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# Measuring the burden of SARS-CoV-2 infection among persons living with HIV and healthcare workers and its impact on service delivery in Mozambique: protocol of a prospective cohort study

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## ABSTRACT

**Introduction** As COVID-19 continues to spread globally and within Mozambique, its impact among immunosuppressed persons, specifically persons living with HIV (PLHIV), and on the health system is unknown in the country. The '**COV**id and h**IV**' (COVIV) study aims to investigate: (1) the seroprevalence and seroincidence of SARS-CoV-2 among PLHIV and healthcare workers providing HIV services; (2) knowledge, attitudes, practices and perceptions regarding SARS-CoV-2 infection; (3) the pandemic's impact on HIV care continuum outcomes and (4) facility level compliance with national COVID-19 guidelines.

**Methods and analysis** A multimethod study will be conducted in a maximum of 11 health facilities across Mozambique, comprising four components: (1) a cohort study among PLHIV and healthcare workers providing HIV services to determine the seroprevalence and seroincidence of SARS-CoV-2, (2) a structured survey to assess knowledge, attitudes, perceptions and practices regarding COVID-19 disease, (3) analysis of aggregated patient data to evaluate retention in HIV services among PLHIV, (4) an assessment of facility implementation of infection prevention and control measures.

**Ethics and dissemination** Ethical approval was obtained from the National Health Bioethics Committee, and institutional review boards of implementing partners. Study findings will be discussed with local and national health authorities and key stakeholders and will be disseminated in clinical and scientific forums.

**Trial registration number** NCT05022407.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Efficient multimethod study design, including a cohort study design that allows for preferred seroincidence measurements, evaluation of multiple disease outcomes and confirmation of the role of service delivery context (adherence to COVID-19 mitigation measures).
⇒ Inclusion of multiple sites ensures geographic representativeness of findings.
⇒ While a robust electronic patient medical record exists, facilitating data management and analysis, data quality is dependent on the completion of clinical records.

## INTRODUCTION

In addition to direct human costs, the COVID-19 pandemic is affecting every facet of society and testing the resilience of national health systems worldwide. In Mozambique, the Ministry of Health (MOH) reported the first case of COVID-19 on 22 March 2020, and since then, >233 343 cases (as of 30 March 2023) have been reported.[1 2] Mozambique has a significant HIV burden, with approximately 2.1 million persons living with HIV (PLHIV) in 2020, the fourth highest globally. Based on recently released national population HIV impact assessment data, the country has an estimated HIV prevalence of 12.5% (15 years and older), having made significant progress towards the UNAIDS 2030 95-95-95 goals, with 71.6% of adults living with HIV 'knowing their status', 96.4% of PLHIV being on treatment and 89.4% of those on combination antiretroviral treatment (ART) being virally suppressed.[3]

The limited data currently available do not indicate that the risk of infection or complications from COVID-19 are different among

PLHIV who are clinically and immunologically stable on ART when compared with the general population.[4–6] However, PLHIV with advanced disease, with a non-suppressed virus (ie, high plasma HIV-1 RNA (viral load) values), and those who are not taking ART may have an increased risk of severe disease and related complications in general.[7 8] In addition, PLHIV may have concomitant known risk factors for severe COVID-19 disease, such as diabetes, hypertension, pulmonary disease, obesity and other non-communicable diseases.[9 10]

A review from data in sub-Saharan Africa showed that access to HIV testing and ART initiation was reduced,[11] while impact on retention was seen as a concern.[12] In Mozambique, differentiated service delivery (DSD) models have been rapidly implemented as part of the COVID-19 mitigation measures, with favourable preliminary HIV continuum of care results being seen in health facilities (HF) where these DSD models have been successfully implemented.[13] A Mozambique National COVID-19 Vaccination Plan describes a phased roll-out, with healthcare and other essential workers, elderly persons and persons with known diabetes mellitus being deemed highest priority for vaccine administration.[14] Mozambique received its first batch of COVID-19 vaccine doses in March 2021.[15] The country initially started vaccine administration only for healthcare providers and high-risk groups, and expanded to the general population in September 2021, with 44% of the population completely vaccinated by May 2022.[16] Although COVID-19 vaccination is not mandatory, acceptance to the prime vaccination was high, particularly in priority groups such as healthcare providers (coverage >90%). Available COVID-19 vaccines include Sinopharm, Covishield, Janssen Ad26.COV2.S and most recently Pfizer BioNTech.[17]

This '**COV**id and h**IV**' (COVIV) protocol is designed to evaluate the impact of the COVID-19 epidemic on clinical and immunological outcomes and healthcare service delivery among PLHIV and healthcare workers (HCW) providing HIV services in Mozambique.

### Objectives

The primary objectives of the study are:

1. To determine the seroincidence and seroprevalence of SARS-CoV-2 among unvaccinated PLHIV enrolled in care.
2. To describe the knowledge, attitudes, practices and perceived risks regarding SARS-CoV-2 prevention, transmission, management and COVID-19 vaccination among PLHIV and HCW providing HIV care.
3. To evaluate the effect of the COVID-19 pandemic on retention in HIV care services among PLHIV.

Secondary objectives are:

1. To describe the clinical, immunological and virological outcomes of HIV among those coinfected with HIV and SARS-CoV-2.
2. To describe the perceptions of PLHIV and HCW providing HIV services regarding the influence of the COVID-19 pandemic on the delivery of HIV/tuberculosis (TB) services.
3. To measure the fidelity of participating HF to the implementation of national COVID-19 prevention guidelines.
4. To describe the occurrence of documented SARS-CoV-2 breakthrough infections among vaccinated PLHIV and HCW providing HIV care.

## METHODS AND ANALYSIS

### Study design

The study has a multimethod approach (table 1): a prospective cohort study design will be used to follow PLHIV attending HIV services and HCW who are providing HIV care. Additionally, a serial cross-sectional study design applying quantitative methods (survey) will be used to assess knowledge, attitudes, practices and perceptions (KAP-P) regarding SARS-CoV-2 prevention, transmission and management among PLHIV and HCW

**Table 1** Overview of study methods and sample size

| Group | Method | Sample size estimation |
|---|---|---|
| Persons living with HIV | Cohort<br>► Repeated visits for seroincidence measurements and factors<br>► Repeated KAP-P surveys | ► Cohort 1: 288 participants per HF<br>► Cohort 2: all with SARS-CoV-2 RNA-PCR test positive<br>► Cohort 3: all with SARS-CoV-2 antibody test positive and negative RNA-PCR<br>► Cohort 4: all enrolled in cohorts 1–3 who are vaccinated during the period of their study participation<br>► KAP-P: subset of 100 included participants |
| HCW | Cohort<br>► Repeated visits for breakthrough infection<br>► Repeated KAP-P surveys<br>► Repeated in-depth interviews | ► 20–25 vaccinated participants per HF<br>► KAP-P: all included participants<br>► In-depth interviews: 6–9 per HF |
| HF level | ► Infection prevention and control assessments<br>► Retention analysis using aggregated data | Not applicable. |

HCW, healthcare worker; HF, health facility; KAP-P, knowledge, attitudes, practices and perceptions.

providing HIV services and their perceptions regarding the influence that the COVID-19 pandemic has on the delivery of essential services. In-depth interviews will be conducted to further understand how HCW providing HIV care perceive their risk of acquiring SARS-CoV-2 infection, the preparedness of HF to respond to the epidemic and the impact of the COVID-19 pandemic on access to health services. To assess the impact of the COVID-19 pandemic on 6-month and 12-month retention in care and viral suppression rates among PLHIV, a medical chart review using the Electronic Patient Tracking System (EPTS) will be done. Finally, quarterly facility assessments will measure the preparedness and fidelity of implementation of the national COVID-19 prevention guidelines.

## Study settings

This study will be conducted in up to 11 HFs of 10 provinces and the city of Maputo, aiming at covering all regions in the country. For operational reasons, only one HF per province will be selected. Criteria for site selection are: high patient volume (ie, minimum of 2000 patients receiving ART (at time of protocol writing)); minimum of overall retention to ART services of 85% to guarantee adherence to study visits; laboratory with capacity for SARS-CoV-2 diagnosis in the same town/city as the selected HF or nearby, and a reference care and treatment centre for COVID-19 disease in the same town/city as the selected HF, or nearby.

## Study participants

The study will be conducted with PLHIV enrolled in HIV care services and HCW providing HIV services. Inclusion criteria for clinic patients are: having documented HIV infection and currently in follow-up care at the selected HF; aged 18 years or older; able and willing to give informed consent; willing to test for SARS-CoV-2 antibodies and infection; willing to be followed and to comply with study visits during the study period, not intending to change residence during the study period; willing and able to provide contact information. Patients enrolled in any DSD model with ART pick-up less than four times per year and patients whose antiretroviral drugs are picked up by a designated confidant will be excluded from the study. For HCW, the inclusion criteria are: providers (eg, medical doctor, medical officer, medical aid, general or maternal and child health (MCH) nurse, pharmacy technicians, laboratory worker, health counsellor, ancillary worker (eg, archivist, receptionist) and cough officer (volunteer trained to identify suspected cases of TB at different entry points)) who are employed full-time and offering HIV services at select HF; aged 18 years or above; having received at least one dose of vaccine against COVID-19; able and willing to give informed consent; willing to test for previous SARS-CoV-2 infection; willing to be followed during the study period; not intending to transfer to another HF for employment during the study period; willing and able to provide contact information. Individuals working in the HF but from the following cadres: drivers, security personnel and community health workers/volunteers are excluded.

## Recruitment

Recruitment of PLHIV enrolled in HIV care can occur at any of the routine or unscheduled visits for their HIV care, while HCW can be recruited at any time, according to their availability. Recruitment will be done at convenience as patients attend their clinic visit and per availability of the HCW, by trained research staff that have no role in service delivery. The consent process will be done by trained research assistants, and a separate consent process will be conducted for the blood sample collection to be stored for future studies (online supplemental material S1–3).

## Data collection

### Cohort data collection

Unvaccinated participants (only PLHIV) will undergo a SARS-CoV-2 rapid antibody test (AB-RT) (Abbott Panbio COVID-19 IgG/IgM[18]), a COVID-19 risk assessment and screening of COVID-19 symptoms. The AB-RT has a sensitivity of 96% and specificity of 95.8% when using venous whole blood, and a sensitivity of 96.2% and specificity of 100% when using fingerprick whole blood.[19] The risk assessment tool was developed for the study, assessing prevention measures over the last 14 days, such as social distancing, use of face masks, recent travel history and contacts (online supplemental material S4). If SARS-CoV-2 IgM is positive, or if risk assessment is positive (regardless of the AB-RT result), the participant will undergo the PCR SARS-CoV-2 test. For those eligible for PCR testing, and if having consented, an additional 10 mL of venous blood will be collected and stored for future research. Depending on the result, the participant will be longitudinally followed in one of three cohorts: 'no active/past infection (cohort 1)' (defined as COVID-19 AB-RT negative and risk assessment negative, or COVID-19 AB-RT negative, risk assessment positive and PCR SARS-CoV-2 negative), 'active infection (cohort 2)' (defined as PCR SARS-CoV-2 positive) and 'past infection (cohort 3)' (defined as COVID-19 AB-RT IgM positive and PCR SARS-CoV-2 negative, or COVID-19 AB-RT IgG positive, risk assessment positive, PCR SARS-CoV-2 negative or COVID-19 AB-RT IgG positive, risk assessment negative).

Participants enrolled in cohort 1 are scheduled for quarterly visits, aligning with routine HIV HF visits, for up to 9 months, to retest for SARS-CoV-2 antibodies through AB-RT and screen for active infection by SARS-CoV-2 PCR, according to the study procedures. If SARS-CoV-2 AB-RT is positive, the participant will be considered a seroincident case and transferred to cohort 3, or if acute SARS-CoV-2 infection is confirmed, to cohort 2 (infected). Participants with active SARS-CoV-2 infection will be followed up as per national guidelines. A telephone contact will be scheduled 7, 14 and 30 days after COVID-19 diagnosis (SARS-CoV-2 PCR positive) to ask

Table 2 Cohort 1 (no active/past SARS-CoV-2) schedule of events

| Visit | 0 (baseline) | 1 | 2 | 3 | Unplanned |
|---|---|---|---|---|---|
| **Activity** | **Entry** | **Month 3** | **Month 6** | **Month 9** | **Unplanned** |
| Consenting procedures | X | | | | |
| Clinical history and COVID-19 risk assessment | X | X | X | X | X |
| Targeted physical examination | X | X | X | X | X* |
| CD4 cell count† | X | If indicated | If indicated | If indicated | If indicated |
| HIV-1 VL‡ | X | If indicated | If indicated | If indicated | If indicated |
| Complete blood count§ | X | If indicated | If indicated | If indicated | If indicated |
| SARS-CoV-2 rapid antibody test (finger prick, or EDTA sample where possible) | X | X | X | X | X |
| RNA-PCR SARS-CoV-2§ | If indicated | If indicated | If indicated | If indicated | If indicated |
| Sample (6 mL EDTA+4 mL serum) for future analyses, if consenting¶ | If indicated | If indicated | If indicated | If indicated | If indicated |
| KAP-P survey** | X | X | X | | |

*Brief clinical history.
†If HIV-positive participant.
‡If HIV-positive; at enrolment, HIV-1 VL test will only be performed if HIV-1 VL results are not available in the last 6 months before enrolment or not eligible for HIV-1 VL as per national guidelines.
§If suspicion of COVID-19 infection.
¶If eligible for SARS-CoV-2 PCR testing and consenting to additional sample.
**In a subset of HIV-positive participants.
KAP-P, knowledge, attitudes, practices and perceptions; VL, viral load.

about symptoms, possible complications and contacts/exposures. Participants with active infection and those who had a previous SARS-CoV-2 infection receive a study visit at 3 and 6 months. Participants will receive a monthly call to screen for possible signs and symptoms since last study contact, and to remind them of their next scheduled study visit. In case of any signs and/or symptoms of COVID-19 infection, the participant will be invited for a thorough check-up to exclude infection.

Participants who declare having received at least one dose of COVID-19 vaccine (verbally or by showing their vaccination card) at inclusion (HCW or PLHIV) or at any follow-up visit (PLHIV) will be enrolled and followed in 'cohort 4' (vaccinated), for up to 9 months or until the end of study implementation. A risk assessment, targeted clinical exam, collection of a dried blood spot sample and if having consented, collection of an additional 10 mL venous blood to store for future research, will be done at enrolment and every subsequent longitudinal visit. If risk assessment positive, a sample collection for SARS-CoV-2 PCR testing will be done to diagnose/exclude breakthrough infection. Study activity schedules are described in tables 2–5, and summary of SARS-CoV-2 testing in online supplemental figure 1.

A subset of enrolled PLHIV and all enrolled HCW will be requested to complete a serial survey on KAP-P regarding SARS-CoV-2 infection and access to care. For enrolled PLHIV, systematic sampling will be followed, where every third participant included will be invited for the survey. The survey will be conducted at baseline and month 6 (for all cohorts), while an additional survey at 3 months will be conducted for participants in cohort 1 to monitor more regularly possible changes in attitudes and practices that could lead to COVID-19 infection. In addition to the KAP-P survey, a subset of the enrolled HCW will be selected to participate in in-depth interviews, using a semi-structured interview guide, at baseline and month 6. Recruitment will be done via non-random, non-systematic convenience sampling, with invitation of eligible HCW participating in the study who are available and agreeing to participate on the day of data collection.

### Aggregated data collection

Retention in HIV services and viral suppression rates will be computed using aggregated HF-level data on ART pick-ups and routine viral load results of the prepandemic period (April 2019–March 2020) and the during-pandemic period (April 2020–end of study). Patient data are routinely available from the EPTS used in Mozambique (OpenMRS (www.openmrs.org)). The 3-month, 6-month and 12-month retention in care is defined as being enrolled in HIV care and active (as not having missed an ART pick-up 59 days or more after last scheduled visit) at 3, 6 and 12 months, respectively. Viral suppression is defined as having a viral load measurement <1000 copies/mL.

### Health facility assessment

An assessment of the HF's adherence to COVID-19 prevention measures will be conducted at baseline, and then quarterly until study completion, using a tool based on the MOH infection prevention and control

**Table 3** Cohort 2 (active SARS-CoV-2 infection) schedule of events

| Visit | 0 (baseline) | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| **Activity** | **Entry** | **Day 7*** | **Day 14*** | **Month 1** | **Month 3** | **Month 6** |
| Consenting procedures | If applicable† | | | | | |
| Clinical history, COVID-19 risk assessment | X | | | | X | X |
| Targeted physical examination | X | | | | X | X |
| Targeted clinical history | X | X | X | X | X | X |
| CD4 cell count‡ | X | | | | X | X |
| HIV-1 VL‡ | X | | | | X | X |
| Complete blood count§ | X | | | | If indicated | If indicated |
| SARS-CoV-2 rapid antibody test | X | | | | X | X |
| RNA-PCR SARS-CoV-2¶ | X | | | | If indicated | If indicated |
| Sample (6 mL EDTA+4 mL serum) for future analyses, if consenting | X | | | | X | X |
| KAP-P survey** | X | | | | | X |

*Phone call.
†Only applicable for participants enrolled into cohort 2 on the first study visit (transitioning participants are covered in the initial consent).
‡If HIV-positive, collect 5 mL on EDTA for CD4 cell count, HIV-1 VL.
§In HIV-positive patients, complete blood count will be done using the 5 mL EDTA collected for CD4 cell count and HIV-1 VL.
¶Only if new COVID-19 infection is suspected, or when symptoms remain.
**In a subset of HIV-positive participants.
KAP-P, knowledge, attitudes, practices and perceptions; VL, viral load.

(IPC) performance assessment tool, covering four areas: general aspects/human resources, aspects per service, COVID-19 prevention measures, material/waste management (online supplemental material S5).

### Outcomes of interest

Clinical outcome measures among unvaccinated participants are the seroprevalence and seroincidence of SARS-CoV-2, while among vaccinated participants, breakthrough SARS-CoV-2 infection will be tracked. Immunological and virological HIV status among PLHIV with active SARS-CoV-2 will be followed (both vaccinated and unvaccinated), and clinical outcomes of COVID-19, including hospitalisation and death, will be recorded. Outcomes measuring knowledge, attitudes, practices and perceived risks regarding SARS-CoV-2, prevention, transmission and management among PLHIV and HCW providing HIV services will be assessed, as well as level of HF adherence/compliance of IPC measures and HF-level retention to HIV care.

**Table 4** Cohort 3 (past SARS-CoV-2 infection) schedule of events

| Visit | 0 (baseline) | 1 | 2 |
|---|---|---|---|
| **Activity** | **Entry** | **Month 3** | **Month 6** |
| Consenting procedures | If applicable* | | |
| Clinical history and COVID-19 risk assessment | X | X | X |
| Targeted physical examination | X | X | X |
| CD4 cell count† | X | X | X |
| HIV-1 VL† | X | X | X |
| Complete blood count‡ | X | If indicated | If indicated |
| SARS-CoV-2 rapid antibody test | X | X | X |
| RNA-PCR SARS-CoV-2‡ | If indicated | If indicated | If indicated |
| Sample (6 mL EDTA+4 mL serum) for future analyses, if consenting | X | X | X |
| KAP-P survey§ | X | | X |

*Only applicable for participants enrolled into cohort 3 on the first study visit (transitioning participants are covered in the initial consent)
†If HIV-positive, collect 5 mL on EDTA for $CD4^+$ T-cell count and HIV-1 VL.
‡Only if new COVID-19 infection is suspected.
§In a subset of HIV-positive participants.
KAP-P, knowledge, attitudes, practices and perceptions; VL, viral load.

Table 5 Cohort 4 (vaccinated) schedule of events

| Visit | −1 | 0 (baseline) | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Activity | Entry | M0* | M3 | M6 | M9 |
| Consenting procedures | X | | | | |
| Clinical history and COVID-19 risk assessment | X | X | X | X | X |
| Targeted physical examination | | X | X | X | X |
| CD4 cell count† | | X | X | X | X |
| HIV-1 VL† | | X | X | X | X |
| Complete blood count‡ | | If indicated | If indicated | If indicated | If indicated |
| Sample DBS | | X | X | X | X |
| Sample (6 mL EDTA+4 mL serum) for future analyses, if consenting) | | X | X | X | X |
| RNA-PCR SARS-CoV-2‡ | If indicated | If indicated | If indicated | If indicated | If indicated |
| KAP-P survey§ | | X | | X | |
| In-depth interview¶ | | X | | X | |

*Baseline visit (M0) to be scheduled at least 2 weeks after complete vaccination, as per vaccination schedule (ie, being fully vaccination).
†If HIV positive, collect 5 mL on EDTA for CD4 cell count and HIV-1 VL.
‡Only if new COVID-19 infection is suspected.
§All HCWs and a subset of PLHIV.
¶In a subset of HCWs.
DBS, dried blood spot; HCW, healthcare worker; KAP-P, knowledge, attitudes, practices and perceptions; PLHIV, persons living with HIV; VL, viral load.

## Covariates

Demographic and clinical data from patients' medical records that include age, sex, education, marital status at enrolment in HIV care, date of enrolment in HIV care, date of ART initiation, ART regimen, body mass index, CD4 cell count (continuous, and by strata, ie, <200, 201–350, 351–500 and >500 cells/mm$^3$), HIV-1 RNA (viral load) (continuous and stratified as virally suppressed or not), WHO clinical stage, prevalence of past or current tuberculosis, haemoglobin and full blood count and records of ART pick-ups will be collected. Variables related to past and current clinical history (including pre-existing conditions such as hypertension, diabetes mellitus, lung disease, malignancy, current signs and symptoms of COVID-19 infection) and risk assessment for SARS-CoV-2 infection will be assessed at the study visits according to the schedule of events (tables 2–5). Study-specific laboratory information such as complete blood count, antibody and RNA-PCR tests for SARS-CoV-2, CD4 cell count will be captured by the study team. The survey includes topics on knowledge of SARS-CoV-2 infection and COVID-19 disease, source of information, attitudes regarding COVID-19 prevention measures and risks, health-seeking behaviour and perceptions on the effect of the pandemic on health service provision and satisfaction regarding the services. HCWs' interviews will include questions regarding risk perception, individual preparedness, HF preparedness and perceptions regarding workload and access to care.

## Data collection and management plan

All involved staff will be trained on the protocol prior to data collection. Data collection will take place in a confidential study room to ensure privacy and avoid response bias. Demographic, clinical and laboratory data will be captured on case report forms (CRF). All extracted data will be labelled with the participant's study identification number. Data captured on CRF will be double entered by trained study staff at the local level into a REDCap data collection repository, a secure, web-based application that stores data on the user institution's secure server.[20 21] All source documents will be kept in a secure room at the site until the study completion. A monthly back-up of the electronic databases will be kept securely at the site and a copy will be sent to the main study database. The in-depth interviews will be audio-recorded and complemented by written notes. The audio recordings and notes will be transcribed verbatim in Portuguese. Data of the study will be owned by the Instituto Nacional de Saúde, and data will be available on reasonable request.

## Sample size

The sample size to estimate incidence proportion of seroconversion in cohort 1 is calculated using the sample size for estimation of a proportion methodology. Based on modelling estimates available at the time of protocol writing,[22] we estimate that within 2 years, 60% of the population will be infected with SARS-CoV-2 virus. As our cohort will be followed for 9 months, we assumed that 23% will be infected during the follow-up period. The sample size to estimate this proportion with a margin of error of 5% and a 95% significance level ($\alpha$=0.05) is 273 for each HF. Allowing for a 5% loss-to-follow-up rate during the study period (9 months), we adjust the sample size to 288 PLHIV to be enrolled, per HF. We allow all HCW meeting the inclusion criteria to be included, estimating that

25–30 will be included. Any study participant diagnosed with SARS-CoV-2 infection at enrolment, or with a SARS-CoV-2 AB-RT positive/PCR negative will be included for follow-up on cohort 2 or cohort 3, respectively.

The KAP-P survey will be conducted among a subgroup of the cohort of PLHIV, and among all participating HCW. Due to the exploratory nature of this study objective, sample sizes were not calculated based on existing assumptions. We estimate that 125–130 interviews (100 PLHIV and 25–30 HCW) per HF will provide us with the requisite baseline preliminary data on knowledge, attitudes and practices around SARS-CoV-2 infection and prevention recommendations. A subset of HCW will be invited for an in-depth interview, to explore the risk perceptions for HCW and the consequences of the pandemic on healthcare provision. As per qualitative research methodology,[23] we estimate that saturation will be reached with a range of two to three HCW at three health sectors: MCH, TB/HIV and ART services, for a total of 6–9 HCW per HF to be interviewed at baseline and 6 months. For retention analysis, we intend to compare the proportion of patients retained in care before and after the pandemic, across all sites. We expect to detect a decrease in patients retained in care of 2%, with at least 95% power and type I error fixed at 5%.

## Analysis plan

### Seroprevalence, seroincidence and risk factors

Descriptive statistics will be used to summarise participant characteristics, overall and stratified by site. For the *unvaccinated cohort*, baseline seroprevalence of SARS-CoV-2 will be defined as the number of patients with a positive SARS-CoV-2 AB-RT at the enrolment visit among the number of patients enrolled. Seroincidence rate of SARS-CoV-2 will be computed by calculating the number of seroconversions per 100 person-years at risk of seroconversion, based on exposure time. Exposure time is defined as the interval from initial negative anti-SARS-CoV-2 antibody RT to seroconversion, for those who seroconvert or to last negative RT for those who do not. The date of seroconversion will be calculated as the midpoint between the visit dates of the last negative test and first positive test. We will consider the participant's first seroconversion occurring during the follow-up. Univariable and multivariable generalised linear mixed models (GLMM) with study sites as clusters will be used to evaluate risk factors for seroprevalence and seroincidence of SARS-CoV-2, as well as variations of viral load (log-transformed), CD4 cell count and immunological response to SARS-CoV-2, over time. A logit link function will be used to regress binary variables (eg, viral suppression) on the variables of interest and a linear link to regress continuous outcomes (eg, CD4 cell count and viral load (log-transformed)); if the normality assumptions are not satisfied, we will use ordinal regression instead. Similar models will be used to assess the impact of demographical, clinical variables and time on ART on disease severity, defined as having any severe or critical disease or not, as per WHO definition.[24] Kaplan-Meier and Cox regression model will be used to model the time to SAR-CoV-2 infection, overall and stratified by PLHIV and HCW.

For the *vaccinated cohort*, descriptive statistics will be done for the occurrence of breakthrough infection.

### Quantitative survey data

Results from KAP-P surveys will be presented via frequency tables and cross-tabulations. Results will be stratified by visits and compared using appropriate non-parametric tests: Friedman test for continuous or McNemar test for categorical variables. Exploratory factor analysis (EFA) will be used to group the survey question in underlying structures (factors) and relate them to the larger KAP-P outcomes: knowledge, attitudes, practices and perceived risks. EFA will first be use for each time period and for individual sections of the survey (knowledge, attitudes, practices and perceived risks) separately. Scree plots will be used to determine the number of factors retained. Each factor will receive a weight, corresponding to its contribution towards the main outcome (eg, knowledge). These weights will later be used as an outcome in a GLMM, adjusting for demographics and clinical variables as fixed effects and study sites will be treated as random effects. This will allow us to identify variables associated with the outcome (eg, variables associated with higher knowledge or, more precisely, with the extracted factors for knowledge). Then, exploratory multilevel factor analysis will be used to account for repeated observations collected at different time points.[25] The final scores will be used in a multivariable regression analysis, adjusting for the same covariates as above, but now taking interview round into account. This will allow us to use the longitudinal nature of the data and again see variables associated with the larger KAP-P outcomes (ie, with the factors related to them). Each outcome, knowledge, attitudes, practices and perceived risks will be analysed separately. Missing data, if any, will be imputed and results will be combined via Rubin's rule.

### Qualitative data

For the qualitative data, thematic analysis will be performed.[26] A codebook will be developed based on the significant factors identified from literature of similar research.[27–31] Inductive codes will be added during the initial analysis, following the qualitative analysis standards. Transcriptions will be coded by two researchers working independently, and results will be compared with assess inter-rater reliability. After being sorted by theme, data will be summarised, synthesised and abstracted in each category and subcategory.

### Aggregated clinical and laboratory data

To evaluate the impact of the COVID-19 pandemic on retention to HIV care, an interrupted time series will be used. Missing data, if any, will be imputed 20 times from an imputation model that will use all baseline variables as predictors. Final results will be computed via Rubin's

rule, and final results will be presented in terms of point estimates and 95% CIs.

### Quantitative health facility assessment data

Descriptive analysis will be used to present compliance to MOH COVID-19 guidelines and patient navigation algorithm in the HF, disaggregated by health staff cadre and sector within the HF.

Quantitative analyses will be conducted in the statistical software R, V.4.2.0 or greater,[32] qualitative analysis using software MAXQDA[33] or similar.

### Limitations

Routinely collected data are sensitive to data entry errors and/or missing data. Multiple imputation will be performed to address missing data. There is a risk of response bias for the surveys. The study team will be trained on interview procedures and interview techniques and pretesting will be done, to minimise bias. The long follow-up period, change in routine care to DSD models such as multimonth ART dispensation, could influence retention. Monthly contact with study participants will be done to decrease risk of lost to follow-up.

## ETHICS AND DISSEMINATION

### Ethical approval

The protocol, consent forms, study forms and any advertising material were approved by the National Health Bioethics Committee of Mozambique (Ref. 169/CNBS/22; March 2022; protocol V.1.7), and the Institutional Review Boards (IRB) of collaborating implementing partners (EGPAF Pro00048445, 30 May 2022; ICAP IRB-AAAT5209, 3 March 2021; Vanderbilt University Medical Center #201887, 20 May 2022; Abt Associates IRB# 2095, 14 March 2021). This project was reviewed in accordance with the US Centers for Disease Control and Prevention (CDC) human research protection procedures (45 CFR part 46; 21 CFR part 56), and was determined to be research. The CDC co-investigators will not be engaged in data collection. Written informed consent will be obtained individually before any study procedure takes place. Adverse events will be notified to the ethics committees and sponsor as appropriate.

### Patient confidentiality

Each participant will be assigned a study identification number for use on all study forms. Personal identifiers in order to trace participants when needed will be collected on separate forms and stored separately, with limited access. All study documents will be stored in locked rooms or cabinets with access limited to appropriate study staff. Sample for future analysis related to immunological or genetic responses will be labelled with a laboratory study identification, composed of the unique study identification number, visit number and date of sample collection. Databases will be password-protected.

### Discontinuation/Withdrawal

Participants can withdraw from the study at any time without prejudice. If a participant misses a study visit, attempts will be made to contact the participant to determine the reason for the missed visit and to schedule the next study visit. If contact is not achieved for two consecutive study visits, the participant will be considered lost-to-follow-up. If participants who are lost-to-follow-up should return, study participation may resume. A participant will also be terminated from the study if the participant develops any significant medical, psychological/psychiatric or social condition which, in the judgement of the study investigator, might interfere with the conduct of the study or the safety of the participant.

### Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

### Dissemination plan

Quarterly reports summarising recruitment progress and initial findings will be shared with health authorities. Results from this study will be shared with IRB committees, health authorities and key stakeholders including those involving patients and healthcare providers. In addition, it is expected that data from this study will be presented at relevant national and/or international scientific conferences with findings being published in manuscript format in peer-reviewed journals.

### Study status

This publication is based on V.1.7 of the COVIV protocol dated 1 February 2022. Study enrolment began under the approved V.1.3 (6 October 2020) on 15 June 2021. As of 01 January 2023, 1416 participants had been enrolled across four active study sites. An amendment of the protocol was developed and approved for inclusion of vaccinated persons. The estimated end of data collection is 30 June 2023; recruitment of participants is completed as per January 2023.

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**Contributors** CDS, EV, NB, PWY contributed to the conception of the study. The protocol was written by CDS, EV, NB, PWY, TM, EPDG, EN and DB. The study instruments were developed by CB, EN, FJ, HM, DB, AM, and reviewed by CDS, EV, NB, EPDG, TM, PWY. TM, EN, AM were involved in the qualitative methodology; HM was responsible for the infection control and prevention assessments tools of the study protocol. Statistical aspects and analysis plan of the protocol were developed by GA. CDS wrote the first draft of the manuscript with input from EN, CB, PWY, NB, FJ, EPDG, HM, AM, DB, MAO, TM, RC, GA. EV provided overall review and technical guidance. All authors reviewed the final manuscript and give final approval for publication.

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**Competing interests** None declared.

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