. YF vaccine was safe and well tolerated in PWH with $CD4^+$ cell count $\geq$200 cells/$\mu$l and no SAE was observed. Further prospective studies with longer follow-up times are needed to provide evidence on long term immunogenicity of the YF vaccine in PWH.

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Data sharing: Data supporting this manuscript may be available upon reasonable request to the corresponding author.

## Conflicts of interest

There are no conflicts of interest.

## References

1. Monath TP, Vasconcelos PFC. **Yellow fever.** *J Clin Virol* 2015; **64**:160–173.
2. Simon LV, Hashmi MF, Torp KD. *Yellow Fever*. StatPearls Publishing; 2022. https://www.ncbi.nlm.nih.gov/books/NBK470425/ [Accessed 15 April 2022]
3. BRASIL. Ministério da Saúde. Secretaria de Vigilância em Saúde. Monitoramento do Período Sazonal da Febre Amarela Brasil – 2017/2018.Brasília: Ministério da Saúde, Secretaria de Vigilância em Saúde; 2018. https://sbim.org.br/images/files/informe-fa-21–11abr18-c.pdf [Accessed 25 July 2022]
4. BRASIL. Ministério da Saúde. Secretária de Vigilância em Saúde. Nota informativa n° 94, de 2017/CGPNI/DEVIT/SVS/MST. Brasília: Ministério da Saúde, Secretaria de Vigilância em Saúde; 2018. Available at http://www.vs.saude.ms.gov.br/wp-content/uploads/2018/01/NotaInformativa94-FA-DOSE-ÚNICA.pdf [Accessed 25 July 2022]
5. Galler R. **Genetic variability among yellow fever virus 17D substrains.** *Vaccine* 1998; **16**:1024–1028.
6. Camacho LAB, Freire M da S, Leal M da LF, Aguiar SGJ de, Nascimento JP do, Iguchi T, *et al*. **Immunogenicity of WHO-17D and Brazilian 17DD yellow fever vaccines: a randomized trial.** *Rev Saúde Pública* 2004; **38**:671–678.
7. Poland JD, Calisher CH, Monath TP, Downs WG, Murphy K. **Persistence of neutralizing antibody 30–35 years after immunization with 17D yellow fever vaccine.** *Bull World Health Organ* 1981; **59**:895–900.
8. UNAIDS/WHO estimates. HIV data and statistics – 2021. 2022. https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/strategic-information/hiv-data-and-statistics [Accessed 7 March 2023]
9. Avelino-Silva VI, Miyaji KT, Hunt PW, Huang Y, Simoes M, Lima SB, *et al*. **CD4/CD8 ratio and KT ratio predict yellow fever vaccine immunogenicity in HIV-infected patients.** *PLoS Negl Trop Dis* 2016; **10**:e0005219.
10. Pistone T, Verdiere C-H, Receveur M-C, Ezzedine K, Lafon M-E, Malvy D. **Immunogenicity and tolerability of yellow fever vaccination in 23 French HIV-infected patients.** *Curr HIV Res* 2010; **8**:461–466.
11. Colin de Verdiere N, Durier C, Samri A, Meiffredy V, Launay O, Matheron S, *et al*. **Immunogenicity and safety of yellow fever vaccine in HIV-1-infected patients.** *AIDS* 2018; **32**:2291–2299.
12. Veit O, Domingo C, Niedrig M, Staehelin C, Sonderegger B, Héquet D, *et al*. **Long-term immune response to yellow fever vaccination in human immunodeficiency virus (HIV)–infected individuals depends on HIV RNA suppression status: implications for vaccination schedule.** *Clin Infect Dis* 2018; **66**:1099–1108.

13. Martins R de M, Maia M de L de S, Santos EM dos, Cruz RL de S, dos Santos PRG, Carvalho SMD, *et al*. **Yellow fever vaccine postmarketing surveillance in Brazil.** *Procedia Vaccinol* 2010; **2**:178–183.
14. Sidibe M, Yactayo S, Kalle A, Sall AA, Sow S, Ndoutabe M, *et al*. **Immunogenicity and safety of yellow fever vaccine among 115 HIV-infected patients after a preventive immunisation campaign in Mali.** *Trans R Soc Trop Med Hyg* 2012; **106**:437–444.
15. Kengsakul K, Sathirapongsasuti K, Punyagupta S. **Fatal myeloencephalitis following yellow fever vaccination in a case with HIV infection.** *J Med Assoc Thail Chotmaihet Thangphaet* 2002; **85**:131–134.
16. Bio-Manguinhos (Fiocruz). Vacina de Febre Amarela (Atenuada). Bula. Brasília, Anvisa, 2015.
17. Abramson JH. **WINPEPI updated: computer programs for epidemiologists, and their teaching potential.** *Epidemiol Perspect Innov EPI* 2011; **8**:1.
18. Simões M, Camacho LAB, Yamamura AMY, Miranda EH, Cajaraville ACRA, da Silva Freire M. **Evaluation of accuracy and reliability of the plaque reduction neutralization test (micro-PRNT) in detection of yellow fever virus antibodies.** *Biologicals* 2012; **40**:399–404.
19. Reis LR, Costa-Rocha IA da, Campi-Azevedo AC, Peruhype-Magalhães V, Coelho-dos-Reis JG, Costa-Pereira C, *et al*. **Exploratory study of humoral and cellular immunity to 17DD Yellow Fever vaccination in children and adults residents of areas without circulation of Yellow Fever Virus.** *Vaccine* 2022; **40**:798–810.
20. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. https://rsc.niaid.nih.gov/sites/default/files/daids-ae-grading-table-v2-nov2014.pdf [Accessed 9 August 2022]
21. Trindade GF, Marchevsky RS, Fillipis AMB de, Nogueira RMR, Bonaldo MC, Acero PC, *et al*. **Limited replication of yellow fever 17DD and 17D-Dengue recombinant viruses in rhesus monkeys.** *An Acad Bras Ciênc* 2008; **80**:311–321.
22. Tavares da Silva Fernandes A, Moreira SB, Gaspar LP, Simões M, Cajaraville AC, dos RA, Pereira RC, *et al*. **Safety and immunogenicity of 17DD attenuated yellow fever vaccine in howler monkeys (*Alouatta* spp.).** *J Med Primatol* 2021; **50**:36–45.
23. R Core Team. Vienna, Austria: R: a language and environment for statistical computing. R Foundation for Statistical Computing; 2022. Available at https://www.R-project.org/.
24. Avelino-Silva VI, Miyaji KT, Mathias A, Costa DA, de Carvalho Dias JZ, Lima SB, *et al*. **CD4/CD8 ratio predicts yellow fever vaccine-induced antibody titers in virologically suppressed HIV-infected patients.** *J Acquir Immune Defic Syndr* 2016; **71**:189–195.
25. Martin C, Domingo C, Bottieau E, Buonfrate D, De Wit S, Van Laethem Y, *et al*. **Immunogenicity and duration of protection after yellow fever vaccine in people living with human immunodeficiency virus: a systematic review.** *Clin Microbiol Infect* 2021; **27**:958–967.
26. Tonacio AC, do Nascimento Pedrosa T, Borba EF, Aikawa NE, Pasoto SG, Filho JCRF, *et al*. **Immunogenicity and safety of primary fractional-dose yellow fever vaccine in autoimmune rheumatic diseases.** *PLoS Negl Trop Dis* 2021; **15**:e0010002.
27. World Health Organization. Sixty-seventh World Health Assembly. Resolution WHA67.13, WHO, 2014. Available at: https://apps.who.int/gb/ebwha/pdf_files/WHA67-REC1/A67_2014_REC1-en.pdf#page=25 [Accessed 25 July 2022]
28. Shi X, Sims MD, Hanna MM, Xie M, Gulick PG, Zheng Y-H, *et al*. **Neutropenia during HIV infection: adverse consequences and remedies.** *Int Rev Immunol* 2014; **33**:511–536.
29. Muturi-Kioi V, Lewis D, Launay O, Leroux-Roels G, Anemona A, Loulergue P, *et al*. **Neutropenia as an adverse event following vaccination: results from randomized clinical trials in healthy adults and systematic review.** *PLoS One* 2016; **11**:e0157385.
30. Levine AM. **Neutropenia in human immunodeficiency virus infection: data from the women's interagency HIV study.** *Arch Intern Med* 2006; **166**:405–410.
31. Giannini EG, Testa R, Savarino V. **Liver enzyme alteration: a guide for clinicians.** *CMAJ Can Med Assoc J* 2005; **172**:367–379.
32. Malakouti M, Kataria A, Ali SK, Schenker S. **Elevated liver enzymes in asymptomatic patients – what should i do?** *J Clin Transl Hepatol* 2017; **5**:394–403.
33. Roukens AH, Soonawala D, Joosten SA, de Visser AW, Jiang X, Dirksen K, *et al*. **Elderly subjects have a delayed antibody response and prolonged viraemia following yellow fever vaccination: a prospective controlled cohort study.** *PLoS One* 2011; **6**:e27753.
34. Croce E, Hatz C, Jonker EF, Visser LG, Jaeger VK, Bühler S. **Safety of live vaccinations on immunosuppressive therapy in patients with immune-mediated inflammatory diseases, solid organ transplantation or after bone-marrow transplantation – a systematic review of randomized trials, observational studies and case reports.** *Vaccine* 2017; **35**:1216–1226.
35. da Silva M, da PC, Bertani GR, Gonzales Gil LHV, Magalhães MCF, Cordeiro MT, Marques ETA, *et al*. **Description of a prospective 17DD yellow fever vaccine cohort in Recife, Brazil.** *Am J Trop Med Hyg* 2011; **85**:739–747.
36. Pereira GFM, Sabidó M, Caruso A, Benzaken AS. **Decline in reported AIDS cases in Brazil after implementation of the test and treat initiative.** *BMC Infect Dis* 2019; **19**:579.
37. Blanco JR, Alejos B, Moreno S. **Impact of dolutegravir and efavirenz on immune recovery markers: results from a randomized clinical trial.** *Clin Microbiol Infect* 2018; **24**:900–907.
38. Souza NCS e, Félix AC, de Paula AV, Levi JE, Pannuti CS, Romano CM. **Evaluation of serological cross-reactivity between yellow fever and other flaviviruses.** *Int J Infect Dis* 2019; **81**:4–5.
39. OPAS. Alerta epidemiológico Febre amarela. Sumário da situação. 31 de agosto de 2022. 2022-august-phe-epidemiological-alert-yellow-fever-port.pdf. [Accessed 24 September 2022]