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Prevalence, Clinical Presentation, and SARS CoV-2 Seroreactivity among HIV infected Adolescents and Youth in Miami

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Abstract

Background: Data on the frequency and associated co-morbidity of COVID-19 in HIV infected pediatric patients is limited.

Methods: Sixty-four HIV-1 infected adolescents/youth were enrolled in Miami into a prospective, observational study of the prevalence of COVID. Participants were screened at entry via PCR and for SARS CoV-2 specific antibodies using a lateral flow based immunochromatographic rapid test and a SARS CoV-2 Receptor Binding Domain of Spike protein EIA.

Participants positive by PCR or serology were followed up at 1, 3, and 12 months and longitudinal changes in their IgG and IgM titers were assessed.

Results: HIV+ adolescents/ youth had higher a COVID seroprevalence (25%, N=16 out of 64) when compared to the seroprevalence reported in a healthy population in Florida during the same period (August-December 2020) based upon data from the Florida Department of Health and the NIH. Two participants were positive by PCR and antibody while 14 were positive for antibody only. One participant had temporary anosmia and ageusia; the remaining 15 were asymptomatic suggesting that most had been infected prior to enrollment. By EIA, there was a significant decline in IgG titer by the 3-month follow-up visit in 11 of the 14 SARS CoV-2 positive HIV+ adolescents followed longitudinally. All 12 seen at 12 months were IgG positive while 5 of were also SARS CoV-2 IgM+. Eight had been vaccinated while 4 experienced asymptomatic reinfection.

Conclusions: The seroprevalence of SARS CoV-2 in HIV+ youth was higher than expected and the majority had asymptomatic infection. While SARS CoV-2 titers declined in many participants within 3 months, these same patients manifested brisk increases in IgG and IgM responses at 12 months' post-entry following vaccination and asymptomatic reinfection.

Keywords: HIV, SARS CoV-2, COVID prevalence and antibody longevity, longitudinal variation in COVID antibodies in HIV infected youth.

Introduction

Since the beginning of the Global COVID-19 pandemic, more than 337 million people have been infected with close to 5.5 million deaths. In the US alone, there have been more than 69 million cases and more than 860,000 deaths. Due to the vulnerability of their immune system, data on the frequency and associated co-morbidity of COVID in HIV infected populations is of utmost importance. HIV-1 infection has been considered a risk factor for progressive COVID disease [1].

Florida's Miami-Dade County (MDC) has been severely impacted by the combined global pandemics of SARS CoV-2 and HIV. MDC has the highest number of COVID cases of any county in the state and the highest incidence of HIV cases of any county in the United States [2,3].

There have been several reports focused on the infection rate of SARS CoV-2 and frequency of severe COVID-19 disease in populations of HIV-1 infected adults [1-6] but there is a dearth of data from HIV- infected children, adolescents, and youth. In this prospective study, we determined the prevalence and morbidity of SARS CoV-2 infection, and the durability of the SARS CoV-2 serological response in our clinic population of HIV- infected adolescents being seen at the Pediatric HIV Primary Care and the Adolescent Medicine Clinics affiliated with the University of Miami Miller School of Medicine.

Methods

Study Design

We performed a Prospective, Observational Study which recruited participants from the clinic populations of HIV-1 infected children, adolescents, and youth who receive their primary HIV care from either the Pediatric Special Immunology Clinic or the Adolescent HIV Care Clinic in the Batchelor Children's Research Institute at the University of Miami Miller School of Medicine(UMMSOM). All participants were screened for any history via a self-administered questionnaire or evidence on physical examination of symptomatic COVID disease and were asked about any COVID contacts. Comparative background SARS CoV-2 New Case Positivity rate (based upon the results of both PCR and antigen testing) and seroprevalence data was derived from the Florida Department of Health COVID Dashboard Website which reported COVID seroprevalence based upon testing of 1800 blood samples drawn in Commercial Laboratories in South Florida for non-COVID related reasons. Between April 6 and 10th, 2020 (when the samples were collected), the overall seroprevalence was 1.8%(95% C.I. 1.0-3.2) with the following age group specific seroprevalences of 2.4% (ages 0-18) and 0.9%(ages 19-49).

Additional comparative seroprevalence data was also drawn from the National Institutes of Health COVID SeroHub [3].

All participants were screened for active SARS CoV-2 infection via nasal-pharyngeal (NP) swab based PCR (Altona Diagnostics) and for SARS CoV-2 specific antibodies using both Laminar Flow and an in-house EIA. Participants positive by either PCR or serology were follow up at [1, 3] and 12 months post entry while negative participants had a second follow-up visit at 3 months.

Lateral flow based immunochromatographic rapid test

Presence of IgG and/or IgM against SARS-CoV2 was evaluated by rapid qualitative lateral flow immune assay (Confirm Biosciences) following manufacturer instructions.

ELISA assay

For EIA, we tested serum from participants to identify the presence of SARS-CoV2 specific IgG and IgM. SARS-CoV-2 Receptor Binding Domain (RBD) protein was obtained courtesy of Dr. Scott Boyd (Stanford). 96-well Corning Costar assay plates (clear, flat bottom, high binding, Ref# 9018, VWR, cat# 29442-32) were coated with 2pg/mL SARS-CoV-2 RBD overnight at 4°C. The EIA protocol generally followed that of the

Krammer laboratory, which previously demonstrated specificity [7,8]. Plates were blocked the next day with 3% milk (Skim Milk Powder American Bio, AB10109-01000) in Phosphate Buffered Saline (PBS) containing 0.1% Tween-20 (Sigma, P2287-100 ml) for 1 hour at room temperature. Serum was then added to the plates and incubated for 1 hour at 37°C. Prior to addition to the plates, serum was heat inactivated at 56°C for 60 minutes and diluted in 1% milk in 0.1% PBS-Tween 20 at a 1:100 dilutions. Plates were washed 3 times with 0.1% PBS-Tween 20. Secondary antibodies were diluted in 1% milk in 0.1% Tween-20 and incubated for 1 hour at room temperature. For IgG, anti-human IgG peroxidase antibody produced in goat (ThermoFisher, 62-8420) was used at a 1:6000 dilutions. For IgM, anti-human IgM peroxidase antibody produced in goat (Southern Biotech, 2020-05) was used at a 1: 10,000 dilutions. Plates were washed 3 times with 0.1% PBS-Tween 20 and then developed with TMB Substrate Kit (ThermoScientific, N301) for 12 minutes at room temperature in the dark. The reaction was stopped with 0.16M sulfuric aci (ThermoFisher, N600). Plates were read on an ELx808 Absorbance Microplate Reader (Biotek) at 450 nm using Gen5 Software, and ODs were background subtracted. A positive control standard was created by pooling serum from 3 convalescing COVID-19 patients. A positive control standard was run on each plate and was used to calculate titers (relative units) for all samples using non-linear regression interpolations, done to quantify the amount of anti-RBD IgG and anti-RBD IgM present in each specimen. Titers were plotted for each specimen and compared to COVID-19 negative specimens.

Statistical Analysis

Longitudinal analyses of ELISA results were performed using a Wilcoxon paired test. Demographics were explored for statistically significant differences using either a Wilcoxon rank sum test or a Fisher's exact test, depending on whether the measure was continuous or categorical, respectively. Results were considered significant with a p-value50.05. Analyses were performed using GraphPad Prism 9.1.2.

Results

Demographics

Ninety HIV-1 infected participants were recruited from the Pediatric Special Immunology Clinic or the Adolescent HIV Clinic in the Batchelor Children's Research Institute, at the University of Miami Miller School of Medicine. Sixty-four HIV-1 infected patients were enrolled between August 12, 2020, and December 17, 2020. Twenty-six patients declined participation. Table 1 describes the demographics of the study cohort by antibody reactivity. A comparison of the demographics of the enrolled participants to the entire Pediatric Special Immunology Clinic population noted no difference in race or ethnicity, viral loads, and median age, although the interquartile range of the median ages was narrower for the study participants (study: age 20.9 [19.2, 22.8] vs. clinic age: 20 [14,22]). There was a differences in mode of acquisition between the study population and the clinic population. While the clinic population had a high proportion of perinatally infected patients, our sample included more sexually acquired infections. Other modes of acquisition were roughly equal (Blood transfusion: 1.9% [study] vs. 1.0% [clinic pop.], Perinatal: 37.0% [study] vs. 81.6% [clinic pop.], Sexual Acquisition: 57.4% [study] vs. 15.5% [clinic pop.], and Not Specified 3.7 [study] vs. 1.9% [clinic pop.].

Sixteen participants tested positive for COVID but 2 participants withdrew from the study following the first visit; one by request, the second following incarceration. Of the remaining 14; 3 missed the 1month visit, while 2 missed the 3-month visit. Twelve participants were seen at 12 months' post-entry. Seven of these 12 were seen at all 4 time points with a median of 3 study visits for the group.

Table:1 Demographics of the Study Population by SARS CoV-2 Antibody Reactivity

	SARS Ab-	SARS Ab +	p. Overall
	N=48	*N=16*	
Age	20.6 (3.92)	20.1 (2.99)	0.655
Race			1
African American	37 (78.7%)	11 (84.6%)	
White	10 (21.3%)	2 (15.4%)	
'Missing'	1	3	
Ethnicity:			1. 0 0 0
Hispanic or Latino	9 (26.5%)	3 (30.0%)	
Not Hispanic or Latino	25 (73.5%)	7 (70.0%)	
'Missing'	14	6	
CD4.	28.5 (10.8)	31.8 (9.84)	0.285
Absolute.CD4	600 (380)	615 (303)	0.875
Viral Load:			1
<200	22 (45.8%)	7 (43.8%)	
200-1000	14 (29.2%)	5 (31.2%)	
>1000	10 (20.8%)	3 (18.8%)	
'Missing'	2 (4.17%)	1 (6.25%)	
Mode of HIV Infection:			0.38
Blood Transfusion	1 (2.13%)	0 (0.00%)	
Perinatally	18 (38.3%)	8 (61.5%)	
Sexual Acquisition	28 (59.6%)	5 (38.5%)	
'Missing'	1	3	
Current HAART			0.82
Intergrase Inhibitor regimen	34(81.0%)	11(78.6%)	
NNRTI regimen	2(4.76%)	2(14.3%)	
Proteus Inhibitor regimen	3(7.1%)	1(7.1%)	
Gender at Birth			0.342
Female	19(39.6%)	3(21.4%0	
Male	29(60.4%)	11(78.6%)	
Missing	0	2	

HIV+ pediatric patients had a high seroprevalence of SARS-Cov-2 infection.

Sixteen of 64 participants were positive in one or both tests; for an overall SARS Cov-2 seroprevalence of 25%; a seroprevalence much higher that the New Case Positivity Rate for 158 Florida (Florida DOH) that in the same period ranged between 15% and 5% (Figure 1A). While *a* number of factors may differ between the average Floridian and a member of our cohort; both groups represent convenience samples drawn from the general population. When compared with data from the CDC from September, 2020 [9], it was higher than the estimated infection induced seroprevalence in the South (6.0% [95%C.I. 5.6-6.5]).

We observed a decline in prevalence with time during the second half of the enrollment period (Figure 1 B). Despite this decline, the prevalence of COVID remained higher when compared to the New Case Positivity Rate for Florida (Florida DOH) for the same period. In the general population on August 12, 2020, this rate was 12.1%; by September 17, 2020, the rate had dropped to 4.5%. The initial rate in our cohort was 38% (11 out of 29) and by September 17, 2020 was 15% (5 out of 33). No differences in age, race, ethnicity, CD4 counts, mode of HIV acquisition or antiretroviral therapy were observed between the COVID infected and uninfected participants in our HIV+ cohort (Table 1). There was also no significant difference between either the Gender at Birth or Gender Identified (latter data not shown).

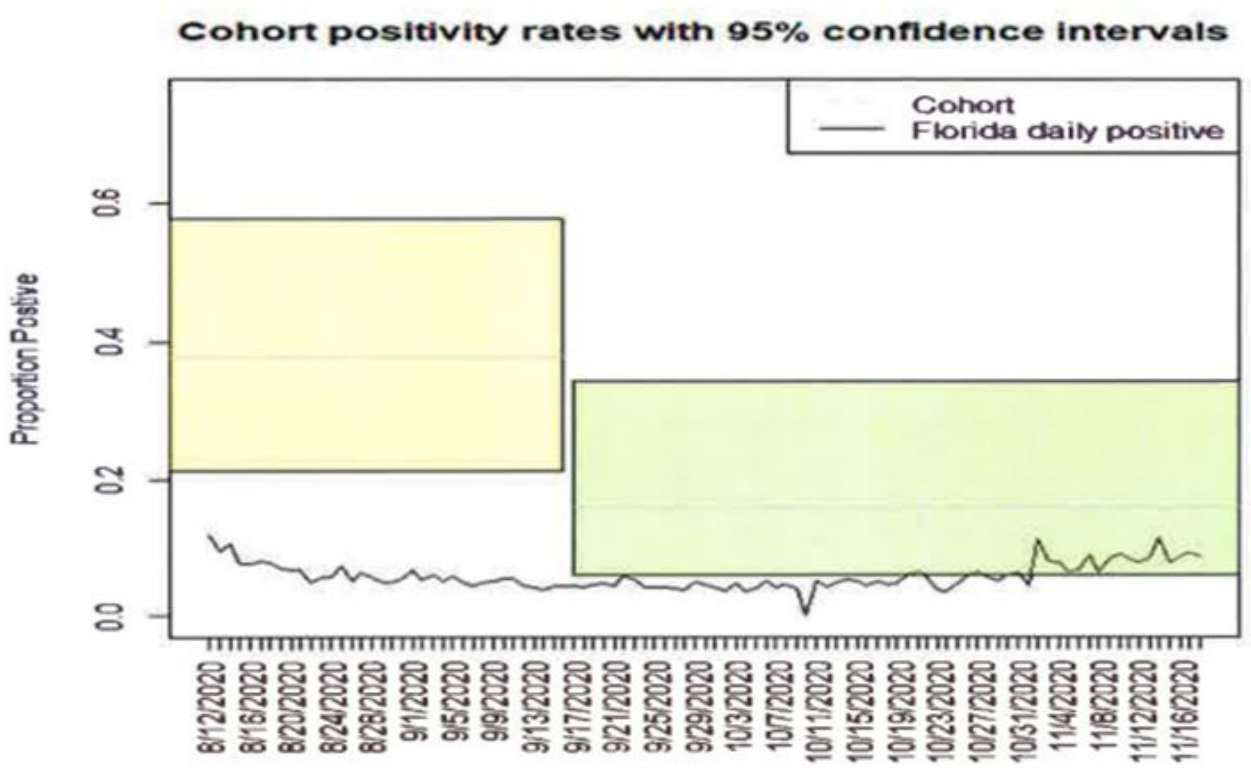

Figure 1: SARS-Cov2 positivity rate in the HIV+ Pediatric Cohort

Cohort positivity rates with 95% Confidence Intervals The 95% confidence interval was divided into 2 periods with the break occurring after the first 50% of patients were recruited. The daily positivity rate for Florida is overlaid on the graph. DOH).

Asymptomatic SARS-Cov-2 infection in HIV+ pediatric patients

Two of the 16 COVID+ HIV+ participants tested positive on both PCR and antibody testing while the remaining 14 tested positive on lateral flow antibody only. All 16 COVID+ HIV participants were IgG+ on the Laminar flow assay but only one was positive for both IgG and IgM.

To confirm the initial lateral flow results at entry, we utilized an in-house developed ELISA [7, 8] for antibodies against the SARS-Cov-2 RBD spike protein on these same participants. The agreement between the Laminar flow and the ELISA assays was almost 100% for IgG, with 15 out of 16 IgG+ by lateral flow, confirmed positive by ELISA. The remaining participant had borderline IgG reactivity at entry but was confirmed positive when tested at later timepoints by ELISA. For IgM, we confirmed the result for the positive participant, but we also found 4 additional participants that tested positive for 1gM against the RBD spike protein. These results suggest that our cohort was primarily infected with COVID-19 sometime prior to enrollment. At entry, none of the patients reported respiratory signs or symptoms. Only one SARS CoV-2 positive patient reported any symptoms; loss of the sense of smell and/or taste; suggesting that the majority had asymptomatic COVID infection:

Longitudinal variation in the COVID antibodies in HIV

COVID+ HIV participants were followed up at 1, 3, and 12 months to gather longitudinal information on the SARS CoV-2 antibodies. Only individuals with entry and at least one follow-up visit were included in the analysis thus 14 out of the 16 COVID+ HIV were selected.

We did not observe any statistical difference in IgG and IgM titers between the first three time points in our cohort (Figure 2). However, 2 different trends could be ascertained. One sub group had a higher IgG titer at T2 compared to TO while a second subgroup showed a decline in the level of COVID-specific antibodies within 3 months (Figure 2.A. and 2.C).We hypothesized that our cohort was composed of individuals at different stages post infection. We then analyzed the Covid+ HIV+ participants by dividing them into 2 groups; those who within the first three months' post entry had either: 1) an increase of IgG titer over the entry time point or 2) individuals with a decrease in IgG titer compared to their entry timepoint (Figure 2.A.2.C). Only 3 of the 14 COVID+ HIV individuals showed a longitudinal increase in the IgG titer against COVID. In line with our hypothesis, the only PCR + individual positive at entry was among these 3. For all 3 individuals, the IgG titer showed a stable increase at both the 1 and 3 months follow up timepoints. When

we looked at the IgM titer in these 3 subjects, we found that only the PCR+ individual had a positive IgM titer which peaked at 1 month and then declined by the 3 months follow-up visit (Figure 2.B). We then studied the group that showed a decline in IgG titer (N=11). We found a significant decline in both the IgG and IgM titers in this group. Furthermore, by the 1-month follow-up there were no additional IgM positive individuals. Despite the significant decline, the IgG titer remained detectable for all but 1 participant (Figure 2.C.).

Twelve participants were seen at 12 months' post entry. Curiously, all 12 had high IgG titers and 5 were also IgM+. All 5 were IgM- at the 3-month visit. Eight had been vaccinated for SARsCoV-2 (5 received Moderna, 2 Pfizer; 1 unknown) a median of 98.5 days (52-156) between the last vaccination and the 12-month visit. Seven patients (6 vaccinated, 1 not vaccinated) demonstrated extremely high IgG ELISA titers (>1: 84,000) which in some was up to >80 fold greater than the titer at the 3-month visit. Four of 5 IgM+ patients had been vaccinated but one had not. This one patient and the other 3 nonvaccinated patients who showed increase in Ab had likely undergone asymptomatic

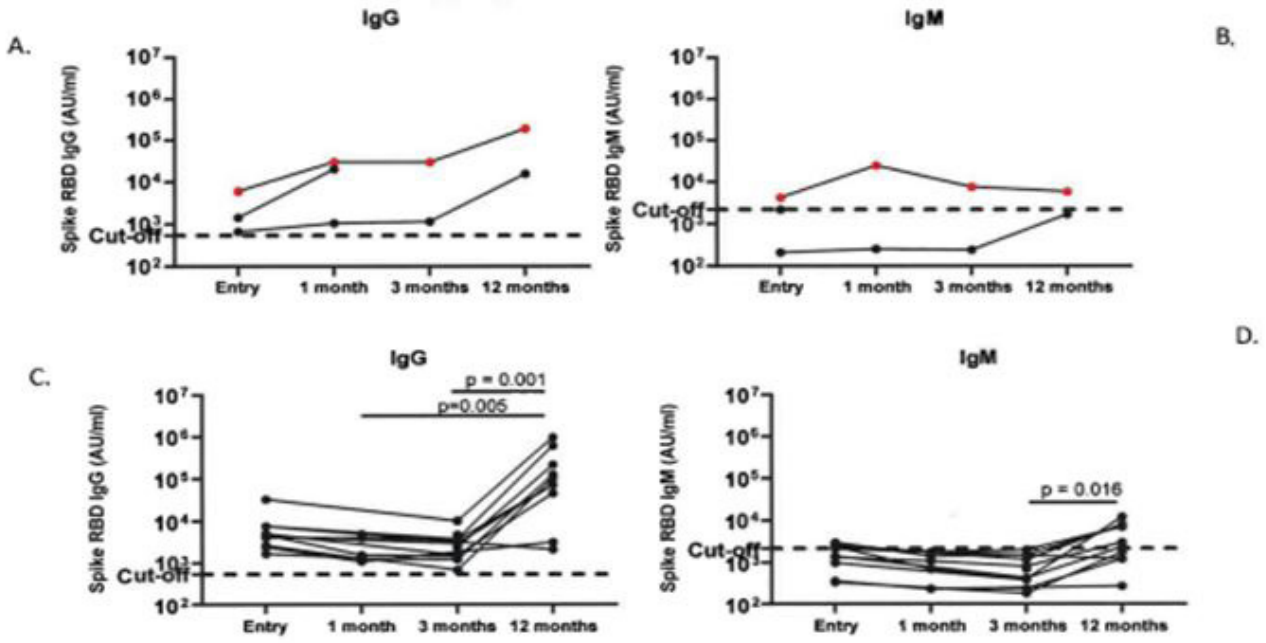

Figure 2: Evaluation of the anti-RBD response at Entry and 1, 3, and 12 months' follow-up visits by ELISA in the HIV+ adolescents. Participants showing an increase in IgG titer at the 3-month follow-up (2.A.). Participants showing decrease in IgG titer at the 3-month follow-up (2.C.) with the corresponding changes in for the IgM titers in each respective subgroup (2.B., and 2.D) The red dots in 2.A. and 2.B. designate that one participant that was both IgM and PCR -F. Cut-Off was calculated based on Covid-19 negative specimens + 3 times the Standard Deviation. P value was calculated by Wilcoxon Paired Test.

reinfection.

Discussion

In this prospective pilot study, we reported that the seroprevalence of SARS CoV-2 in HIV+ adolescents and youth, was higher than most reported rates from testing of the general population. Studies on seroprevalence and antibodies kinetics in HIV negative SARS-Cov-2 infected adults showed that IgM titer increases in the first weeks after infections reaching a peak around 3 weeks but it seroreverts around 6 weeks after infection. In contrast, IgG titer rises but it remains positive up to 3 months after infections [9, 10]. We observed a significant loss of anti-SARS-CoV-2 IgG antibodies within 3 months in the study participants that warrant further characterization to understand whether this is a physiological decline of antibodies as showed in HIV negative individuals [11] or if it is symptomatic of a more profound defect in the generation of long-lasting B cell response. HIV infection has been associated with a higher risk of severe outcomes from respiratory infections, including seasonal influenza. Indeed, people living with HIV at any stage of infection are considered a clinical risk group relative to seasonal influenza vaccination guidance. Despite a dearth of data as yet, this seems to be the case for COVID-19 as well. In fact, a large study in South Africa [5] found COVID-19 mortality risk among people living with HIV to be double compared to the risk of those without HIV. Another study from Spain found high prevalence of critical illness among HIV-infected patients with COVID-19, although there was no HIV negative comparison group [6]. Finally, another very large and extensive study in England on 27,480 HIV+ and 17,255,425 HIV negative individuals also found out the risk of death by COVID-19 in HIV+ individuals to be 2 times higher compared to HIV negative [1]. Despite the apparent increased risk, the seroprevalence of SARS-Cov2 infection in HIV+ patients is still not fully quantified with the presence of potential asymptomatic infections being one of the major confounding factors. In this study, we aimed to evaluate the seroprevalence of SARS CoV-2 in HIV infected individuals from a pediatric population. In order to have a comprehensive evaluation of the seroprevalence and to account for asymptomatic infections, we screened a cohort of HIV+ infected patients from the University of Miami while they were undergoing their routine clinic visits. We found that the seroprevalence in our cohort was much higher than expected based on seroprevalence data reported for the overall Miami Dade County by the Florida Department of Health [2]. However, the majority of the SARS-CoV-2+ participants in our cohort showed a non-active infection (PCR negative but antibodies positive) and they were asymptomatic based on the results from a self-administered questionnaire. We concluded that the fact that the actual rate of infections observed during this study was higher than expected was likely due to the fact that we also screened for asymptomatic infections. This result confirms a greater exposure of this

at-risk category to the virus than previously anticipated. Since we do not have a non-HIV control group, we cannot conclude whether HIV patients have a higher or lower seroprevalence compared to HIV uninfected participants. Indeed, this question remains unanswered and in this regard studies in adults have shown conflicting results. Studies in adults evaluating the seroprevalence of SARS CoV-2 in HIV+ and HIV negative individuals not based on hospitalization found that the seroprevalence is not increased in HIV+. Another study instead found a lower seroprevalence of COVID-19 among people living with HIV [12,13].

While we tested for active and inactive infection, we drew conclusions only about the rate of exposure and not of active infection. In this study, it was appropriate to compare the prevalence of infection in the study population with the data from the Florida DOH, and the NIH COVID-19 SeraHub. since we are only looking at them as rolling averages of exposure. In comparing the two we also split our analysis between two eras of recruitment, this was based on the date where 50% of the patients had been enrolled.

This exploratory analysis was conducted because rates had started to come down during this second era and the first half was pulling the overall average up. The rate of exposure is represented both ways for a more granular look at the rate over time compared to the overall Florida rate.

Another critical point that requires attention, especially for HIV chronically infected individuals, is the generation of fully functional and long-lasting antibodies against SARS CoV-2. In fact, studies in influenza have shown how the HIV+ individuals generate a response of lower magnitude compared to uninfected individuals [14-17]. However, studies on SARS-CoV-2 showed conflicting results, with one study showing that IgG concentrations as well as pseudo-virus neutralizing antibody titers were lower among people living with HIV compared with those without HIV [10]. However, another study observed that the titer of antibodies against the nucleocapsid of SARS CoV-2 was similar in the HIV+ and HIV negative groups [18]. In our study, we focused on the aspect of persistence of the anti-SARS-CoV-2 IgG in these participants. We observed that the majority of HIV+ individuals showed a significant decline of anti-SARS-CoV-2 IgG within 3 months' post-entry. In this study, HIV+ individuals experienced a significant decline in antibody titer and suggests that these individuals could lose their protection against the virus. Another important point that we were unable to address due to the nature of the project (prospective pilot study) is whether this loss of antibodies is directly related to the immune defects present in HIV+ participants, as for influenza, or it is the natural course of the infection [9,19-21]. That all 12 participants had markedly higher IgG titers at 12 months' post entry and 5 were IgM+ may be explained by the fact that 8 had been vaccinated while 4 had likely experienced reinfection suggesting continuing active circulation of the virus in Miami. People living with HIV were included the initial SARS CoV-2 vaccine clinical trials, but thorough safety data specific to the HIV infected population in these studies is not available as yet [22]. While the absence of any serious COVID vaccine side effects in these studies is reassuring, the number of participants was relatively small and the question of safety of the vaccines in HIV patients is still pending. The high prevalence of COVID infection in our clinics suggests that HIV-infected adolescents and youth over age 12 who are on HAART and clinically stable should be offered vaccination against COVID once issues of safety and efficacy are adequately addressed.

Overall, our pilot study revealed a high seroprevalence of COVID-19 in a cohort of adolescents and youth living with HIV in Miami. Future research is warranted to determine the specific mechanism which drives this higher rate. We also showed a significant decline of anti-SARS- CoV-2 IgG in these individuals indicating a waning antibody response that warrant additional studies investigating the role that chronic HIV infection may have played in this decline.

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