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February 23, 2024

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Incidence of and Risk Factors of Non-AIDS Comorbidities Development Following SARS-CoV-2 Infection in People Living with HIV in Atlanta, Georgia

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Advisors: Cecile Lahiri, MD, MSc; Caitlin Moran MD, MSc; Minh Nguyen MD, MPH

An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science in Clinical Research
2024

Abstract

Incidence of and Risk Factors for Non-AIDS Comorbidities Following SARS-CoV-2 Infection in People Living with HIV in Atlanta, Georgia

By: Cecilia A. Castellano

Since the start of 2020, coronavirus disease 2019 (COVID-19), a clinical syndrome caused by infection with the novel coronavirus, SARS-CoV-2, has been at the forefront of the minds of researchers and citizens of the world alike. This virus has disproportionately affected persons with underlying health conditions and those living at a lower socioeconomic status. People living with HIV (PLWH) are infected with SARS-CoV-2 at a higher rate than their seronegative counterparts. Recent research has indicated that persons who acquire COVID-19 are at risk for developing incident comorbidities after acute infection. Risk factors for and incidence of post-COVID-19 non-AIDS comorbidities (NACM) in PLWH specifically remain unknown. Among PLWH co-infected with SARS-CoV-2 cared for at the Ponce de Leon Center in Atlanta, GA between March 1, 2020, and September 30, 2022, we 1) investigated the incidence of post-COVID-19 NACM and 2) identified risk factors among PLWH associated with post-COVID-19 NACM. Among 3540 PLWH included, 261 had documented COVID-19 and 3279 did not have documented COVID-19, with similar median age, race, CD4+ cell count, and HIV viral load (VL) between the groups. We assessed 8 categories of non-AIDS comorbidities, including cardiometabolic disease, cardiovascular disease, chronic kidney disease, diabetes mellitus, hypertension, lung disease, neurologic disease, and psychiatric disease both as the overall burden (e.g, presence of any NACM) and separately (e.g., incidence of each individual NACM). COVID+ participants had a longer time to development of any NACM, with a shorter time to development of cardiometabolic disease, compared with the COVID- group. The COVID+ group also had a lower risk of developing any incident NACM. A subgroup analysis revealed that participants with more prevalent NACM are at greater risk for developing incident NACM compared to those with fewer pre-existing NACM. Across COVID groups, female PLWH had a greater annual risk of developing any NACM, compared to males in both COVID groups. Our study among PLWH at a single center highlights that the subset of women with both HIV and COVID-19 are at particularly high risk for incident NACM and also underscores the negative effects that the pandemic had even on persons uninfected with COVID-19.

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Acknowledgements

- Mentoring team: Dr. Cecile Lahiri, Dr. Caitlin Moran, Dr. Minh Nguyen
- CFAR Collaborators: Shirin Jabbarzadeh, Ying Sun, Vijay Ramaesh
- Thesis Advisor: Dr. Jordan Kempker
- Thesis Reader: Dr. Lauren Collins
- MSCR course professors
- MSCR classmates
- Family and friends who have supported and inspired me over the years!
- This work is supported in part by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR002378 and TL1TR002382; AOA Carolyn L. Kuckein Student Research Fellowship, and the Center for AIDS Research at Emory University (P30AI050409).

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Introduction

Background and Study Inspiration

As of February 2024, more than 700 million people worldwide have had the novel coronavirus SARS-CoV-2 infection, which causes COVID-19 disease, and more than 7 million have died from the disease and its sequelae.[1] In addition to beginning to better understand the acute problems, our knowledge of post-infectious complications is also evolving. For instance, regardless of initial severity, research suggests a link between COVID-19 and the incidence of new-onset (< 6 months from acute infection) heart disease and diabetes.[2,3] The presence of underlying comorbidities has also been shown to increase the risk of subsequent complications after COVID-19.[4] Though recent data support that comorbidities occur after COVID-19, there is not a current consensus regarding the types and patterns of the post-acute sequelae and comorbidities, the individual burden of post-COVID-19 comorbidities, or impact on health systems in general.[5] Documented incident comorbidities following COVID-19 include cerebrovascular accident, chronic kidney disease, liver disease, neurocognitive disease, psychiatric complications, and range from hair loss to thromboembolism, including nearly every organ system.[6] Especially at risk for both COVID-19 and post-COVID-19 complications are persons with immunosuppression, including people living with HIV (PLWH).[7] A recent investigation showed that PLWH were almost twice as likely to test positive for SARS-CoV-2 compared with HIV seronegative individuals despite similar testing rates and mitigation practices in both populations.[8]

Non-AIDS Comorbidities (NACM) in People Living with HIV (PLWH)

While antiretroviral therapy (ART) has extended the life expectancy of PLWH, morbidity and mortality among PLWH is increasingly due to aging-related non-AIDS comorbidities (NACM) as opposed to AIDS-related complications. Further, NACM among PLWH occur at higher prevalence and earlier onset (up to decade sooner) compared with HIV-seronegative individuals.[9]

Although PLWH are at risk of the same aging-related complications as HIV seronegative individuals, PLWH have a higher prevalence of these comorbidities including hypertension, hypertriglyceridemia, and low bone mineral density.[10] PLWH are at particular risk of mortality due to comorbidity with diabetes mellitus, cardiovascular disease, non-AIDS defining malignancies, and osteoporosis.[11]

Chronic Post-COVID-19 Complications

The proposed mechanism behind development of post-viral comorbidities in the setting of COVID-19 is a combination of host factors and viral effects. A study of patients at the US Department of Veterans Affairs assessed comorbidities that developed between 30 days to 6 months after COVID-19 and observed that the variety of clinical comorbidities included every organ system.[12] In a separate study of the general population, factors associated with increased risk for developing post-COVID-19 complications included the presence of pre-existing comorbidities, COVID-19 infection requiring hospitalization, presence of persistent symptoms, a higher BMI and female sex.[13] In addition, studies have shown that having more severe COVID-19 disease, defined as admission to an intensive care unit or need for mechanical ventilation, predicted increased likelihood of developing comorbidities after the initial infection.[14]

Endothelial damage is a key component in the pathogenesis of COVID-19 and endothelial cell disruption can alter vessel integrity, promote a hypercoagulable state, and facilitate lymphocyte infiltration of the vasculature.[15] It is unknown whether patients with a comorbidity like diabetes or hypertension, which is associated with pre-existing endothelial damage, are pre-disposed to developing comorbidities after acute COVID-19. It is also unclear whether the type of incident post-COVID-19 comorbidity may be related to the type of pre-existing comorbidity. The patient characteristics that are more prevalent in severe disease (such as older age, many pre-existing conditions, need for hospitalization) have also been found to be more prevalent in patients with post-COVID-19

comorbidities.[16, 17] It is unknown if these characteristics are independent or dependent on comorbidities present prior to COVID-19, and whether these patterns may also be seen in PLWH.

COVID-19 in People Living with HIV

The incidence of severe COVID-19 is higher in males than in females; similarly, the incidence of HIV infection in the United States is also higher in males than in females.[18] Women living with HIV, however, have been shown to have an overall higher burden of AIDs-related comorbidities compared to men with HIV.[19] A study of sex differences in susceptibility to and severity of COVID-19 found that overall pre-existing comorbidities were higher in males, and after adjusting for demographic variables such as age, self-reported race, ethnicity, body mass index (BMI), and others, males had a higher likelihood of SARS-CoV-2 positivity as compared to females.[20]

In a study of PLWH who were admitted with COVID-19 to three hospitals in Atlanta, half of the patients had at least five comorbidities at the time of initial COVID-19 diagnosis, and hypertension (70%), dyslipidemia (60%), and diabetes (45%) were most prevalent.[16] This study suggests that certain comorbid conditions may predispose PLWH to COVID-19. It is unknown if these comorbidities in PLWH predict additional incident comorbidities following COVID-19.

In addition, it appears as though PLWH may be uniquely at risk of SARS-CoV-2 infection. In a study from the MACS/WIHS Combined Cohort Study, PLWH were almost twice as likely to test positive for SARS-CoV-2 compared with seronegative counterparts despite similar testing rates and mitigation practices.[8] Finally, racial and ethnic disparities in the United States and elsewhere contribute to the burden of COVID-19, and may be exacerbated among PLWH as both HIV and COVID-19 disproportionately affect minority communities.[21, 22] The combined impact among PLWH of susceptibility to infection with SARS-CoV-2 and underlying comorbidities may make this population particularly at risk for developing incident comorbidities following COVID-19.

Previous work from Dr. Lahiri and colleagues investigated the prevalence of COVID-19 symptoms and subsequent comorbidities in PLWH. This work revealed that the types of COVID-19

symptoms were similar in PLWH and seronegative controls, but PLWH had increased incidence of SARS-CoV-2 infection.[8] Their group leveraged the Emory Centers for AIDS Research (CFAR) data registry that was also used in this study to examine baseline comorbidities in PLWH who had COVID-19. Their work demonstrated that in a cohort of PLWH across a public safety-net health system and a Veterans Affairs Medical Center in Atlanta, Georgia, age and non-AIDS comorbidities were associated with hospitalization for COVID-19 in a dose dependent fashion.[23] There is well-documented evidence of the increased risk for non-AIDS comorbidities in PLWH when compared to people living without HIV and independent of COVID-19[10], but it is unclear how patient demographics and existing comorbidities may also predispose PLWH to developing post-COVID-19 NACM specifically. Building on this work by using the same robust longitudinal multisite data registry, we determined the rate of, and risk factors for, incident comorbidities among PLWH following COVID-19.

Study Aims

The impact of colliding viral infections (HIV and SARS-CoV-2) on the development of post-COVID-19 NACM is unknown and highlights an opportunity for clinical intervention such as closer monitoring and more intense comorbidity screening. We assessed the risk for NACM in adult PLWH with versus without a previous COVID-19 diagnosis who received medical treatment at a single center in the Southeastern United States.

AIM 1. Assess the annual incidence of NACM and the time to development of any of 8 total assessed incident NACM and to each of 8 specific NACM among PLWH following COVID-19.

- Hypothesis: COVID + PLWH have a greater annual incidence of NACM and have a shorter time to development of each NACM than COVID- PLWH.

AIM 2. Assess clinical characteristics associated with an increased risk of developing any incident NACM, and each of the 8 NACM studied.

- Hypothesis: Females versus males and older versus younger PLWH are at greater risk for any NACM development.

Methods

Study Design

This study was a secondary analysis of longitudinal data collected via the CFAR HIV Disease Registry within the Grady Health System. The CFAR program began at the National Institutes of Health with the purpose of sharing and coordinating AIDS-related research projects. The Emory CFAR includes data from three sites in Atlanta and contains patient data from the year 2000 on over 11,000 unique patients.[24] We analyzed data collected among PLWH who were receiving medical care at the Grady Ponce de Leon Center in Atlanta, Georgia from Match 1, 2020, the start of the COVID-19 pandemic, to September 30, 2022. The Grady Ponce de Leon Center is one of the largest free-standing HIV clinics in the U.S., providing comprehensive ambulatory HIV/AIDS care for over 6,000 PLWH (mean age 46 years, 83% Black race, 27% women). The Emory CFAR HIV Disease Registry captures real-time electronic health record (EHR) data on clinical history, including laboratory elements such as $CD4^+$ cell counts and HIV viral load, medication history, and co-infection status of PLWH cared for at an Emory-affiliated HIV clinic, of which Grady Ponce is included. Two groups were compared: those who did and did not have documented SARS-CoV-2 infection between March 1, 2020, and September 30, 2021, with the outcome event of interest being new diagnosis of a non-AIDS comorbidity.

Sample Size

A prior study among insured patients living with and without HIV at medical centers of Kaiser Permanente across the United States, with 87% male, a mean age of 41 years, and 25.1% non-Hispanic Black assessed incident comorbidities using 6 major aging-related conditions (chronic liver disease, chronic kidney disease, lung disease, diabetes, cancer, and cardiovascular disease) and found that rates of any comorbidity for PLWH across 16 years before the COVID-19 pandemic, from 2001 – 2016, was 10.0 per person-year (95% CI, 9.8-10.2).[25] Another study assessing incident comorbidity burden (of 10 total NACM assessed) among U.S. women living with HIV across the adult lifespan, using data from the

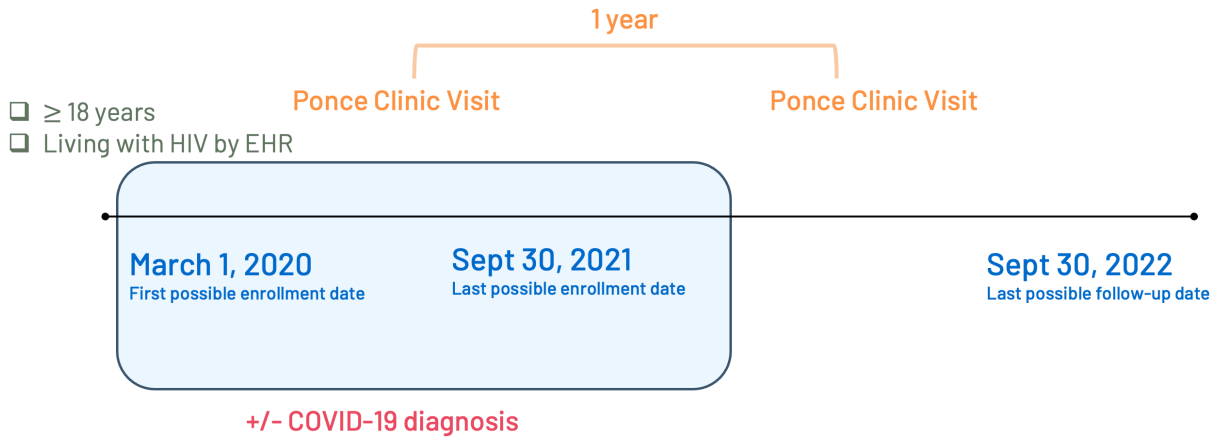
Women's Interagency HIV Study, found an incident rate of 21.0 comorbidities per person-year.[26] As the majority of participants in the CFAR registry database are men, we conservatively assumed that 12% of people in our cohort who were unexposed to COVID-19 would develop an incident comorbidity over 12 months. The incidence of comorbidity following COVID-19 disease is unclear, as most studies to date have focused on post-COVID chronic symptoms versus comorbidities specifically,[2, 3, 14, 27] and few studies have focused only on PLWH. Nonetheless, we conservatively assumed that 23% of people in our cohort exposed to COVID-19 would develop an incident comorbidity over 12 months. A sample size of 1216 (n=85 exposed and n=1131 unexposed) would provide 80% power to detect a risk/incidence ratio of 2.0 with 95% confidence (Appendix 1).[28, 29]

Study Population and Enrollment Criteria

Participants were PLWH ≥18 years of age who receive medical care at the Ponce de Leon Center in Atlanta, Georgia and who had at least one documented clinic visit between March 1, 2020 and September 30, 2021, and at least one additional visit within 12 months of that initial visit. Participants were followed for 365 days from index date – which is defined as either the time of a documented positive SARS-CoV-2 test (COVID+) or from the time of the earliest documented clinic visit (for participants who did not have documented COVID-19; COVID-) through September 30, 2022 at latest to evaluate for any new incident NACM (Figure 3). COVID-19 status was classified dichotomously as COVID+ or COVID-. For analysis of each of the 8 NACM individually, participants with that prevalent NACM were excluded (e.g. if pre-existing hypertension, was not included in the population for incidence calculations) but for any new incident NACM (as a combination of all 8 NACM), no participants were excluded based on prevalent NACM. Participants were considered to have prevalent NACM and NACM burden if they had a one of the 8 NACM of interest (Table 1).

PLWH cared for at the Grady Ponce de Leon Center who were under 18 years of age at their index date (not necessarily March 1, 2020) and those with no follow-up data during the study period were excluded. Participants with missing HIV status (by HIV antibody testing), sex, or age were also excluded

(Figure 3). Patients with a missing COVID-19 status were considered to not have contracted COVID-19 within the study period (i.e., were assigned as COVID-). Because asymptomatic people were not typically tested for COVID-19, particularly at the start of the pandemic when testing was less available, we chose not to select controls from people with documented negative COVID-19 tests.



EHR=electronic health record

Figure 1
Study Timeline, enrollment, and follow-up periods.

Exposure Variable

Cases of COVID-19 were determined by having a positive SARS-CoV-2 PCR or antigen test documented between March 1, 2020, and September 30, 2021. The group of patients without COVID-19 was selected by having no positive SARS-CoV-2 PCR, antigen, or antibody test AND no diagnosis of COVID-19 disease based on problem list diagnoses or International Classification of Diseases (ICD) version 10 (ICD10) codes during that period plus the 12 months of follow-up. Participants were classified as COVID+ or COVID- and were confirmed as living with HIV by laboratory tests (Appendix 2).

Non-AIDS Comorbidity Incidence

Incident NACM were determined using problem list and/or diagnoses ICD10 codes in the electronic health record. Incident NACM was defined as a comorbidity that was not listed in problem lists

or ICD10 codes within 12 months before index date, and that then appeared on problem lists or ICD10 codes at a clinic visit occurring > 30 days from and within 12 months of index date. To distinguish post-COVID-19 NACM from acute COVID-19 complications, NACM were included if they occurred >30 and <365 days after date of COVID-19 diagnosis and were not previously documented in the EHR. NACM were ascertained for each patient by using a combination of the ICD10 diagnosis codes and problem list diagnoses (Table 1).

To ensure we did not miss any NACM that may not have been document in the EHR via diagnosis code or in the problem list, we used laboratory data as an adjunct to define diabetes and CKD/ESRD. CKD/ESRD was considered a present NACM if a patient had 2 or more eGFR ≤ 60 on 2 separate dates without a problem list or diagnosis code for CKD/ESRD. If one value for HbgA1c was ≥ 10%, diabetes was considered present even without problem list or diagnosis code (notably, there were no patients in this category). Diabetes is diagnosed at a HbgA1c of 6.5%[30]; we chose 10% because patients with such an elevated HbgA1c would likely have glucose dysregulation which can cause the complications we are interested in.

For ICD codes that do not have a decimal place, all ICD codes within that whole number are included (e.g I50 means that I50.9 is captured as well). Fibrotic lung disease, J84.10 is not included as a diagnosis of the NACM of lung disease because it is a known acute complication of COVID-19 and thus is not considered a NACM.[31]

Since COVID-19 laboratory values were used to define exposure status, and ICD codes were used to define NACM, if laboratory values for COVID-19 or ICD codes for a NACM definition were missing, COVID-19 or the comorbidity, respectively, were considered absent. Otherwise, for those missing completely at random, the last observation within the study period, within 365 days of index date, was carried forward because of the short study period. As many of the NACM included in this study were chronic diseases, diagnosis of a condition once was considered to have persisted throughout the duration of the study. For example, if a patient was diagnosed with diabetes but then had later visits where the

diagnosis of diabetes was not documented, the diagnosis of diabetes remained throughout the study period. NACM definitions are included in Table 1. While calculating the incidence, we also determined the prevalence, which is defined as NACM that participants had in the 12 months prior to index date, or within 30 days of index date (Appendix 5, Figure 5).

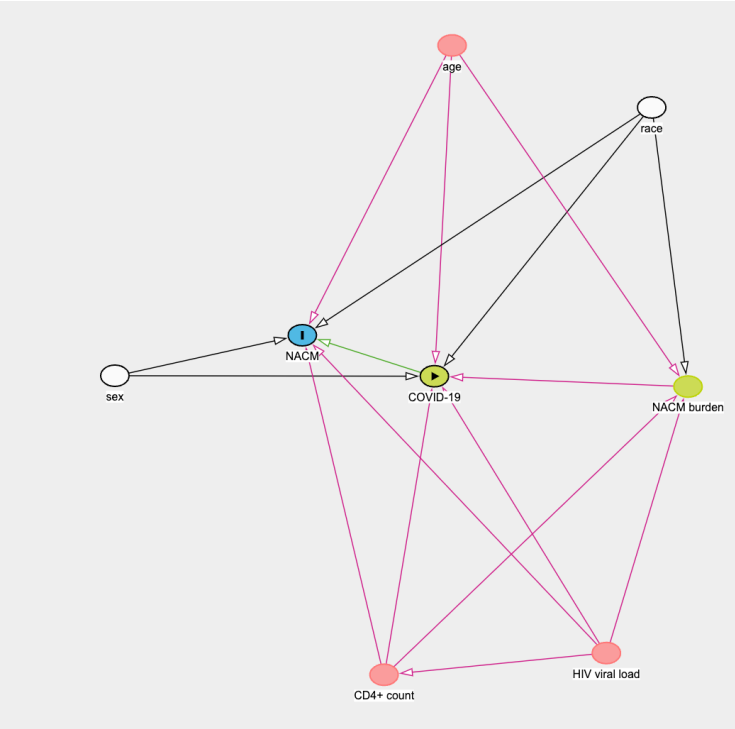
Table 1
Definitions of Selected Classes of Non-AIDS Comorbidities (NACM)

NACM	Definition	Source	ICD Code(s)
Cardiovascular disease	Coronary artery disease, myocardial infarction, ischemic stroke, heart failure, arrhythmia	listed on problem list or in diagnosis code	Z86.7, I25, I63, I50, I49
Hypertension	ICD codes for hypertension	listed on problem list or in diagnosis code	I10, I11, I12, I13, I15, I16
Chronic Kidney Disease/ESRD	ICD codes for CKD, ESRD, laboratory evidence of eGFR < 60 twice	listed on problem list or in diagnosis code or laboratory data	N18
Psychiatric Illness	ICD codes for depression, anxiety, psychiatric diagnosis, substance use disorder	listed on problem list or in diagnosis code	F32, F33, F31, F20, F25 F10, F11, F12, F13, F14, F15, F16, F18, F19
Diabetes/Prediabetes	ICD codes for diabetes, or ≥1 HbgA1c ≥ 10%	listed on problem list or in diagnosis code or laboratory data	E10, E1; R73.03
Cardiometabolic Disease	ICD codes for dyslipidemia, ICD codes for obesity (BMI>30)	listed on problem list or in diagnosis code	E78.5 E66
Lung Disease	ICD codes for lung disease, asthma, COPD	listed on problem list or in diagnosis code	J45, J44
Neurologic disorders	ICD codes for dementia, mild cognitive impairment, "brain fog," dizziness/vertigo, peripheral neuropathy, Guillain-Barre Syndrome	listed on problem list or in diagnosis code	F03, G31.84, R41, R42, G90, G61.0

CKD: Chronic Kidney Disease
ESRD: End Stage Renal Disease
eGFR: estimated Glomerular Filtration Rate (mL/min per 1.73 m2)
HbgA1c: Hemoglobin A1c (%)
COPD: Chronic Obstructive Pulmonary Disease

Covariate Selection

To identify potentially confounding covariates, a directed acyclic graph (DAG) was constructed using potential confounders of incident NACM after COVID-19 among PLWH specifically (Figure 2).



NACM = non-AIDS comorbidity
HIV = Human Immunodeficiency Virus
Definitions here
NACM Burden = prevalent comorbidities prior to COVID-19

Figure 2
Directed Acyclic Graph evaluating Potentially Confounding Clinical Characteristics on the Effect of COVID-19 on development of NACM (Made with Daggity).

Models were adjusted for previously identified variables that are known to impact age-related non-AIDS comorbidities including age, sex, race, $CD4^+$ count, and HIV viral load.[32, 33] Continuous variables (age, CD4+ count, time to NACM, NACM burden) met normality assumptions (Shapiro-Wilk $p<0.05$, however n = large and graphically normal, Appendix 3). NACM burden is defined as the number of pre-existing NACM (of the 8 studied here) at index date, prior to COVID-19. Categorical variables (race, sex, HIV viral load) were categorized as shown in Table 3. Race was classified as Black or African American, Hispanic, Other, White or Caucasian; Legal sex was defined as male or female; HIV Viral load was classified as detectable or undetectable, with a detectable viral load defined as a HIV VL Log_{10} >2.3 which corresponds to a VL of 200 copies/mL. Potential confounders were established by having significant Wald p-values in bivariate logistic regression analyses with COVID-19 status as the dependent

variable. None of the clinical characteristics, other than NACM burden, illustrated in the DAG were significantly different between COVID-19+ and COVID-19- groups (Table 2).

Table 2
Bivariate Analyses for Potential Confounders with Exposure and Outcome of Interest

Exposure (COVID-19)	Statistical Test of Association	p-value
Legal Sex*	chi squared test of association, χ^2	p=0.7522
Race*	chi squared test of association, χ^2	p=0.1295
Age at Index Date^	logistic regression odds ratio	p=0.075
CD4+ count^	logistic regression odds ratio	p = 0.9877
Viral Load* (detectable or undetectable)	logistic regression odds ratio	p=0.6138
NACM Burden	logistic regression odds ratio	p<0.0001

Data Analysis Plan

Cox proportional hazards regression analysis was performed to assess the risk of incident NACM within 12 months between COVID-19+ versus COVID-19- PLWH. Patients who did not receive a new NACM diagnosis during the follow-up period were right censored at the end of their follow-up time (365 days from index date or September 30, 2022) or at the date of death (per electronic medical records). Time to event was calculated as the number of days between the index date until date of diagnosis of a new comorbidity or date of right censorship. To assess the proportional hazards assumption for the Cox model, log-log survival curves were created (Appendix 6). For incident NACM that did not satisfy the proportional odds assumption (cardiometabolic disease, neurologic disease, psychiatric disease), a time-dependent extended Cox model was used to investigate the significance of time in the model (Appendix 6).

Multivariable models were adjusted for significant (per bivariate analyses and DAG) demographic and clinical characteristics known to impact both COVID-19 and NACM diagnoses, including race, age, sex, CD4+ count, and viral load, all at index date. NACM burden was not included as

a covariate due to the concern for collinearity with the other predictor variable, COVID-19 status. We performed a subgroup analysis based on NACM burden and calculated the risk of incident NACM for the group of patients with a low burden of pre-existing conditions, defined as having 0, 1, or 2 pre-existing NACM, and for the group with a higher burden of NACM (defined as ≥3 NACM).

An overall model evaluated the dichotomous outcome of diagnosis of any incident NACM (yes/no), and separate models assessed incidence of each of the 8 NACM as listed in Table 1 (for example yes/no for outcome of incident hypertension). New diagnosis of any incident NACM is independent of the NACM burden; participants could have had zero prevalent NACM and developed one or could have had 3 prevalent NACM and developed 5 incident NACM. Logistic regression models were developed to assess predictors of incident NACM; stratified multivariate models for incidence of each NACM were then also run to analyze incident NACM by legal sex. Patients were not matched on sex because of the small sample size and the short study period. Data was extracted from the CFAR registry in Microsoft Excel and was imported into SAS version 9.4 (SAS Institute Inc.) for all statistical analysis, and graphs were constructed using RStudio.[34]

Results

Baseline Participant Demographics

The CFAR registry identified patients seen at the Ponce clinic who are living with HIV and the investigators then identified 261 individuals in the cohort living with HIV who tested positive for COVID-19 between March 1, 2020, and September 30, 2021, with at least 365 days of follow up. There were 3279 people without documented SARS-CoV-2 positive testing or COVID-19 disease (Figure 3).

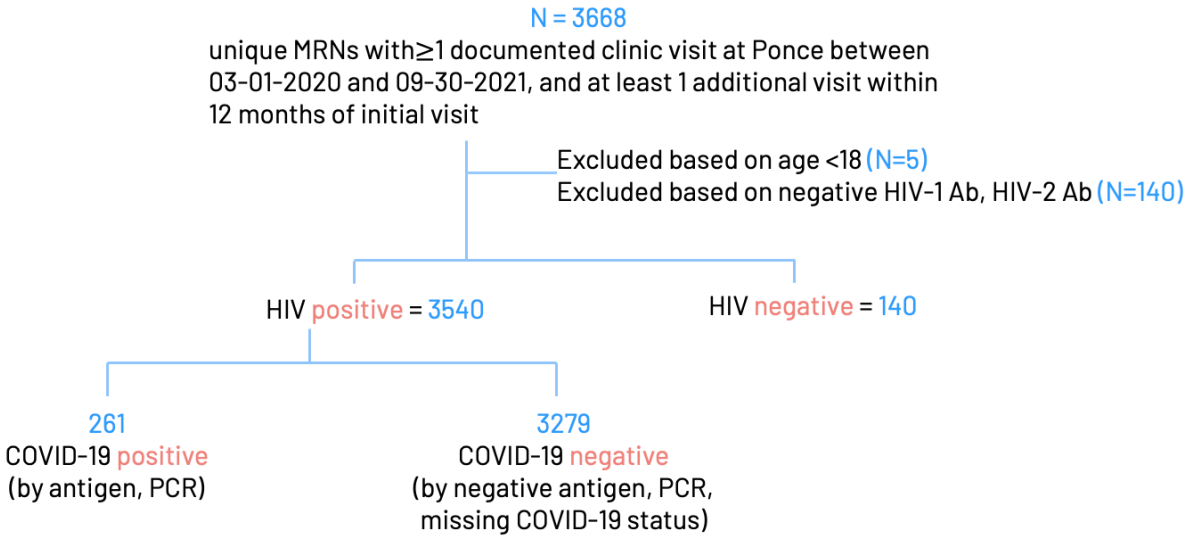


Figure 3
Flowchart of CFAR registry participants with eligibly criteria for this study.

Participant demographic data is reported in Table 3. Age at index date, race, and baseline HIV viral load and CD4+ count were not significantly different between COVID+ and COVID- groups. Burden of NACM at index date (presence of any of the 8 NACM of interest) is significantly different between groups, with the COVID+ group having significantly more NACM at baseline: median (Q1, Q3) number of NACM in COVID+ vs COVID-: 2 (1, 3) vs. 0 (0, 1). The median index date (date of first clinic visit within study period) for the COVID- group was April 2019 and the median index date (date of COVID diagnosis) for the COVID+ group was December 2020.

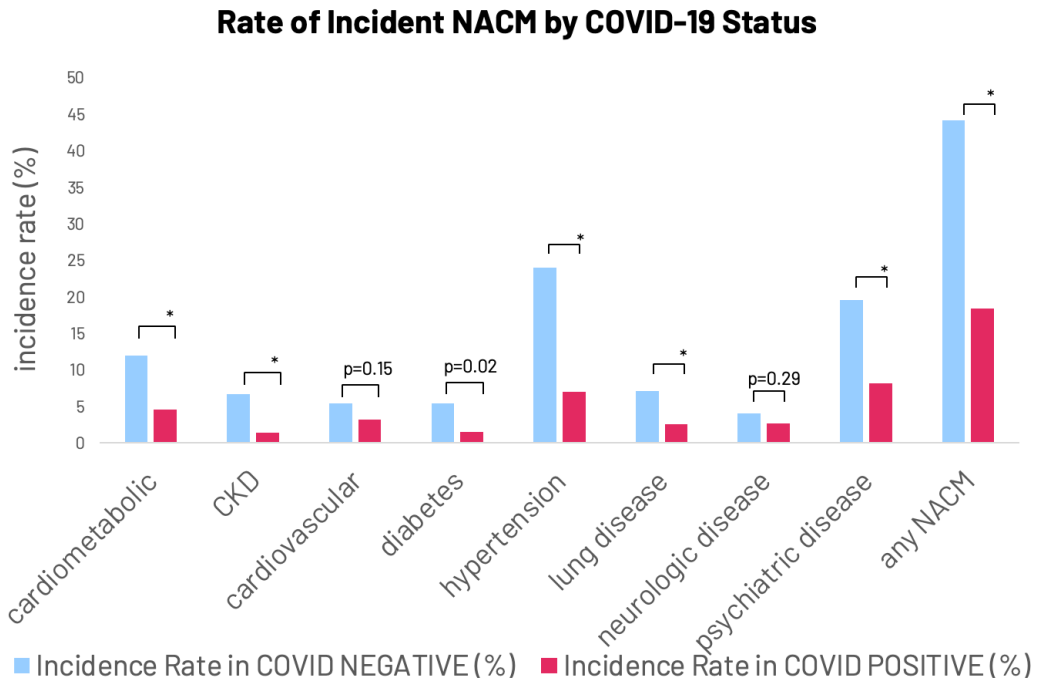
Table 3
Participant Demographic Data at Index Date

	COVID- (N=3279)	COVID+ (N=261)	p-value
Age at Index Date, Median (IQR)			p=0.08$
Median Age, years	50.7 (38.0, 59.2)	52.8 (39.8, 60.4)	
Missing = 0			
Reported Race, No. (%)			p=0.13#
Black or African American	2837 (86.52%)	224 (85.82%)	
Hispanic	121 (3.69%)	16 (6.13%)	
Other	44 (1.34%)	1 (0.38%)	
White or Caucasian	277 (8.45%)	20 (7.66%)	
Missing	0 (0%)	0 (0%)	
Sex, No. (%)			p=0.76#
Male	2243 (68.4%)	181 (69.4%)	
Missing = 0	0 (0%)	0 (0%)	
NACM Burden, Median (IQR)			p<0.0001*,&
Number of NACM	0 (0, 1)	2 (1, 3)	
HIV Viral Load (HIV LOG10 > 2.3 copies/mL), No. (%)			p = 0.61#
HIV VL LOG10 < 2.3	1838 (72.1%)	160 (73.7%)	
Missing HIV VL	731	44	
CD4+ Count, Median (IQR)			p=0.99#
CD4+ cells/mL	413.0 (237, 646)	432.5 (264.0, 634.5)	
Year of COVID-19 Diagnosis (or month + year) No.			
2020	n/a	131	
2021	n/a	129	
Index Date			
Median Index Date, mm/yyyy	April 2019	December 2020	

*= significant at the α=0.05 level
$ = pooled t-test
# = chi-squared test
&= 14atterthwaite t-test
if missing laboratory data to define comorbidity, coded as not having comorbidity

Prevalent and Incident Non-AIDS Comorbidities

To address Aim 1, we calculated the rate of incident NACM per one year by COVID-19 status (Figure 4). As mentioned, participants with a prevalent NACM for a the particular NACM analyzed were excluded from the analysis of individual NACM, but for the analysis of incidence of any NACM, no participants were excluded regardless of the number of pre-existing NACM.

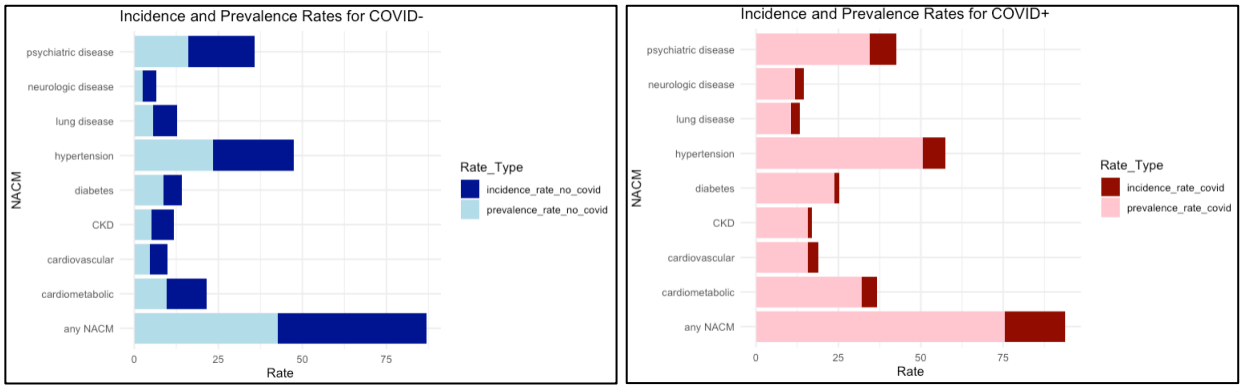


*: p-values < 0.05

Figure 4
Annual Incidence of NACM in COVID+ and COVID- PLWH.

The incidence rates for any NACM, and for each of the 8 NACM of interest were higher in COVID- participants. There were 1498 incident NACM that developed over the study period with 1450 in the COVID- group and 48 incident NACM in the COVID+ group, making the overall incidence rate of any NACM 0.42 NACM per person per year. The annual incidence of all NACM is greater, and in many cases statistically significantly greater, in COVID- participants. Figure 5 illustrates the prevalence and

incidence of NACM for the COVID+ and COVID- groups. The COVID- group (Figure 5a) has greater rates of incident NACM whereas the COVID+ group (Figure 5b) has greater rates of prevalent NACM.



5a. 5b.

Figure 5
Annual prevalence and incidence of NACM for COVID- (a) and COVID- (b) PLWH.

Although the COVID- group has a higher rate of incident NACM across comorbidity classes and the COVID+ has a greater proportion of prevalent NACM, the distribution of prevalent and incident NACM is similar by COVID status among PLWH. The sum of the rates of incident and prevalent hypertension, for example, is the highest in both graphs, indicating hypertension is most common comorbidity across COVID groups.

Time to and Risk of Developing non-AIDS Comorbidities

We calculated the median time to incident NACM, addressing Aim 1. Median time to any NACM was 197.5 days in the COVID+ group and 97.0 in the COVID- group (Appendix 4). Median time to NACM was shorter in the COVID- vs COVID+ group for 7 of the 8 NACM of interest. Time to development of incident cardiometabolic disease, however, was shorter for the COVID+ group occurring over a median of 91 versus 129 days for the COVID- group (Figure 6 and Appendix 4).

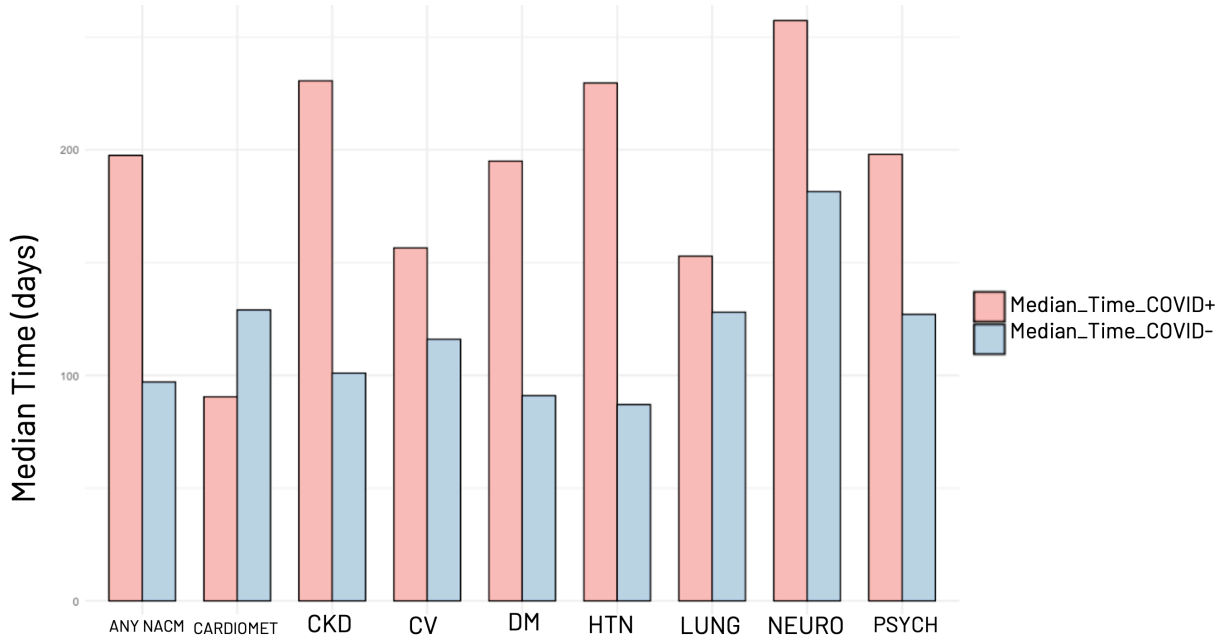
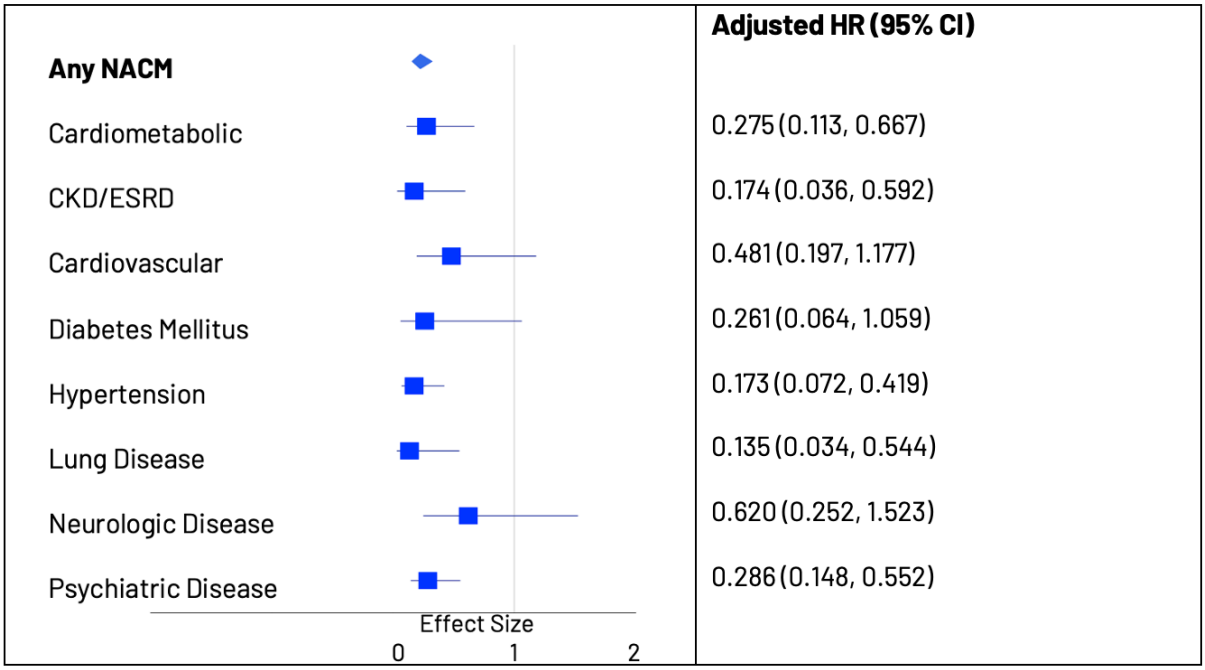


Figure 6
Median time to development of NACM in COVID+ and COVID- PLWH. Include abbreviations here.

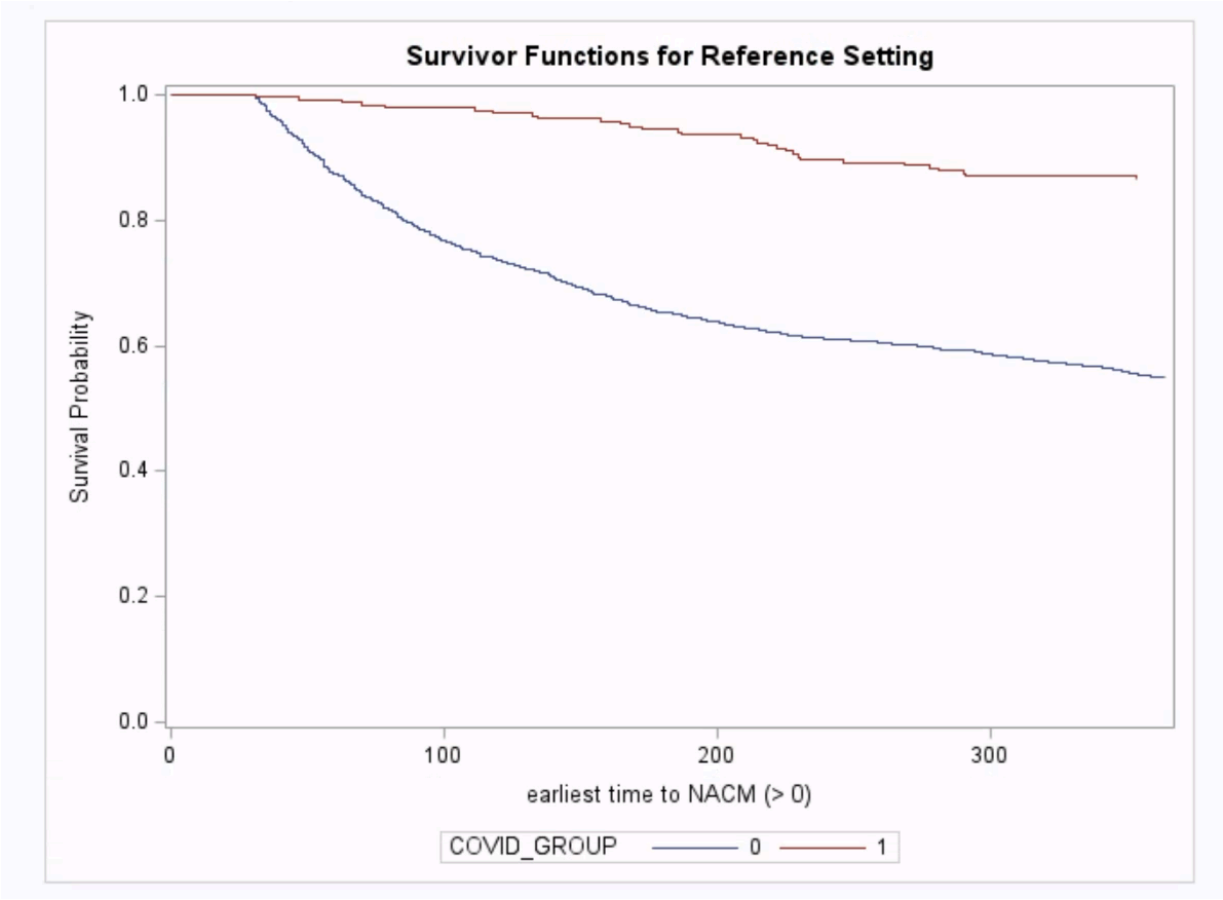
Using Cox proportional hazard regression, we modeled risk for incident NACM in COVID+ vs COVID- PLWH and found that across all 8 NACM, and for the combination of any incident NACM, the COVID+ group had a lower risk of incident NACM. For the NACM that did not satisfy the proportional odds assumption and a time-dependent model was run, time was not significant in any of the time-dependent models (Appendix 6). Adjusted hazard ratios (adjusted for age, sex, race, CD4+ count, HIV viral load) are illustrated in Figure 7. The risk for any NACM, and for each of the NACM of interest is lower in the COVID+ group (all HR < 1).



*adjusted for age, sex, race, CD4+, HIV VL

Figure 7
Adjusted Hazard Ratios for Development of Incident NACM in COVID+ versus COVID- PLWH.

We graphed the survivor functions to visualize how and when the COVID groups developed any incident NACM (Figure 8).

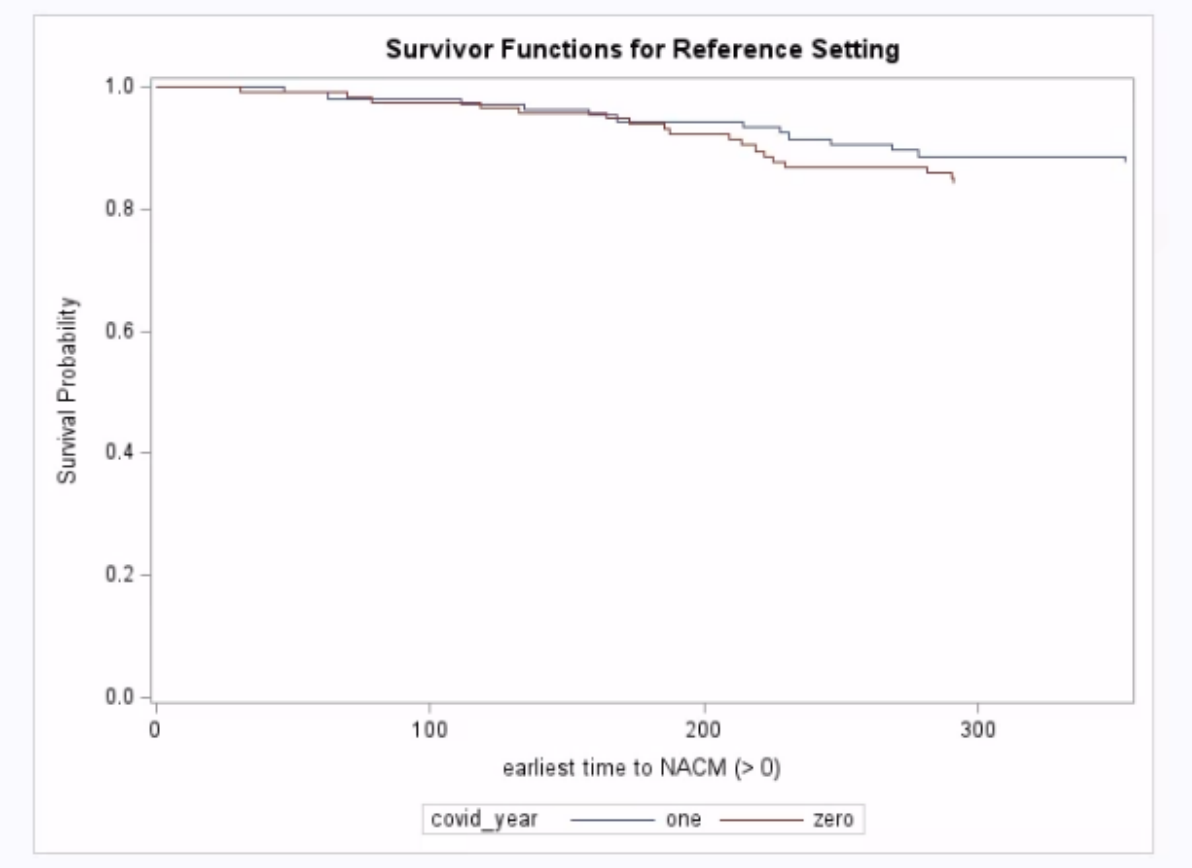


*adjusted for age, sex, race, CD4+, HIV VL

Figure 8
Adjusted Survival Probability Curves for incident NACM in COVID+ and COVID- PLWH.

Effect of Date of COVID-19 Diagnosis

As the pandemic continued, differences in SARS-CoV-2 wave (e.g. alpha, delta, omicron), vaccination, and knowledge about COVID-19 prevention evolved and improved. Due to these differences, we separated participants by date of index date – by separating the group of PLWH who developed COVID-19 in 2020 or 2021. 131 participants had COVID in 2020, and 129 in 2021 (Table 3).



*adjusted for age, sex, race, CD4+, HIV VL

Figure 9
Adjusted Probability Curves for development of any incident NACM based on index year.

We calculated the hazard for incident NACM in the COVID+ versus COVID- groups for each year and found that the risk of incident NACM is lower for COVID+ participants regardless of index year (Table 4).

Table 4
Hazard Ratio for Risk of Incident NACM by year of COVID Pandemic

Year of COVID Diagnosis or Index Year	HR for risk of NACM in COVID+ vs COVID-	95%CI	p-value
2020	0.652	0.327, 1.302	0.2258
2021	0.758	0.306, 2.015	0.6417

*adjusted for age, sex, race, CD4+, HIV VL

The risk of incident NACM in COVID+ PLWH versus COVID- PLWH is similar across years of the pandemic, with the group with index date in 2020 being at a slightly greater risk for incident comorbidity.

Effect of Non-AIDS Comorbidities Burden

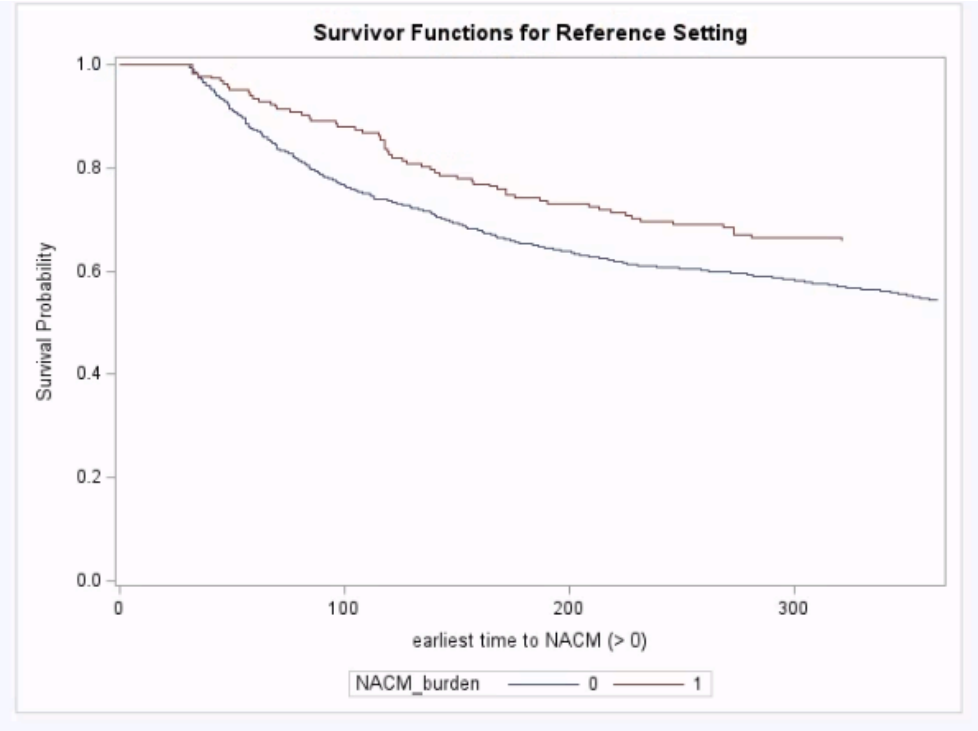
Burden of NACM, also known as pre-existing conditions, is a known risk factors for incident post-COVID-19 comorbidities.[13, 16, 35] NACM burden was significantly associated with the exposure of interest, COVID-19. Due to concern for NACM burden collinearity with the other predictor variable, COVID-19 status (Table 2), we did not include NACM burden as a covariate in the adjusted model and instead used NACM burden in a subgroup analysis. The median number of NACM in the COVID+ group was 2 and the median number of NACM in the COVID- group at the start of the study was 0 (Table 3). We categorized number of pre-existing NACM as NACM burden (Table 5).

Table 5
NACM Burden by COVID-19 Status

NACM Burden	Number of COVID- PLWH (%)*	Number of COVID+ PLWH (%)*
0 (0, 1, 2 NACM)	2989 (91.2%)	162 (62.1%)
1 (3+ NACM)	290 (8.84%)	99 (37.9%)

*Column percentages

Among PLWH COVID+ vs COVID-, 38% vs 9% had a high NACM burden. A majority of the COVID- group had a low burden of pre-existing comorbidity, and a smaller majority of the COVID+ group had a low burden of pre-existing comorbidity (91% vs 62%).



*adjusted for age, sex, race, CD4+, HIV VL

Figure 10
Adjusted Survival Probability for Incident NACM stratified by pre-existing NACM burden.

Figure 12 illustrates that patients with a greater burden of NACM have a higher survival probability curve, indicating that they have a lower risk of developing incident NACM. We calculated the risk of incident NACM in the COVID+ versus the COVID- group for each of the subgroups (low burden and high burden) (Table 6a).

Table 6a
Sub-Group Analysis for incident NACM, grouped by high versus low NACM Burden

Incident NACM for COVID+ vs COVID- PLWH	Adjusted* Hazard Ratio (95% CI)	p-value
Comparing 0, 1, 2 versus 3+ NACM		
Burden = 0, 1, 2	0.199 (0.123, 0.322)	<0.0001
Burden = 3+ NACM	0.478 (0.263, 0.870)	0.0157

*adjusted for age, sex, race, CD4+, HIV VL

The risk of incident NACM is greater in the group of PLWH with a greater pre-existing burden of disease; the COVID+ group categorized as having both low and high NACM burden is at a lower risk for incident NACM than their COVID- counterparts.

We also performed a sensitivity analysis by performing this analysis of incident NACM based on different NACM burden cutoffs for "high" and "low" NACM burden: one where we evaluated those with 0 NACM versus those with 1-2, versus those with 3+ and one where we evaluated those with 0, 1 versus those with 2+ NACM (Table 6b).

Table 6b
Sensitivity Analysis for incident NACM, with different cutoffs used for NACM Burden

Incident NACM for COVID+ vs COVID- PLWH	**Adjusted* Hazard Ratio (95% CI)**	**p-value**
Comparing 0, 1 NACM versus 2+		
Burden = 0, 1	0.188 (0.106, 0.332)	<0.0001
Burden = 2+	0.401 (0.248, 0.649)	0.0002
Comparing 0 versus 1, 2 versus 3+ NACM		
Burden = 0	0.206 (0.098, 0.435)	<0.0001
Burden = 1, 2	0.240 (0.128, 0.450)	<0.0001
Burden = 3+	0.478 (0.263, 0.870)	0.0157

*adjusted for age, sex, race, CD4+, HIV VL

Due to differences in NACM burden between the COVID+ and COVID- groups, we also calculated the risk for any incident NACM only in those participants where NACM Burden = 0 (Table 7).

Table 7
Adjusted Risk for Any Incident NACM in participants with NACM Burden = 0

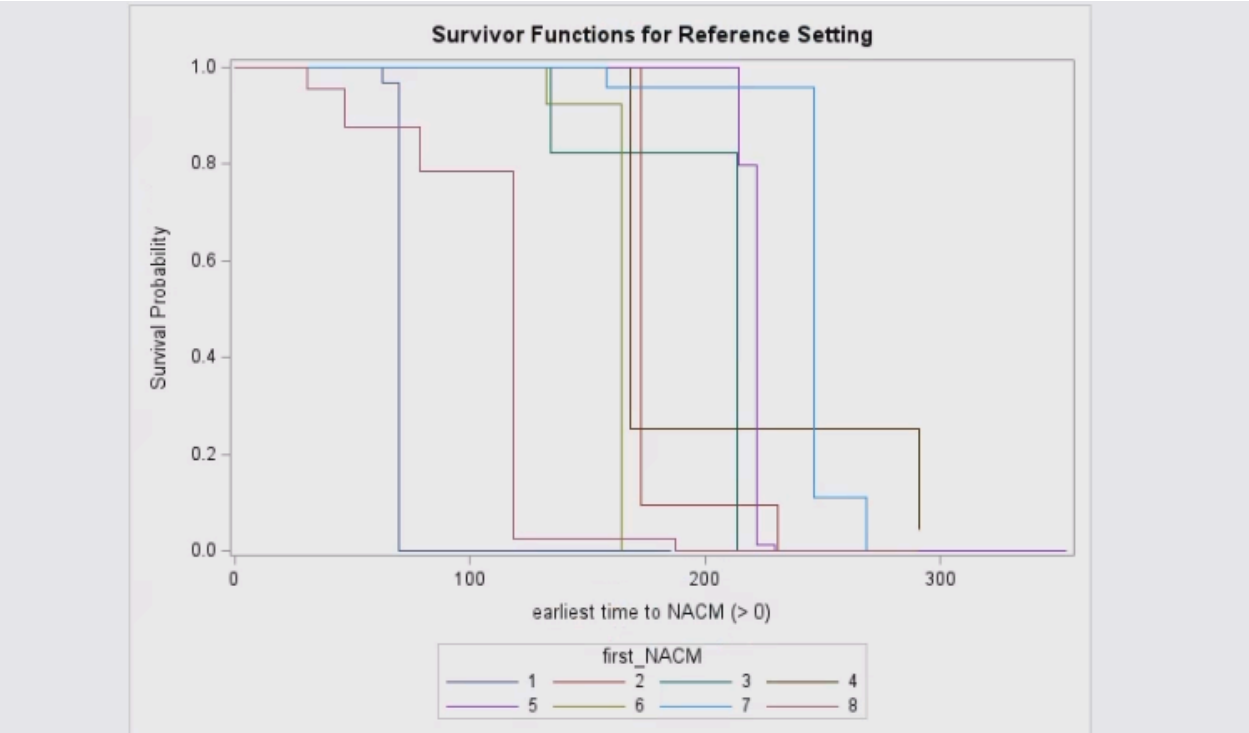
Clinical Characteristic	Adjusted* Hazard Ratio	95% Hazard Ratio Confidence Limits	p-value
COVID Group = COVID+	0.206	0.098, 0.435	<0.0001
Female Sex	1.503	1.280, 1.764	<0.0001
Age at Index	1.030	1.024, 1.035	<0.0001
Detectable Viral Load	0.901	0.751, 1.082	0.2653
CD4+ Count	1.000	1.000, 1.000	0.0497
Hispanic (vs Black)	0.644	0.408, 1.019	0.0600
Other (vs Black)	1.461	0.858, 2.486	0.1623
White (vs Black)	0.982	0.766	1.259

*adjusted for age, sex, race, CD4+, HIV VL

The COVID+ group is at a significantly lower risk for incident NACM compared to the COVID- group even when analyzing participants with no documented NACM at baseline.

Incident Non-AIDS Comorbidities within COVID+ Group Only

Due to the differences in baseline characteristic of the COVID+ and COVID- groups, we analyzed incident NACM within just the COVID+ group using the same proportional hazards model and stratifying by NACM (Figure 11).



1. cardiometabolic
2. CKD
3. CV
4. DM
5. HTN
6. lung
7. neurologic
8. psychiatric

Figure 11
Time to Incident NACM within the COVID+ group.

The first survival curve to drop is cardiometabolic (NACM 1) indicating that the COVID+ group developed cardiometabolic disease first, followed by psychiatric disease (NACM 8).

Risk Factors Associated with Annual Incidence of Non-AIDS Comorbidities

To explore potential factors associated with risk of annual incidence of NACM, we also calculated hazard rates for the covariates included in the adjusted Cox proportional hazard regression model: age, sex, race, CD4+ count, HIV viral load (Table 8) for risk of any incident NACM (as a combination of the 8 comorbidities).

Table 8
Hazard Ratio for Covariates associated with Annual Incident Risk of Any NACM

Clinical Characteristic	Adjusted* Hazard Ratio	95% Hazard Ratio Confidence Limits	p-value
Female Sex	1.429	1.255, 1.626	<0.0001
Age at Index	1.020	1.016, 1.025	<0.0001
Detectable Viral Load	0.763	0.654, 0.890	0.0006
CD4+ Count	1.000	1.000, 1.000	0.1714
Hispanic (vs Black)	0.662	0.441, 0.995	0.0470
Other (vs Black)	1.114	0.679, 1.827	0.673
White (vs Black)	1.070	0.879, 1.303	0.5009

*adjusted for age, sex, race, CD4+, HIV VL

Female sex and one year older in age were significantly associated with incident NACM, whereas detectable viral load (VL) was protective. We also calculated these hazard rates for the COVID- and COVID+ groups separately to determine the association between potential risk factors and incident NACM, within each COVID group (Table 9).

Table 9
Adjusted Hazard Ratio for Covariates associated with Annual Incident Risk of Any NACM, separated by COVID-19 Status

COVID- PLWH			
Clinical Characteristic	**Adjusted* Hazard Ratio**	**95% Hazard Ratio Confidence Limits**	**p-value**
Female Sex	1.444	1.256, 1.634	<0.0001
Age at Index	1.020	1.016, 1.025	<0.0001
Detectable Viral Load	0.761	0.651, 0.890	0.0006
CD4+ Count	1.000	1.000, 1.000	0.2218
Hispanic (vs Black)	0.670	0.442, 1.014	0.0583
Other (vs Black)	1.116	0.680, 1.831	0.6646
White (vs Black)	1.083	0.888, 1.321	0.4316
COVID+ PLWH			
Clinical Characteristic	**Adjusted* Hazard Ratio**	**95% Hazard Ratio Confidence Limits**	**p-value**
Female Sex	1.332	0.615, 2.882	0.4673
Age at Index	1.16	0.986, 1.046	0.3045
Detectable Viral Load	0.826	0.299, 2.286	0.7132
CD4+ Count	1.000	1.000, 1.000	0.1714
Hispanic (vs Black)	0.546	0.073, 4.068	0.5547
Other (vs Black)	n/a	n/a	n/a
White (vs Black)	0.680	0.157, 2.954	0.6069

*adjusted for age, sex, race, CD4+, HIV VL

Female sex and each year older in age were only significantly associated with an increased risk of any incident NACM in the COVID- group.

Since female sex was significantly associated with increased risk of incident NACM in the entire cohort, we further explored the relationship between female sex and incident NACM by calculating the risk of incident NACM in females versus males for each of the 8 NACM within the entire cohort, COVID+ and COVID- (Table 10).

Table 10
Risk of Incident NACM in Females versus Males Living with HIV (both COVID+ and COVID-)

NACM	Adjusted* Hazard Ratio for Incident NACM in Female versus Male PLWH	95% CI	p-value
Cardiometabolic Disease	2.026	(1.571, 2.612)	p = <0.0001
CKD/ESRD	1.204	(0.857, 1.692)	p=0.2853
Cardiovascular Disease	1.034	(0.692, 1.543)	p=0.8712
Diabetes Mellitus	1.471	(0.983, 2.201)	p=0.0606
Hypertension	1.682	(1.382, 2.048)	p<0.0001
Lung Disease	2.277	(1.670, 3.106)	p<0.0001
Neurologic Disease	2.098	(1.394, 3.159)	p=0.0004
Psychiatric Disease	1.363	(1.111, 1.672)	p=0.0030
Any NACM	1.43	(1.26, 1.63)	p<0.0001

*adjusted for COVID group, age, race, CD4+, HIV VL

Female PLWH are at a significantly greater risk for development of cardiometabolic disease, hypertension, lung disease, neurologic disease, and psychiatric disease.

All-Cause Mortality in People Living with HIV During the COVID-19 Pandemic

Lastly, we calculated all-cause mortality for the COVID+ and COVID- groups (Table 11).

Table 11
All-Cause Mortality at 365 Days from Index Date

All-Cause Mortality	COVID- N=3279	COVID+ N=261	chi squared χ^2 p-value
Died (%)*	79 (2.41%)	12 (4.60%)	p=0.0304
Alive (%)*	2616 (79.78%)	202 (77.40%)	
Missing (%)*	584 (17.81%)	47 (18.01%)	

Although mortality rate was low overall at 2.6%, the proportion of COVID+ PLWH who died within one year of index date was significantly larger than the proportion of COVID- PLWH who died within the year.

Discussion

This secondary analysis of 3540 PLWH seen at the Grady Ponce Center in Atlanta, GA, between the start of the COVID-19 pandemic, March 1, 2020, and September 30, 2022, found that among people living with HIV median time to incident NACM was longer in those who had documented COVID-19 in the study period than those who did not. The risk for new comorbidity was also lower in the COVID+ group. Female sex and older age are associated with an increased risk of incident NACM. We concluded that: people living with HIV who are COVID+ have a lower annual incidence of NACM compared to those who are COVID-; that the COVID+ group of PLWH is at a lower risk of any incident NACM and has a longer time to development of all NACM except for cardiometabolic disease; and that women and older PLWH have a greater risk of developing any, and several selected, NACM compared to males and younger PLWH.

Participant Differences by COVID-19 Status

Participant demographics were similar across groups with a median age of 50.9 years. Most participants were Black or African American, male, and had well-controlled HIV (undetectable viral load and high CD4 count). There was a significant difference in NACM burden (number of pre-existing conditions) between COVID groups, with PLWH who developed COVID having a greater number of pre-existing NACM. Of note, 90% of patients seen at the Ponce clinic have an undetectable viral load; in this study, because of the eligibility criteria for participants to be included in our study, there is a lower proportion of patients with undetectable HIV viral load.

The rate of incident NACM was higher in the COVID- group across all NACM and was significantly higher for all groups except for incident cardiovascular disease and incident neurologic disease where the incidence was higher, but not significantly higher (at a 0.05 level of significance), which is inconsistent with prior work.[36] The most prevalent NACM overall was psychiatric disease and the least prevalent were neurologic disease and cardiovascular disease. The NACM with the greatest

annual incidence were hypertension and psychiatric disease (Figure 5). The COVID+ group was "sicker" to begin with, having a greater proportion of prevalent comorbidities, whereas the COVID- group developed more comorbidities during the pandemic era study period.

PLWH with COVID+ appear to be less negatively affected, in terms of annual incident comorbidities, than do COVID- PLWH. This group had more pre-existing NACM to begin with and if, for example, participants already had diabetes or hypertension, they could not develop such NACM during the study period. The difference in pre-existing NACM could contribute to the apparent effect COVID had on participants – those who developed COVID were sicker to begin with, and thus were more susceptible to developing COVID-19, but less susceptible to developing new NACM since they already had multiple comorbidities. Due to this finding, an appropriate follow up analysis would evaluate just participants who were free of NACM at baseline to eliminate the confounding from pre-existing disease and extend follow-up time.

Median time to incident NACM was longer in the COVID+ group for all NACM except for cardiometabolic disease, where PLWH and COVID-19 had a shorter time to development of cardiometabolic comorbidities compared to the COVID- group. The adjusted hazard rate ratios for risk of developing incident NACM were lower for the COVID+ group across all comorbidities, and was significantly lower for cardiometabolic disease, chronic kidney disease, hypertension, lung disease, psychiatric disease. When stratifying on COVID group, the survival probability curve is higher in the COVID+ group, indicating that the COVID- participants develop the outcome of interest, new NACM, sooner than do the COVID+ participants (Figure 8). This finding was also unexpected and may be due to the baseline differences in the COVID+ and COVID- groups, and the fact that so few COVID+ participants developed incident comorbidity within 365 days of COVID. Following participants for a longer time may alter these findings.

Sex Differences in and the Effect of Age and Detectable VL on Incident Post-COVID-19 Incident Non-AIDS Comorbidities

Males are at increased risk for HIV[37] and severe COVID-19[38] and males are also the majority of the patients included in this study, representative of the Ponce Clinic population. Previous work, however, has demonstrated that women have a higher burden of non-AIDS comorbidities than do males – regardless of COVID-19 status.[19] Current data posit that sex differences in NACM may be due to higher levels of inflammation and immune activation in females due to both social determinates of health and trauma history as well as higher levels of inflammation in women with HIV even with viral suppression[39], and due to the effect of sex hormones.[19] To understand the mechanisms behind this and our other findings, a randomized control study would be required to investigate such causation between female sex and incident post-COVID comorbidities among PLWH.

Our study further explores the greater burden of NACM that women have been described to have by studying the unique subset of females living with HIV and COVID-19 and finding that females with HIV are at a greater risk of developing any NACM within one year than their male counterparts are. We calculated the risk for incident NACM in the female participants and found that for any, and all incident NACM, female participants had a greater risk of developing incident NACM. The female PLWH were at a significantly greater risk of cardiometabolic disease, hypertension, lung disease, neurologic disease, and psychiatric disease. When we separated the COVID+ and COVID- groups, we found that the risk for developing any incident NACM in the COVID+ group was greater for females as compared to males, but not significantly so (Table 9). Although female PLWH are at greater risk for developing any incident NACM, female sex was not significantly associated with a greater risk of developing each NACM. There was a trend towards increased risk among females, although the difference did not reach statistical significance (Table 10). The lack of significance in the risk that female participants with COVID have for developing incident comorbidity may be due to the small number of participants with incident disease after COVID-19 – as small as 3 incident cases of diabetes in the COVID+ group – which limits the

numbers of confounders that we can adjust for while remaining powered to detect meaningful associations.

We found that with each year older in the COIVD- group, there is a greater risk of developing any incident NACM whereas in the COVID+ group, there is not a significantly greater risk of developing comorbidity with each year older. The findings in the COVID- group are consistent with prior literature[23], and the unexpected findings within the COVID+ group may be due to the fact that this group is sicker, or due to the small number of participants in this group, or due to the short follow-up time.

We also found that having a detectable HIV viral load was a protective factor in terms of incident non-AIDS related comorbidities (HR = 0.763). When separated by COVID status, the COVID+ group with a detectable viral load had a lower, although not statistically significantly lower risk of incident NACM. This finding is supported by other recent work[19] and may be due to the fact that patients with detectable HIV VL have more interface with the healthcare system and thus can participate in and engage in preventative measures against new comorbidities.

Time-Dependent Effects on Annual Incidence of Non-AIDS Comorbidity

We found that, across all NACM of interest, COVID+ PLWH had a shorter time to development of only cardiometabolic disease even though the risk for developing cardiometabolic disease was lower than the risk in the COVID- group. Regardless of COVID-19 status, the rate of incident cardiometabolic disease was greater than the rate of cardiovascular disease, a sequala of longstanding cardiometabolic disease.[40] For COVID+ PLWH, the incidence of cardiometabolic disease was 4.5% whereas the incidence of cardiovascular disease was just 3.18%. This difference was starker in the COVID- group where the incidence of cardiometabolic disease was 11.9% and the incidence of cardiovascular disease was 5.4% (Figure 5, Appendix 5).

One study[41] showed that during the pandemic there was an increase in proportion of people with dyslipidemia and diabetes more so than was there an increase in people with elevated body mass index. These findings indicate that the changes in diet and physical activity during the pandemic likely had a

more immediate effect on lipid levels and impact this trend. Here, we found that a smaller proportion of incident NACM was cardiovascular disease or diabetes, whereas the proportion of participants with incident cardiometabolic disease was larger. This effect, and some other effects observed during the pandemic, may have been due to the pandemic, quarantine, and factors other than the virus itself, since both COVID- and COVID+ PLWH developed more cardiometabolic disease than cardiovascular disease.

Cardiometabolic disease, which includes dyslipidemia and obesity, is a known risk factor for cardiovascular disease, including myocardial infarction, stroke, and coronary heart disease[42]. A recent randomized control study based on the notion that PLWH are at risk for consequences from cardiometabolic disease demonstrated the protective effect of statins in people living with HIV. They found that PLWH randomized to receive pitavastatin had a lower risk of major adverse cardiovascular event than those who received placebo over a median follow-up of 5 years.[41] Given our data which demonstrates that people living with both HIV and COVID-19 are at even greater increased risk for annual cardiometabolic disease, it would be interesting to further explore this study's finding of the effect of statin use on outcomes in COVID+ people living with HIV.

Year of COVID-19 Diagnosis

We also found that date of COVID-19 did not affect risk of incident NACM. As COVID-19 has evolved and new strains have developed, so have questions regarding the increased severity of evolving strains. When we stratified our model by year of COVID diagnosis, all COVID+ and COVID- participants seen in 2020 had a slightly higher NACM incidence that those seen in 2021 (Figure 9), but the risks were not significantly different. The similar risk of incident NACM between index years (representing both different strains and an evolving knowledge of the virus including vaccination) suggest again that the virus itself is less likely the sole cause of post-viral complications, and that host factors are also associated with risk of post-COVID non-AIDS comorbidities.

Effect of Burden of Pre-Existing Non-AIDS Comorbidities on incident Non-AIDS Comorbidities

Because there is a significant difference in NACM burden by COVID groups, we did not include that variable in the overall model, despite its presence in the DAG (Figure 2). To include this important and known risk factor in analysis while also avoiding collinearity, we performed a subgroup analysis. We examined the risk of any incident NACM in PLWH with a high NACM burden (3+) versus those with 0, 1, or 2 pre-existing NACM. We found that in both groups, participants with COVID were at lower risk of incident NACM than the COVID- group, as we found in the overall model. We also found that the COVID+ group with a larger burden of pre-existing comorbidity, was at increased risk of incident NACM than PLWH without COVID within one year of (HR = 0.199 vs 0.478, Table 6a).

In the sensitivity analysis, we changed the cutoffs for low and high NACM burden. The results of this analysis (Table 6b) also displayed a dose-dependent pattern. Regardless of the cutoff for low versus high burden, the risk of incident NACM increases with increased NACM burden.

The findings from this subgroup analysis further support the current leading hypothesis that pre-existing NACM contribute new NACM. PLWH have a higher level of baseline inflammation[19], and with the additional inflammatory insult from COVID-19, these participants are well positioned to develop incident NACM, including cardiovascular disease, within one year. It is also known that COVID-19 is associated with many cardiovascular complications including coronary artery plaque inflammation, which can cause acute and long term cardiovascular complications.[43] For example, the interaction between COVID and cardiometabolic disease may accelerate the development of cardiovascular disease in this group.

When we analyzed the risk of incident NACM in the group of participants with zero pre-existing conditions, those with a NACM Burden of 0, we found again that the COVID+ group is at an increased risk of incident NACM (adjusted HR = 0.206). The risk in this group is slightly shifted towards the null compared with the adjusted HR for any incident NACM in the entire cohort (HR = 0.22, Appendix 7), indicating that although the COVID+ group is still at a lower risk than the COVID- group, that difference is attenuated when analyzing only participants with no pre-existing comorbidities. This finding is still

contrary to our hypothesis and to the current consensus and is likely due to the fact that participants who got COVID were more isolated and could not be diagnosed with a new NACM due to increased self-quarantine when compared to the participants who did not develop COVID.

Pandemic Effects on COVID- People Living with HIV

Several of the trends we noted, including the greater risk of cardiometabolic disease compared to the risk of cardiovascular disease across COVID groups, and the greater risk females living with HIV have as compared to males, did not appear to be directly associated with COVID-19 infection as the trends were similar in both COVID+ and COVID- groups. Similarly, year of index date was not significantly associated with differences in risk of incident NACM. Burden of pre-existing disease was the characteristic that was associated with COVID+ PLWH having an increased incidence of new NACM.

Because of these unexpected findings, we considered other quarantine-related effects. Perhaps we did not detect a greater incidence of NACM in COVID+ PLWH, as hypothesized, because these participants were sicker at baseline, as represented by increased NACM burden, they had more comorbidities and were unable to then develop those they already had. It is also possible that these sicker patients were quarantining and not being seen as regularly for clinic visits. Even if these sicker patients had virtual visits, telehealth appointments cannot diagnose many of the NACM that we studied, which are diagnosed via vital sign measurements or laboratory measurements. These findings suggest that participants without COVID- were also affected by the quarantine or self-quarantine, resulting in decreased physical activity, increased stress and anxiety, and worsening eating patterns[44], and thus also were at risk for developing new comorbidities.

Limitations and Future Directions

Our secondary analysis draws patients from a very small and unique population, the population of PLWH in Atlanta, GA, and is not generalizable to the United States or to the global population of PLWH.

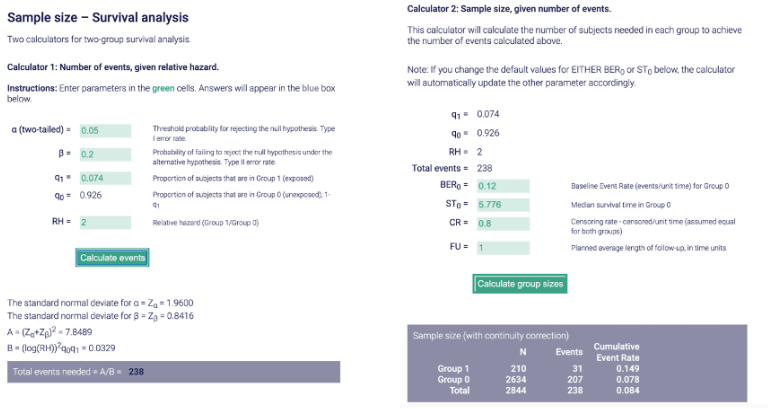
The population seen at the Ponce Clinic is however an underserved population with a high burden of social determinates of health disparities and is located in the epicenter of the HIV/AIDS epidemic in the United States.[16, 45] Our findings are important for understanding how to effectively support and care for a historically marginalized group. Additionally, we followed participants for 365 days only, even if they had data past that timeframe. There are certainly participants who developed NACM 366 days after, and before September 22, 2022, for example, however these were not included in order to balance follow-up time across all participants. As a retrospective study, we relied on Electronic Health Record data, so there is the possibility that first, some participants we categorized as COVID- were actually COVID+ either from being asymptomatic and not testing, or from a testing center not captured by the EHR. There is also the possibility that some NACM were not documented in the patient's EHR.

Moving forward, it would be excellent to expand this sample size by using data from other CFAR across the country, to collect data from other sites for a more generalizable population, outside of Atlanta, and to follow patients for longer. This study can be used as a pilot study for future investigation to come. It is also important to understand the mechanisms behind some of the trends we observed, which would require a randomized control study to demonstrate any causation between the potential risk factors we noted and incident post-COVID-19 non-AIDS comorbidities. Future studies should also analyze those participants "risk free", with an NACM burden of zero at baseline, to eliminate confounding due to inclusion of participants who were sicker at baseline.

Appendix

Appendix 1. Sample Size Calculation

- α= 0.05
- β =0.80
- Assume 10% will be exposed to COVID-19
- Baseline event rate = 12%
- Relative Hazard = 2

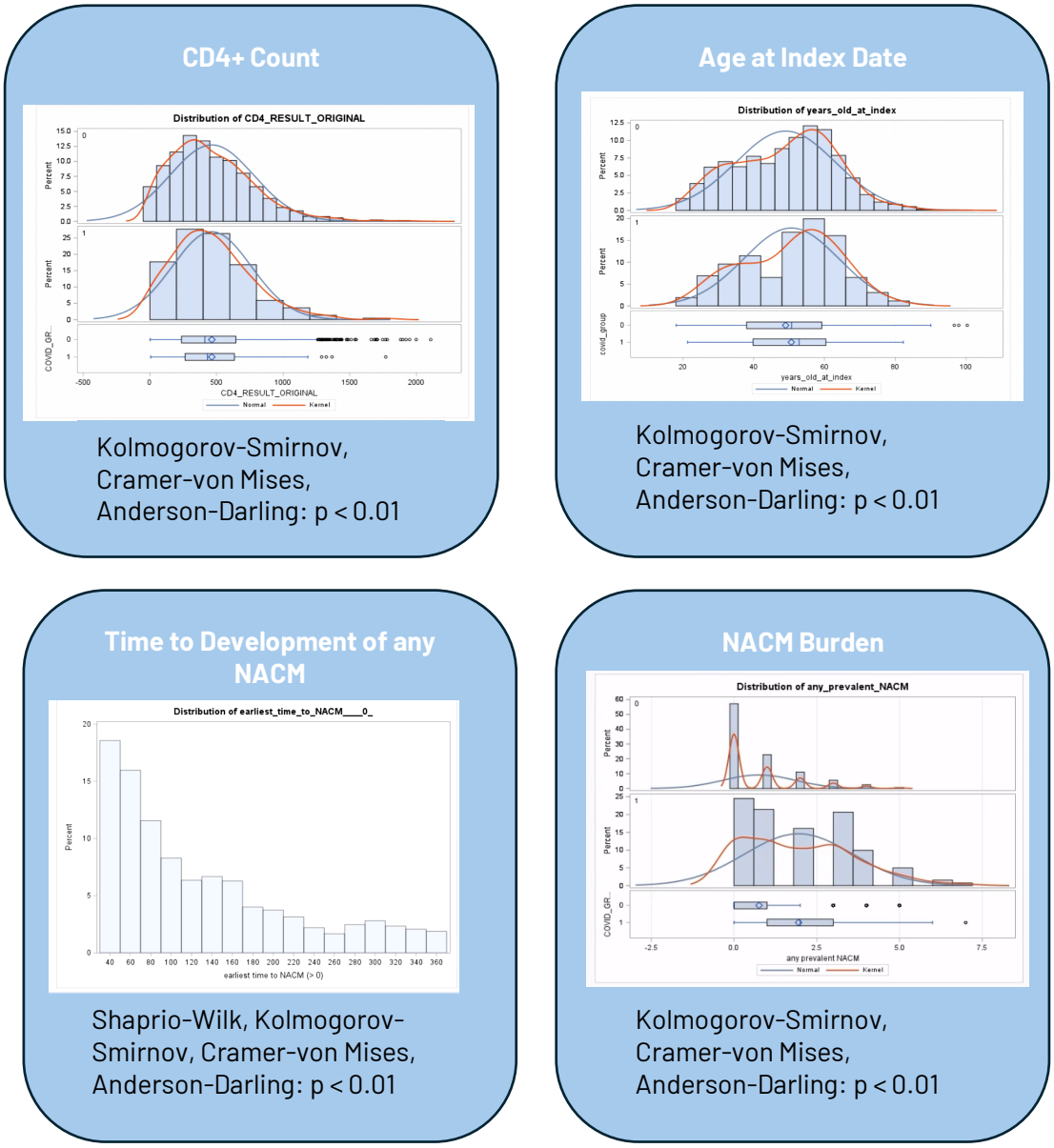


A sample size of 2844 (n=210 exposed and n=2634 unexposed) will give us 80% power to detect a risk/incidence ratio of 2.0 with 95% confidence

Appendix 2. Laboratory Tests used to Define COVID-19, HIV, and Select NACM

Lab Category	Laboratory Test	NACM
HIV Labs	% CD 4 POS> LYMPH.-LABCORP % CD4(HELPER CELLS)-QUEST ABSOLUTE CD 4 HELPER-LABCORP ABSOLUTE CD4+ CELLS-QUEST CD3+ CD4+# CD3+ CD4+% CD4+/CD8+ Ratio	For HIV status
CKD/ESRD	eGFR	To classify CKD/ESRD
HbgA1c	Hb A1c HEMOGLOBIN A1C-LABCORP HEMOGLOBIN A1C-QUEST Hgb A1c %	To classify diabetes mellitus
COVID-19 Labs	SARS CoV-2 Antibody IgG SARS-CoV-2 SARS-CoV-2 PCR	To classify into COVID-19 + or - group

Appendix 3. Normality Tests for Numerical Covariates



Appendix 4. Mean and Median Time to Incident NACM

NACM	COVID STATUS	Number of Incident Cases (COVID+ 261 COVID- 3279	Median Time to NACM (IQR), days	Mean Time to NACM (sd), days
ANY NACM	**+**	48	197.5 (109.8, 252.5)	180.5 (89.4)
	-	1449	96.0 (56, 171)	127.0 (88.8)
CARDIOMETABOLIC	+	8	90.5 (47.7, 254.8)	143.6 (124.1)
	-	353	129.0 (75.0, 209.0)	150.4 (92.7)
CHRONIC KIDNEY DISEAE	+	3	230.6	225.3 (50.5)

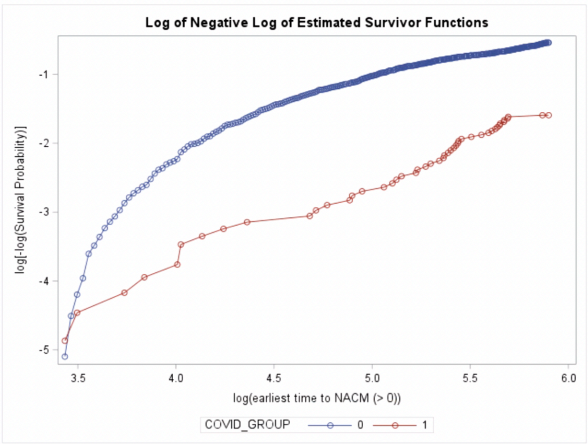
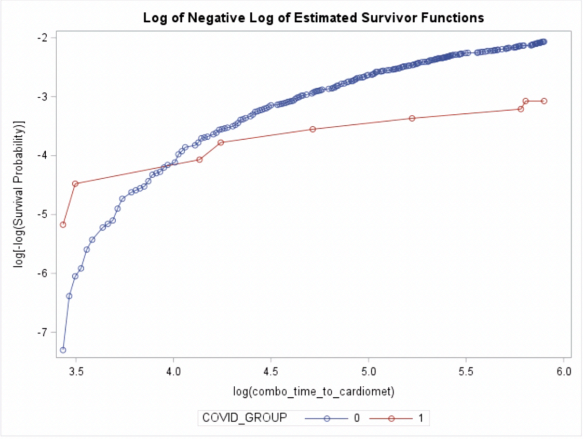
			(172.4, 273.0)	
	-	208	181.0 (77.5, 315.5)	195.2 (115.7)
CARDIOVASCULAR DISEASE	+	7	156.5 (56.0, 218.6)	149.7 (77.0)
	-	169	116.0 (66, 205)	145.2 (96.3)
DIABETES MELLITUS	+	**3**	195.0 (168.0, 291.0)	218.0 (64.7)
	-	160	**91.0 (56.5, 162)**	**122.4 (86.4)**
HYPERTENSION	+	9	229.6 (214.4, 285.0)	245.9 (73.8)
	-	603	87.0 (55, 147)	114.6 (81.3)
LUNG DISEASE	+	6	152.8 (132.4, 284)	179.2 (93.7)
	-	221	**128.0 (58.0, 215)**	**147.8 (98.2)**
NEUROLOGIC DISEASE	+	**6**	257.3 (157.6, 278.0)	214.4 (90.6)
	-	128	181.5 (100.5, 300.5)	193.9 (104.0)
PSYCHOLOGIC DISEASE	+	14	198.0 (109.0, 259.0)	184.0 (94.0)
	-	539	127.0 (68.0, 215.0)	150.0 (95.7)

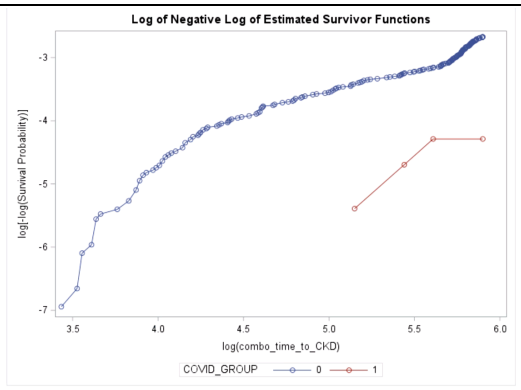
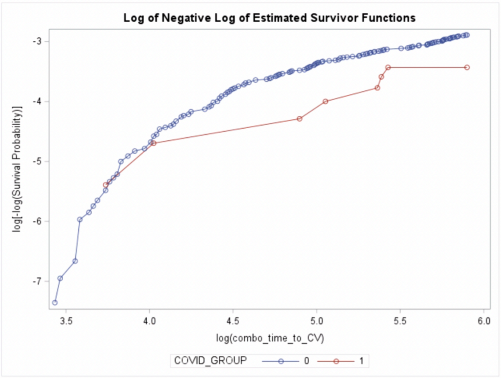
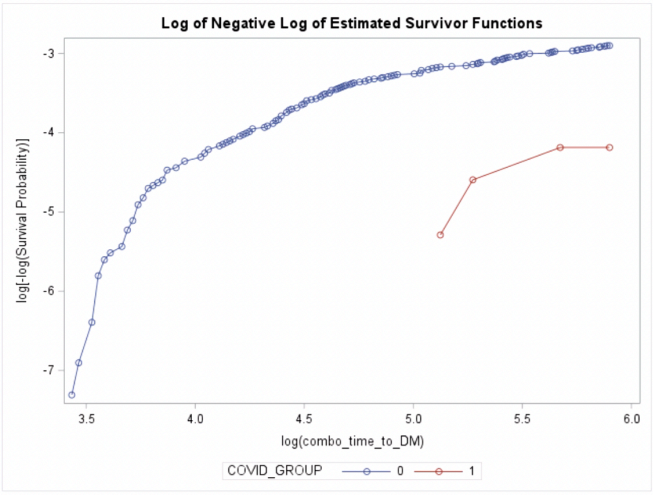
Appendix 5. Prevalence and Incidence of NACM for COVID+ and COVID- PLWH

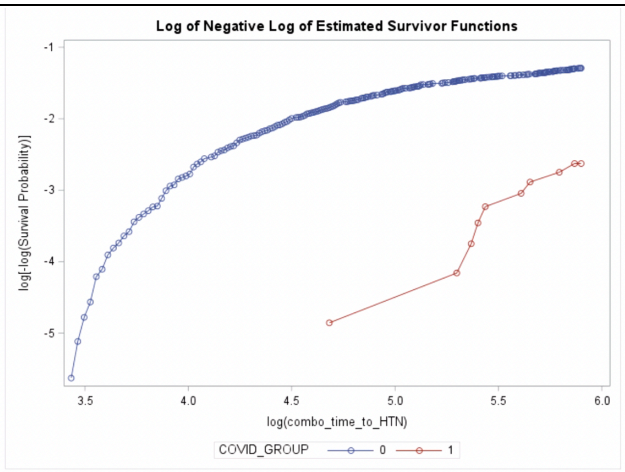
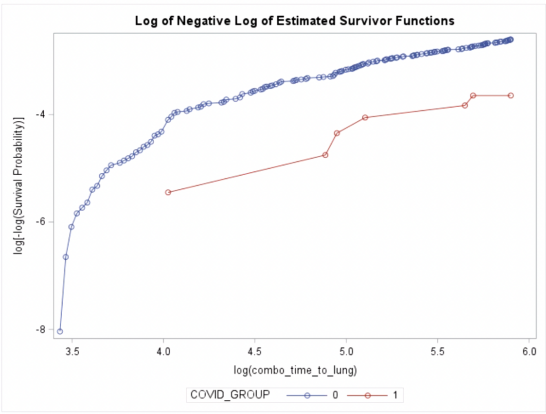
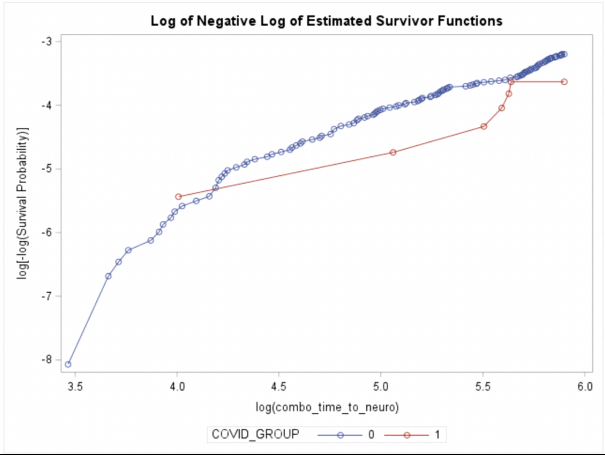
Prevalent NACM		**Total COVID- (n=3279)**	**Prevalence in COVID NEGATIVE (%)**	**Total COVID+ (n=261)**	**Prevalence in COVID POSITIVE (%)**	**chi squared χ^2 p-value**
CARDIOMETABOLIC DISEASE	No. prevalent cases	312	9.52	84	32.18	p<0.001
CHRONIC KIDNEY DISEAE	No. prevalent cases	165	5.03	41	15.71	p <0.0001
CARDIOVASCULAR DISEASE	No. prevalent cases	149	4.54	41	15.71	p <0.0001
DIABETES MELLITUS	No. prevalent cases	287	8.75	62	23.75	p <0.0001
HYPERTENSION	No. prevalent cases	769	23.52	132	50.57	p <0.0001
LUNG DISEASE	No. prevalent cases	183	5.58	28	10.73	p=0.0007
NEUROLOGIC DISEASE	No. prevalent cases	83	2.53	31	11.88	p <0.000
PSYCHOLOGIC DISEASE	No. prevalent cases	528	16.10	90	34.48	p <0.000
ANY NACM	No. prevalent cases	1400	42.70%	197	75.48%	p <0.0001
Incident NACM		**Total COVID- (n=3279)**	**Incidence in COVID NEGATIVE (%)**	**Total COVID+ (n=261)**	**Incidence COVID POSITIVE (%)**	**chi squared χ^2 p-value**
CARDIOMETABOLIC	No. incident cases	353	11.90	8	4.52	p=0.0028
CHRONIC KIDNEY DISEAE	No. incident cases	208	6.68	3	1.36	p=0.0017

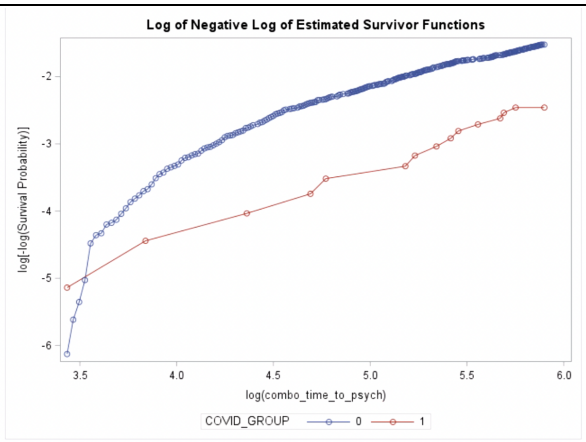
CARDIOVASCULAR DISEASE	No. incident cases	169	5.40	7	3.18	p=0.1542
DIABETES MELLITUS	No. incident cases	160	5.35	3	1.51	p=0.0172
HYPERTENSION	No. incident cases	603	24.02	9	6.98	p <0.0001
LUNG DISEASE	No. incident cases	221	7.14	6	2.58	p=0.0077
NEUROLOGIC DISEASE	No. incident cases	128	4.01	6	2.61	p=0.2914
PSYCHOLOGIC DISEASE	No. incident cases	539	19.59	14	8.19	p=0.0002
ANY NACM	No. incident cases	1449	44.19	48	18.39	p <0.0001

Appendix 6. Testing the Proportional Odds Assumption with Log-Negative-Log Curves for any and 8 NACM

NACM	**Log Negative Log Curves**	**Satisfy Proportional Odds Assumption?**
ANY NACM		Yes
CARDIOMETABOLIC*		No: Time-dependent model p-value for time variable =0.7843

CHRONIC KIDNEY DISEAE		Yes
CARDIOVASCULAR DISEASE		Yes
DIABETES MELLITUS		Yes

HYPERTENSION		Yes
LUNG DISEASE		Yes
NEUROLOGIC DISEASE*		No: Time-dependent model p-value for time variable =0.6394

PSYCHOLOGIC DISEASE*		No: Time-dependent model p-value for time variable =0.2461

*Indicates that the unadjusted model did not meet the graphical proportional odds assumption, by intersecting log negative log graphs. For these, a time-dependent model was constructed, and time was not found to be significant in any models.

Appendix 7. Unadjusted and Adjusted Hazard Ratio for Risk of Incident NACM in COVID+ versus COVID- PLWH

NACM	Unadjusted HR (95% CI)	Adjusted HR (95% CI)+
ANY NACM	0.34 (0.26, 0.45)	0.22 (0.18, 0.32)
CARDIOMETABOLIC	0.43 (0.12, 1.61)*	0.28 (0.11, 0.67)
CHRONIC KIDNEY DISEAE	0.20 (0.06, 0.62)	0.17 (0.04, 0.59)
CARDIOVASCULAR DISEASE	0.58 (0.27, 1.24)	0.48 (0.20, 1.18)
DIABETES MELLITUS	0.28 (0.09, 0.86)	0.26 (0.06, 1.06)
HYPERTENSION	0.26 (0.13, 0.50)	0.17 (0.07, 0.42)
LUNG DISEASE	0.35 (0.16, 0.79)	0.14 (0.03, 0.54)
NEUROLOGIC DISEASE	0.44 (0.07, 2.91)*	0.62 (0.25, 1.52)
PSYCHOLOGIC DISEASE	0.23 (0.08, 0.69)*	0.29 (0.15, 0.55)

*Indicates that the unadjusted model did not meet the graphical proportional odds assumption, by intersecting log negative log graphs. For these, a time-dependent model was constructed, and time was not found to be significant in any models.
+Adjusted for age at index date, sex, race, CD4+ count, viral load.

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