COVIDHIV
Clinical Characterisation Protocol for COVID-19 in People living with HIV

Version no. 1.0 dated 08/04/2020 Project Code: **APHP200475**/IDRCB no.: 2020-A00984-35

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SIGNATURE page for a research PROTOCOL

Research code number: **APHP200475**

Title: Clinical Characterisation Protocol for COVID-19 in People living with HIV
Acronym: COVIDHIV

Version no. 1.0 dated 08/04/2020

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

Coordinating Investigator:

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1 SUMMARY

Full title	Clinical Characterisation Protocol for COVID-19 in People living with HIV
Acronym/reference	COVIDHIV
Coordinating investigator	*Dr* Antoine Chéret, Internal medicine department of Pr Cécile Goujard, Bicêtre hospital
Scientific Director (if applicable)	Scientific responsible for laboratory examinations : Dr Avettand Fenoël Véronique, Dr Delphine Dujardin, Dr Anne Marie Roque Afonso
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Infectious diseases are a major cause of death worldwide. Recently a new coronavirus named SARS-CoV-2 has been identified as responsible of an initial epidemic respiratory disease, named COVID-19, in China since the 31 December 2019[1]. COVID-19 has developed into a pandemic, with small chains of transmission in many countries and large chains resulting in extensive spread in a few countries, such as Italy, Iran, South Korea, and Japan [2] . Most countries are likely to have spread of COVID-19, at least in the early stages, before any mitigation measures have an impact and the COVID -19 epidemic is gradually taking hold in France [3]. There is very little data so far to determine whether people living with HIV (PLWHIV) are at greater risk of COVID-19 acquisition or severe disease. HIV infection is associated with deficiencies in both humoral and cell-mediated immunity that could potentially alter the course and severity of common infections. Although use of cART partially restore immune system, HIV-infected persons may remain at increased risk for morbidity associated with viral illnesses, especially if the ability to generate antigen-specific responses remains impaired 5. Additional factors, such as the high prevalence of smoking and chronic lung diseases among such patients, may further predispose HIV-infected patients to respiratory tract infections. Finally, they could be considered more vulnerable to SARS-CoV-2 infection because their immune systems are already under strain and cannot avoid the possibility of atypical presentations in these patients. Thus, we would like to implement a research as soon as possible concerning PLWHIV in order to adapt the care of these patients as fast as possible. **We will study the correlation between clinical and immunovirological data. The singularity of this work is to have an in-depth immunovirological approach linked to the clinical characteristics in COVID-19 HIV co-infected patients. COVIDHIV is the only study to date to offer this combined approach in PLHIV.**
Main objective and primary	In potential participants meeting the entry criteria, our

endpoint	primary objectives is to describe course of COVID-19 disease in patients infected with HIV-1, and more specifically to: • Describe the clinical and the biological features of the COVID-19 disease in PLWHIV • Correlate the clinical characteristics with the immunovirological characteristics obtained. • Describe the major complications and determine the factors associated with a worse evolution in PLWHIV • Compare the data obtained to those of the similar works in progress in non PPLWHIV • Evaluate post-infectious clinical effects at a distance from the acute phase. Primary endpoint are : • Clinical and biological features of the COVID 19 in PLWHIV. • Rate of major complications and factors associated with a worse evolution in PLWHIV. • Clinical and biological features, complications and risk factors in non PLWHIV studies vs similar data in the present study. • Rate of post-infectious clinical events after the acute phase.
Secondary objectives and endpoints	Secondary objectives are to collect evidence in order to: • Observe, where appropriate and feasible, pathogen replication, excretion and evolution, within the host, and identify determinants of severity and transmission using viral quantification and high-throughput sequencing of pathogen genomes obtained from respiratory tract, blood, urine, stool, saliva, semen, CSF or other samples if indicated. • Characterise, the host responses to infection and therapy over time, including innate and acquired immune responses and specifically the SARS-CoV-2 specific T-cell immune responses in the patients (specific T-cells), and gene expression profiling in peripheral blood. • Identify host genetic variants associated with disease progression or severity • To assess the impact of SARS-CoV-2 infection on clinical outcome of HIV infection • Evaluate the impact of the SARS-CoV-2 infection on HIV viral dynamics including HIV reservoir, HIV transcriptional activity and residual viremia. • Evaluate the impact of the COVID-19 on HIV immune responses • Describe response to combined antiretroviral therapy and COVID 19 novel therapies

	• Evaluate patient reported outcomes: care satisfaction, quality of life, knowledge and understanding of the procedure care. Secondary endpoints • Rate of pathogen replication, excretion and evolution in the host and determinants of severity and transmission (using viral quantification and high-throughput sequencing of pathogen genomes from respiratory tract, blood, urine, stool, saliva, semen, CSF or other samples). • Description of host responses to infection and therapy over time (including HIV treatment), including innate and acquired immune responses and specifically the COVID-19 specific T-cell immune responses and gene expression profiling in peripheral blood. • Host genetic variants associated with disease progression or severity. • Rate of transmissibility and of the different clinical outcomes following exposure and infection. • Impact of COVID-19 on HIV viral dynamics including HIV reservoir, HIV transcriptional activity and residual viremia. • Impact of the COVID-19 infection on HIV immune responses. • Rate of clinical and immunovirological responses to treatment including novel therapeutics. • Patient reported outcomes: care satisfaction, quality of life, knowledge and understanding of care procedure, to all outpatients and if possible to inpatients: HADS Hospital anxiety and depression scale, PCL-5 (post-traumatic stress disorder checklist version DSM-5), symptoms with the modified Justice Symptom Index
Design of the study	This protocol is a **historical and prospective cohort study** of PLWHIV presenting COVID-19
Population of study participants	This study will enroll 250 adult patients living with HIV (PLWHIV) with confirmed infection with SARS-CoV-2 since 1st January 2020. Recruitment of patients with Day 1 (enrolment) data is the priority. Twenty adult patients living with HIV (PLWHIV) without confirmed infection with SARS-CoV-2 will be enrolled only for qualitative interview. In order to be the most representative of PLHIV population and reach the number of patients to be included : - People who do not have social security affiliation or who are eligible may be included in the study. A derogation will be requested from the CPP for this. - The study will include pregnant or lactating women

	who meet the study's eligibility criteria.
Inclusion criteria	➢ <u>Inclusion criteria for patients with COVID19</u> • Patient living with HIV (PLWHIV) • Patient with confirmed infection with SARS-CoV-2 **since 1st January 2020** with and without criteria of hospitalisation. ➢ <u>Inclusion criteria for the 20 patients without COVID19 (who will only realize the qualitative interview)</u> • Patient living with HIV (PLWHIV) • Patient who did not have COVID-19
Exclusion criteria	➢ <u>Exclusion criteria for patients with COVID19</u> • Confirmed diagnosis of another pathogen than SARS-CoV-2 • Refusal by participant, or appropriate representative. • Being under guardianship or trusteeship mandate for future protection • Participate to another study without consent of the promoter • Patients less than 18 years old • No Beneficiary or entitled to a social security scheme or state medical aid. ➢ <u>Exclusion criteria for the 20 patients without COVID19 (who will only realize the qualitative interview)</u> • Refusal by participant, or appropriate representative. • Being under guardianship or trusteeship mandate for future protection • Participate to another study without consent of the promoter • Patients less than 18 years old • No Beneficiary or entitled to a social security scheme or state medical aid.
Other interventions added by the study	Research interventions include prospective collection of clinical data and biological sampling (blood,saliva, tear urine, stool, respiratory tract, semen, CSF or other samples if indicated.). Auto-Questionnaire will be collected too. Qualitative interview will be realized only in 40 patients (20 with COVID-19 and 20 without COVID-19)
Expected benefits for the participants and for society	There will be no direct benefit to research participants. The study may include biological sampling in addition to sampling required for medical management. The results of the tests done on these samples may not contribute to improving the participant's health. The results of this study will not be available in time to contribute to the participant's care. Where possible, test results with potential relevance to patient care will be informed to the participant and/or treating doctor. The

	feasibility of this will depend on local resources. Some assays cannot immediately benefit the patient because data will need to be pooled with others, or because the assays take time. Expected collective benefits if the research results are conclusive, are : • Correlate the clinical characteristics with the immunovirological characteristics obtained. • Facilitate effective triage and clinical management of PLWHIV with COVID-19 • Determine infectivity and appropriate infection control measures of the various pathogens • Develop clinical guidance documents and offer clinical recommendations for PLWHIV to policy makers on the basis of evidence obtained.
Minimal risks and burden added by the study	Known and foreseeable risks for the research are : Inconvenience, phlebotomy, discomfort of respiratory swab, risk of bleeding from venepuncture sites.
Scope of the study	Patients who meet the inclusion/non-inclusion criteria and who have given informed consent to participate directly or have been consented by a trustworthy person if she/he is not in a state to consent at the time of inclusion. All patients will have clinical information collected either directly through examination including a review of medical, **or from available medical notes in case of a retrospective inclusion**. Clinical data and biological sampling (blood,saliva, tear urine, stool, respiratory tract, semen, CSF or other samples if indicated.) will be collected. Auto-Questionnaire will be collected too. Qualitative interview will be realized only in 40 patients (20 with COVID-19 and 20 without COVID-19)
Number of participants included	This study will enroll 250 adult patients living with HIV (PLWHIV) with confirmed infection with SARS-CoV-2 **since 1st January 2020**. Recruitment of patients with Day 1 (enrolment) data is the priority. Twenty adult patients living with HIV (PLWHIV) without confirmed infection with SARS-CoV-2 will be enrolled only for qualitative interview. a total of 270 patients to be included in this project
Number of centres	37 recruiting centers in France
Schedule for the study	Inclusion period : 12 months Follow-up period : 6 months Total duration : 18 months
Number of enrolments expected per site and per month	*1*
Statistical analysis	The statistical analyses will be carried out by URC APHP-PARIS SACLAY
Funding sources	*PHRC 2020*

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 CURRENT STATE OF KNOWLEDGE IN VIEW OF THE RESEARCH

Infectious diseases are a major cause of death worldwide. Recently a new coronavirus named SARS-CoV-2 has been identified as responsible of an initial epidemic respiratory disease, named COVID-19, in China since the 31 December 2019[1]. COVID-19 has developed into a pandemic, with small chains of transmission in many countries and large chains resulting in extensive spread in a few countries, such as Italy, Iran, South Korea, and Japan [2] . Most countries are likely to have spread of COVID-19, at least in the early stages, before any mitigation measures have an impact and the COVID -19 epidemic is gradually taking hold in France [3]. Among the confirmed cases of infection with the new coronavirus notified by the Chinese authorities, the frequency of the most severe forms is between 17 and 23%, and the lethality between 2 and 3%. However, mild or asymptomatic forms of the disease, which are more difficult to detect, appear to be common. It is therefore very likely that the severity of the disease estimated from the data currently available is overestimated. The overall case-fatality rate (CFR) was 2.3% (1023 deaths among 44 672 confirmed cases). No deaths occurred in the group aged 9 years and younger, while cases in those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8%CFR. CFR was elevated among those with preexisting comorbid conditions—10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer [4] . New infectious agents, such as the SARS, require investigation to understand pathogen biology and pathogenesis in the host. In order to develop a mechanistic understanding of disease processes, such that risk factors for severe illness can be identified and treatments can be developed, it is necessary to understand pathogen characteristics associated with virulence, the replication dynamics and in-host evolution of the pathogen, the dynamics of the host response, the pharmacology of antimicrobial or host-directed therapies, the transmission dynamics, and factors underlying individual susceptibility. *Members of ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium) in collaboration with the World Health Organisation* have developed a standardized protocol to help Infectious Diseases Team to elaborate a protocol for the rapid, coordinated clinical investigation of severe or potentially severe acute infections by pathogens of public health interest. It has been used previously to design protocol in response to Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV) in 2012-2013, Influenza H7N9 in 2013, viral haemorrhagic fever (Ebolavirus) in 2014, Monkeypox & MERS-coronavirus in 2018, Tick-borne encephalitis virus (TBEV) in 2019 and nCoV-2019 in 2020.

There is very little data so far to determine whether people living with HIV (PLWHIV) are at greater risk of COVID-19 acquisition or severe disease. HIV infection is associated with deficiencies in both humoral and cell-mediated immunity that could potentially alter the course and severity of common infections. Although use of cART partially restore immune system, HIV-infected persons may remain at increased risk for morbidity associated with viral illnesses, especially if the ability to generate antigen-specific remains impaired [5]. Additional factors, such as the high prevalence of smoking and chronic lung diseases among such patients, may further predispose HIV-infected patients to respiratory tract infections. Finally, they could be considered more vulnerable to SARS-CoV-2 infection because their immune system is already under strain; we also can hypothetize the possibility of atypical presentations in these patients. Thus, we would like to rapidly implement research among PLWHIV in order to adapt the care of these patients as fast as possible.

Correlate the clinical characteristics with the immunovirological characteristics obtained We also propose to study the host immune responses in the course of COVID-19 disease to evaluate: (i) the impact of the immune deficiency in PLWHIV on viral replication; (ii) the immunological mechanisms involved in the pathogenesis in PLWHIV This work has been conceived as a complement to and in conjunction with the following two ongoing projects carried out by Doctor Roger Legrand's team:

FIGHTING-OFF CORONAVIRUS (SARS-CoV-2) WITH BROAD-SPECTRUM ANTIVIRALS: ESTABLISHING ANIMAL VIRAL CHALLENGE MODEL, H2020-SC1-PHE-CORONAVIRUS-2020 EU and the study " Mise en place d'un modèle d'infection expérimentale par le virus SARS-CoV-2 chez le macaque cynomolgus" Reacting/Inserm.

We will study the correlation between clinical and immunovirological data. The singularity of this work is to have an in-depth immunovirological approach linked to the clinical characteristics in COVID-19 HIV co-infected patients. COVIDHIV is the only study to date to offer this combined approach in PLHIV.

The work proposed here, require sampling that will not immediately benefit the participants. ISARIC protocol was partially followed for the writing of this manuscript.

2.2 Hypothesis for the study

There is very little data so far to determine whether people living with HIV (PLWHIV) are at greater risk of COVID-19 acquisition or severe disease. HIV infection is associated with deficiencies in both humoral and cell-mediated immunity that could potentially alter the course and severity of common infections. Although the use of cART partially restores immune system, HIV-infected persons may remain at increased risk of morbidity associated with viral illnesses, especially if the ability to generate antigen-specific responses remains impaired [5]. Additional factors, such as the high prevalence of smoking and chronic lung diseases among such patients, may further predispose HIV-infected patients to respiratory tract infections. Finally, they could be considered more vulnerable to SARS-CoV-2 infection because their immune system is already under strain and cannot avoid the possibility of atypical presentations in these patients. This research in PLWHIV will allow to timely adapt the care of these patients.

2.3 Description of the population to be studied and justification for the choice of participants

This study will enroll 250 adult patients living with HIV (PLWHIV) with confirmed infection with SARS-CoV-2 **since 1st January 2020**. Recruitment of patients with Day 1 (enrolment) data is the priority.

Twenty adult patients living with HIV (PLWHIV) without confirmed infection with SARS-CoV-2 will be enrolled only for qualitative interview.

In order to be the most representative of PLHIV population and reach the number of patients to be included :

- People who do not have social security affiliation or who are eligible may be included in the study. A derogation will be requested from the CPP for this.

- The study will include pregnant or lactating women who meet the study's eligibility criteria.

2.4 Interventions and products which will be performed or used as standard

Medical management will be according to standard of care at the treating site and not a part of this research protocol.
You will be allowed to continue taking the treatments prescribed to you as part of the treatment or as part of another clinical trial. If you participate in a therapeutic trial, the treatment protocol data may be observed if possible.

2.5 Interventions added for the research

Research interventions include prospective collection of clinical data and biological sampling (blood, urine, saliva tear, stool, respiratory tract, semen, CSF or other samples if indicated). Auto-Questionnaire will be collected too. Qualitative interview will be realized only in 40 patients (20 with COVID-19 and 20 without COVID-19)

2.6 Summary of the known and foreseeable benefits and risks for the research participants

There will be no direct benefit to research participants. The study include biological sampling in addition to sampling required for medical management. The results of the tests done on these samples may not contribute to improving the participant's health. The results of this study will not be available in time to contribute to the participant's care. Where possible, test results with potential relevance to patient care will be informed to the participant and/or treating doctor. The feasibility of this will depend on local resources. Some assays cannot immediately benefit the patient because data will need to be pooled with others, or because the assays take time.

Expected collective benefits if the research results are conclusive, are :

- Correlate the clinical characteristics with the immunovirological characteristics obtained.
- Facilitate effective triage and clinical management of PLWHIV with COVID-19
- Determine infectivity and appropriate infection control measures of the various pathogens
- Develop clinical guidance documents and offer clinical recommendations for PLWHIV to policy makers on the basis of evidence obtained.

Known and foreseeable risks for the research are:

Inconvenience.

Participation in this research study poses a minimal risk of inconvenience through household visits and attendance of follow-up visits. Appropriate compensation for travel costs to attend follow-up visits and for time of attending visits will be given according to the standard policies of the sponsor.

Phlebotomy.

Participants may have blood drawn more often than is required for standard care. Phlebotomy can be associated with pain at the draw site and rarely with infection. Daily blood draw volumes have been restricted according to weight so that combined clinical and research sampling is within recommended limits. Discomfort will be minimized by having expert staff obtain blood samples, and by combining research sampling with routine clinical sampling, where possible, which normally occurs daily in acutely unwell patients in hospital.

Discomfort of respiratory swabs.

Collecting respiratory swabs may be cause transient discomfort. Discomfort and risk will be minimized by using experienced clinical staff at each site, and samples will be taken at the same time as clinical samples in order to minimize these risks.

Incidental findings in genetic testing.

This study includes genetic testing to identify host genetic variants associated with disease progression or severity. There is a very small chance that these tests may result in the incidental discovery of information that is relevant to the participant's health. Since the samples will be analysed anonymously in batches, and generally in non-clinical laboratories with investigational techniques, we will not attempt to identify and inform participants of any results from genetic tests. If we were to do so, there would be a considerable risk of accidental harm in the form of unnecessary anxiety and distress.

Specific risks for VHF patients

Participants with VHF may be at increased risk of bleeding from venepuncture sites. The decision to perform venepuncture for research purposes will only be performed following discussion with the attending clinician and only if venepuncture is deemed not to pose unacceptable risk to the patient and/or staff. When at risk venepuncture will be minimised by limiting research venepuncture to coincide with clinical venepuncture.

3 OBJECTIVES OF THE RESEARCH

3.1 Main objectives of the research

In potential participants meeting the entry criteria, our primary objectives is to describe course of COVID-19 disease in patients infected with HIV-1, and more specifically to:

- Describe the clinical and the biological features of the COVID-19 disease in PLWHIV
- Correlate the clinical characteristics with the immunovirological characteristics obtained.
- Describe the major complications and determine the factors associated with a worse evolution in PLWHIV
- Compare the data obtained to those of the similar works in progress in non PPLWHIV
- Evaluate post-infectious clinical effects at a distance from the acute phase.

3.2 Secondary objectives

Secondary objectives are to:

- Observe, where appropriate and feasible, pathogen replication, excretion and evolution, within the host, and identify determinants of severity and transmission using viral quantification and high-throughput sequencing of pathogen genomes obtained from respiratory tract, blood, urine, stool, saliva, semen, CSF or other samples if indicated.

- Characterise, the host responses to infection and therapy over time, including innate and acquired immune responses and specifically the SARS-CoV-2 specific T-cell immune responses in the patients (specific T-cells), and gene expression profiling in peripheral blood.
- Identify host genetic variants associated with disease progression or severity
- To assess the impact of SARS-CoV-2 infection on clinical outcome of HIV infection
- Evaluate the impact of the SARS-CoV-2 infection on HIV viral dynamics including HIV reservoir, HIV transcriptional activity and residual viremia.
- Evaluate the impact of the COVID-19 on HIV immune responses
- Describe response to combined antiretroviral therapy and COVID 19 novel therapies
- Evaluate patient reported outcomes: care satisfaction, quality of life, knowledge and understanding of the procedure care.

4 DESCRIPTION OF THE RESEARCH

4.1 Primary endpoint

• Clinical and biological features of the COVID 19 in PLWHIV.
• Rate of major complications and factors associated with a worse evolution in PLWHIV.
• Clinical and biological features, complications and risk factors in non PLWHIV studies vs similar data in the present study.
• Rate of post-infectious clinical events after the acute phase.

4.2 Secondary endpoints

• Rate of pathogen replication, excretion and evolution in the host and determinants of severity and transmission (using viral quantification and high-throughput sequencing of pathogen genomes from respiratory tract, blood, urine, stool, saliva, semen, CSF or other samples).
• Description of host responses to infection and therapy over time (including HIV treatment), including innate and acquired immune responses and specifically the COVID-19 specific T-cell immune responses and gene expression profiling in peripheral blood.
• Host genetic variants associated with disease progression or severity.
• Rate of transmissibility and of the different clinical outcomes following exposure and infection.
• Impact of COVID-19 on HIV viral dynamics including HIV reservoir, HIV transcriptional activity and residual viremia.
• Impact of the COVID-19 infection on HIV immune responses.
• Rate of clinical and immunovirological responses to treatment including novel therapeutics.
• Patient reported outcomes: care satisfaction, quality of life, knowledge and understanding of care procedure, to all outpatients and if possible to inpatients: HADS Hospital anxiety and depression scale, PCL-5 (post-traumatic stress disorder checklist version DSM-5) symptoms with the modified Justice Symptom Index.

5 DESCRIPTION OF RESEARCH METHODOLOGY

5.1 Design of the study

This protocol is a **historical and prospective cohort study** of PLWHIV presenting COVID-19.

5.2 Number of participating sites

The study is multicentre involving 37 recruitment centers in France.

5.3 Description of measures taken to reduce and prevent biases

5.3.1 Identification of participants

The participants in this research will be identified as follows:
Site number (3 digits) - Sequential enrolment number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the study.

6 IMPLEMENTATION OF THE STUDY

6.1 Schedule for the study

Duration of enrolment period	12 months
The length of participation for participants, of which:	6 months
Duration of the study	18 months

The duration of the inclusions is fixed at one year because the duration of the epidemic is unknown, in particular there could be a second epidemic peak
The patient participation period will be 6 months
The duration of the research will be of 18 months.

6.1.1 Screening visit

Identification of Potential Patients
In hospitals, eligible participants will be identified through hospital workers upon presentation at recruiting sites. **PLWHIV with a positive diagnostic test for SARS-CoV-2 will be included prospectively, as soon as possible in the following the seven days of the positive result of PCR SARS-CoV-2 test on Nasopharyngeal swab. We will also look at enrolling retrospectively all PLWHIV** participants known to be infected with SARS-CoV-2 since January 2020, with paying attention to an exhaustive recollection, comprising patients known to be dead at the time of beginning of the cohort.

6.1.2 Inclusion visit

Enrolment procedures for patients

Patients who meet the inclusion/non-inclusion criteria and who have given informed consent to participate directly or have been consented by a trustworthy person if she/he is not in a state to consent at the time of inclusion. All patients will have clinical information collected either directly through examination including a review of medical, **or from available medical notes in case of a retrospective inclusion**. Information will be recorded in the case report form. At enrolment, sites with available resources will collect sample collection (blood,saliva, tear urine, stool, respiratory tract, semen, CSF or other samples if indicated.). The day of initial sample collection will be counted as day 1. Clinical information will also be collected on discharge.

6.1.3 Follow-up visits

Follow-up of the patients

Three situations can be considered after inclusion

1-The patient is admitted in hospitalization

2-The patient will benefit of an ambulatory follow-up in medical visit at the local site

Provision of care will vary by site and by treating physician. It is not possible to define a single standard of care. Follow-up procedures will be undertaken when resources allow according to calendar describe in table 1 and 2. Regular assessment will follow local guidelines. All patients will have further clinical information recorded in the case report form events during hospitalization or during ambulatory follow-up. Biological samples will be collected for the research and the maximum volumes provided for by the regulations will be respected. Self-administered questionnaires will be completed to evaluate the Patient-Reported Outcomes (PRO) as described in table 1and 2.

The details of clinical and biological data are resumed in table 1and 2 with a different schedule depending on whether patients are inpatient or ambulatory follow-up.

3- If the patient is included retrospectively, the clinical and biological data will be retrieved from the medical record. If the diagnosis of SARS-CoV-2 infection is less than 6 months old, then it can be followed up prospectively on possible points up to M6 after the date of diagnosis.

Clinical data collected

On admission: collection of socio-demographic data, origin geographic, history (travel, return from endemic area, contact with a case), associated comorbidities, usual treatment, other treatments such as nonsteroidal anti-inflammatory. Clinical collected data (cf CRF form, addendum 6) on admission, and during follow-up: in case of ambulatory follow-up, at D1 and D20, in case of hospitalization, daily until the 14th day or discharge or death. Collecting during the follow-up of stop/modification of antiretroviral treatment, other treatments received (type, date, duration), such as antibiotics, others, oxygen therapy, mechanical ventilation.

Date of hospitalization, if this is necessary for a patient previously with an ambulatory follow-up: reason, type of complication, type of service, clinical-biological data on admission. Date of transfer to an intensive care unit, date of discharge from hospital, date of death. Clinical assessment are resumed in table 1 and 2 and addendum 6 for clinical signs collected.

Biological data collected

Standard biological containing NFS with platelets and Blood Ionogram, PAI-1 (Plasminogen Activator Type 1 Inhibitor), urea, creatinine, blood glucose, liver biology transaminases, bilirubin, alkaline phosphatase, GGT, CPK, CRP, PCR, ferritin, dDimere, fibrinogen, LDH, VHC and VHC (if necessary), TP TCA, SARS-CoV-2 on nasal secretion and TCD4 count and HIV-RNA. Immunological and virological for prospective follow-up are describe in specific part for virological and immunological aspects.

Biological sample (blood,saliva, tear, urine,stool, respiratory tract, semen, CSF or other samples if indicated.) for research are explained in table 1 and 2.

Data Collection and Sampling for Patients:

Samples and data will be collected.

Samples required for clinical management will at all times have priority over samples taken for research tests. Aliquots or samples for research purposes should never compromise the quality or quantity of samples required for medical management. Wherever practical, taking research samples should be timed to coincide with clinical sampling. Data collection is resumed in table 1 and 2

Interviews

We will carry out an exploratory qualitative study of PLVHIV. The objective of this qualitative phase of the study will be to explore the knowledge, perceptions and practices of PLHIV regarding Covid19 infection. The overarching aim of this qualitative study will be to determine major issues to cover by the quantitative questionnaire. We will specifically explore the level of knowledge of PLHIV regarding Covid19 infection, including knowledge of transmission and prevention measures and knowledge of specific support or counseling resources for PLHIV with Covid 19. We will explore the perceptions of PLHIV: whether or not PLHIV

feel more at risk, whether they experience a specific level of anxiety, whether or not they are satisfied with the care and support they receive. Finally, we will explore the practices of PLHIV, whether or not they practice social distancing and other preventative measures as recommended, and if not, what are the underlying reasons.

Sample for qualitative study

The sampling will consist of people living with HIV, with people infected and not infected with SARS-CoV-2. We will attempt to recruit a diversity of participants in terms of socio-demographic characteristics. Indeed, diversity of participants enhances the validity of the results of a qualitative study. The sample size will be determined by the saturation of information – when new interviews no longer bring new information. Saturation of data is usually achieved after interviewing 20 participants. Therefore, we will interview 20 PLHIV with Covid19 and 20 PLHIV not with Covid19, with a total of 40 participants.

Interviews

We will conduct in-depth semi-directive qualitative interviews of open-ended questions based on an interview guide gathering the components mentioned in the objectives above. The interview guide will be created using themes gathered after reviewing the literature on the subject. The interview guide will be created, then tested amongst a sample of 5 participants, then pre-analyzed and enriched. Voluntary participation will be ensured by collecting consent of the participants before the interviews that will stay anonymous and confidential. Participants will be interviewed over the telephone or face-to face during a study visit.

Analysis

Interviews will be voice recorded and transcribed verbatim then analyzed with the help of the NVivo software. The coding will be done in triangulation. The analysis will be done by constant comparisons. The interview guide will be enriched if new concepts appear during the interviews, and questions will be reformulated if necessary. The data will be triangulated in order to increase the validity of the results: two researchers will independently code a sample of interviews (N=5), and compare their codes in order to form a coding tree. The coding tree will also be enriched with the perspectives of the study team. A description of the phenomenon and an inductive analysis will allow conceptual categories to be extracted. The initial phase of these results will validate the concepts and content of the self-questionnaires for the quantitative survey that will follow.

Patient-Reported Outcomes (PRO) collected

For patients with an ambulatory follow-up at baseline, D7, D20, M3, M6
For patients hospitalized, if compatible with patient health status at baseline, D7 D20, M3, M6,
It is important to evaluate these patient perspective. Ongoing Covid-19 epidemics in general population has raised several important issues: the knowledge, understanding and beliefs of mode of transmission of respiratory viruses are limited and interpretation of the messages in (social) media can be various. Several aspects of Health-Related Quality of life (HRQL) may be impacted by the outbreak, such as anxiety.

In order to be able to compare the socio-behavioural and mental health approaches we will harmonize the questionnaires with those currently used of the Inserm French Covid-19 protocol, i.e. HADS Hospital anxiety and depression scale, PCL-5 (post-traumatic stress disorder checklist version DSM-5) , symptoms with the modified Justice Symptom Index).Similarly, we purpose to explore major determinants of behaviour of PLVHIV in this context especially regarding the respect of the barrier rules and prevention of the transmission, access and adherence to the care. To this end, HRQL will be evaluated by the specific and validated questionnaire PROQOL–HIV[6]. Specific modules will be developed to assess the knowledge and beliefs, adherence and behaviour in the context of transmission of the Covid 19. This module will be tested on five patients during a cognitive debriefing before implementation. Patient Reported Outcomes scales will be filled also in electronic form such as on smartphone. Univariate and multivariate analyses will allow study factors related to the adherence to the transmission prevention recommendations. PRO endpoints will be completed at several time assessments: baseline, D6, D20 and 3 months.

Patient-Reported Outcomes (PRO) collected

We will collect Patient-Reported Outcomes for patients with an ambulatory follow-up at baseline, D7,D20, M3, M6 and for patients hospitalized, if compatible with patient health status at baseline, D7, D20, M3, M6. It is important to evaluate these biological parameters in the context of patient perspective, as ongoing Covid-19 epidemics in general population have raised several important issues: the knowledge, understanding and beliefs of mode of transmission of respiratory viruses is limited and interpretation of the messages in (social) media can be various. Several aspects of Health-Related Quality of life (HRQL) may be impacted by the outbreak, such as anxiety. In order to be able to compare the socio-behavioural and mental health approaches we will harmonize the questionnaires with those of the inserm French Covid-19 protocol, i.e. HADS Hospital anxiety and depression scale, PCL-5 (post-traumatic stress disorder checklist version DSM-5), symptoms with the modified Justice Symptom Index).Similarly, we purpose to explore major determinants of behaviour of PLVHIV in this context especially regarding the respect of the barrier rules and prevention of the transmission, access and adherence to the care. To this end, HRQL will be evaluated by the specific and validated questionnaire PROQOL–HIV6. Specific modules will be developed to assess the knowledge and beliefs, adherence and behaviour in the context of transmission of the Covid 19. This module will be tested on five patients during a cognitive debriefing before implementation. Patient Reported Outcomes will be able to be filled also in electronic form such as on smartphone. Univariate and multivariate analyses will study factors related to the good or wrong adherence to the transmission prevention recommendations. PRO endpoints will be completed at several time assessments: baseline, D7, D20 and 3 months.

6.1.4 Last study visit

The last study visit will be at M6 for all patients.

6.1 Table or diagram summarising the chronology of the study

Hospitalized patients	Acute phase				Convalescent phase		
	D1 (Day of inclusion)	D7 +/- 1 DAY	D13 +/- 1 DAY	D20 +/- 3 DAYS	DD + 2 to 4 Weeks	3 months (from D1)	6 months (from D1)
CLINICAL ASSESSMENT							
Inform consent	X						
Urine pregnancy test	X						
Clinical assessment[9]	DAILY UNTIL DAY OF HOSPITAL DISCHARGE					X	X
Chest radiography	X	IF CLINICALLY INDICATED				CLINICALLY INDICATED AND ABNORMAL PREVIOUS	
Thoracic CT scan	IF CLINICALLY INDICATED					CLINICALLY INDICATED AND	
SaO2	X	X	X	X	X		
Functional respiratory explorations						IF CLINICALLY INDICATED	
Arterial blood gas	IF SaO2 < 94%					IF CLINICALLY INDICATED	
Questionnaire symptom index	X			X		X	
PROQOL- HIV	X			X		X	X
HAD	X			X		X	X
PCL5	X			X			X
BLOOD SAMPLES							
Standard Biology (2 edta 3,5 ml, tube sec 3,5 ml)	10,5[1,2]	10,5 each week until resolution			10,5	10,5[4]	10,5[4]
Blood sample for host genetic analysis (1 EDTA tube 7 mL)			7				
Blood sample for viral PCR SARS, and other viruses (2 EDTA 7 ml : 2 WB aliquots + 2 plasma aliquots)	14	14	ADD A SAMPLE THE DAY OF PATIENT WORSENING AND CONTINUE UNTIL RESOLUTIVE PHASE (D13 D20 D28 DD)		14		14
ARN-VIH + ADN-VIH (2 EDTA de 7 ml : 14 ml	14					14	
Blood sample serology/immunology (IP) (1 Dry	7			7			7
Blood sample /PBMC immuno (7 EDTA tube 6 ml)	42[5]			42	42	42	42
Blood sample /PLASMA immuno (EDTA tube 3,5 ml)	3,5[5]			3,5	3,5	3,5	3,5
Blood sample/Tempus (IMMUNO) (1 tube 3 ml)	3			3	3	3	3
Total volume per day (ml)	94	24,5	17,5	66	73	73	80
Cumulated volume for the first 30 days		118,5	136	202			
BIOLOGICAL SAMPLES OTHER THAN BLOOD							
Nasopharyngeal swab for viral PCR	X	X	X[7]	X[7]	X[7]	X[7]	X[7]
Nasal lavage (RNA later)[5]	X						
Urine (up to 10 mL)	X			X		X[8]	
Stool (up to 10 mL) or rectal swab	X			X		X[8]	
Sample from other infected sites as Cerebrospinal fluid if indicated	IF ANY						
Flocked conjunctiva swab	X			X		X[8]	
Saliva or endotracheal aspirate if intubated	X			X		X[8]	

Table 1 : Chronology of the study for hospitalized patients

Ambulatory follow-up	Acute phase			
	D1 (Day of inclusion)	D20 +/- 3 DAYS	3 months (from D1)	6 months (from D1)
CLINICAL ASSESSMENT				
Inform consent	X			
Urine pregnancy test	X			
Clinical assessment[9]	X	X		
Chest radiography	X	IF CLINICALLY INDICATED		
Thoracic CT scan	IF CLINICALLY INDICATED AND ABNORMAL PREVIOUSLY			
SaO2	X	X		
Functional respiratory explorations	IF CLINICALLY INDICATED			
Arterial blood gas	IF SaO2< 94%			
Questionnaire symptom index	X	X	X	
PROQOL- HIV	X	X	X	X
HAD	X	X	X	X
PCL5	X	X		X
BLOOD SAMPLES				
Standard Biology (2 edta 3,5 ml, tube sec 3,5 ml)	10,5[1,2]	10,5[3]	10,5[4]	10,5[4]
Blood sample for host genetic analysis (1 EDTA tube 7 mL)		5		
Blood sample for viral PCR SARS, and other viruses (2 EDTA 7 ml : 2 WB aliquots + 2 plasma aliquots)	14		14	14
ARN-VIH + ADN-VIH (2 EDTA de 7 ml : 14 ml	14	14	14	
Blood sample serology/immunology (IP) (1 Dry or clotted tube 7 ml → 4 Aliquots)	7	7		7
Blood sample /PBMC) immuno (7 EDTA tube 6 ml)	42[5]	42[5]	42[5]	42[5]
Blood sample /PLASMA) immuno (EDTA tube 3,5 ml)	3,5	3,5	3,5	3,5
Blood sample/Tempus (IMMUNO) (1 tube 3 ml)	3	3	3	3
Total volume per day (ml)	ml	85		
Cumulated volume for the first 30 days	94	179		
BIOLOGICAL SAMPLES OTHER THAN BLOOD				
Nasopharyngeal swab for viral PCR	X	X[7]	X[7]	X[7]
Nasal lavage (RNA later)[5]	X			
Urine (up to 10 mL)	X	X	X[8]	
Stool (up to 10 mL) or rectal swab	X	X	X[8]	
Sample from other infected sites as Cerebrospinal fluidif indicated	IF ANY			
Flocked conjunctiva swab	X	X	X[8]	
Saliva or endotracheal aspirate if intubated	X	X	X[8]	

Table 2 : Chronology of the study for patients with ambulatory follow-up

Blood samples

[1] Weekly if hospitalized > 29 days

[2]Blood and platelet count, ionogram creatinine urea, glycemia, liver enzymes, PAI-1 (Plasminogen Activator Type 1 Inhibitor),liver biology transaminases, bilirubine, alkaline phosphatase, GGT, CPK, CRP, PCR, ferritin, dDimere, fibrinogen, TP TCA, LDH, VHC and VHC (if necessary)

[3] Blood and platelet count, ionogram creatinine urea, glycemia, liver enzymes ggt, Pal

[4]Blood and platelet count CD4 T cell count

[5]Between D1 and D3

Biological samples other than blood

[6] *Weekly if hospitalized > 29 days and /or si previous test if positive*

[7] *Only if previous swab is positive*

[8] *Only if positive sample during follow-up*

Clinical assessment

[9] See details in addendum 6

Moreover, for interviews will be realized on 20 PLHIV with Covid-19 and 20 PLHIV without Covid19.

6.2 Distinction between standard care and study

TABLE: "Standard care" vs. "additional interventions" required specifically for the study

Interventions carried out for the research purposes	**Interventions, procedures and treatments associated with standard care**	**Interventions, procedures added for research purposes[1]**
Visits	D1 (day of diagnostic, and inclusion in the study), hospitalisation if necessary, D20 et M6	M3
Clinical assessment	Urine pregnancy test, SaO2, functional respiratory explorations if indicated, arterial blood gas if Sa02 < 94 %	
Blood samples	Standard biological containing NFS with platelets and Blood Ionogram, PAI-1, urea, creatinine, blood glucose, liver biology transaminases, bilirubine, alkaline phosphatase , GGT, CPK, CRP PCR, ferritin, dDimere, fibrinogène, TP TCA, LDH, VHC and VHC (if necessary) and TCD4 count and HIV-RNA	Blood samples for standard biology, genetic analysis, Viral SARS analysis, viral VIH analysis and immunological analysis (cf. paragraph 6.2)
Others samples	Nasal lavage	Urine
	Nasopharyngeal swab	Saliva or endotracheal aspirate the patient is intubated
	Saliva or endotracheal aspirate the patient is intubated	Stool
	Urine	Tear
	Flocked conjunctiva swab	Respiratory tract
	Stool or rectal swab	other samples if indicated
	Sample from infected site as cerebrospinal fluidif If any	
Imaging	Chest radiography	
	Thoracic CT scan, if indicated	
Questionnaires		Post-traumatic stress disorder Questionnaire, autoquestionaire HADS, Event Scale-Revised

Interview		Interview (telephone or face-to-face) on 20 PLHIV with Covid19 and 20 PLHIV not with Covid19

[1] **Samples required for clinical management will at all times have priority over samples taken for research tests. Aliquots or samples for research purposes should never compromise the quality or quantity of samples required for medical management. Wherever practical, taking research samples should be timed to coincide with clinical sampling. Data collection is resumed in table 1 and 2.**

6.3 Biological samples collection

Samples (or a component of the samples) taken as part of the study will be stored in a biological sample collection.

During the study the sample collection(s) will be stored in the 3 laboratories :

Professor Anne-Marie Roque-Afonso
Virology department
12 Avenue Paul Vaillant-Couturier 94800 Villejuif
anne-marie.roque@aphp.fr

Dr. Véronique Avettand-Feroel
INSERM U1191University Paris-Saclay
Cochin-APHP Necker Virology Institute
149, rue de Sèvres 75014, Paris
veronique.avettand@aphp.fr

Dr Roger Legrand - Dr Delphine Desjardins
Immunomonitoring Laboratory, Unit UMR1184 IMVA-HB - Paris-Sud Faculty of Medicine
Tel: 01 49 59 67 19 / delphine.desjardins@u-psud.fr

At the end of the study, the samples will be kept (until exhaustion) for future analysis not described in the initial protocol but which may be useful for investigation about HIV and Covid19 infections and their comorbidities and complications. in light of advances in scientific knowledge, provided the participant is informed and does not oppose this, as stated in the information note/consent form.

Access to samples for additional analyses will be governed by the scientific committee comprising the clinical lead investigators and scientific investigators for this study in collaboration with the individual recruiting sites.
Samples collected will be used for the purpose of this study as stated in the protocol and consented for future use. The standard consent form will request consent from subjects for sample storage and/or export of specific samples to collaborating institutions for investigations that cannot be performed locally, and for use for genetic studies about AIDS and Covid19 and their comorbidities and complications. Any proposed plans to use samples other than for those investigations detailed in this protocol will be submitted to the scientific committees. Collaborating centres must have appropriate biological safety measures and regulatory approvals in place in order to receive samples.
Any database detailing clinical data will only identify participants by a participant number. Participant names or any other identifying details will NOT be included. Data may be used alone or in combination with data from related studies in secondary analyses.

The sampling collection will be declared to the ministry of research and to the director of the competent regional healthcare authority (Article L. 1243-3 *Code de la Santé Publique* [French Public Health Code]).

Appropriate selection and timely collection of high-quality specimens, proper storage procedures and comprehensive diagnostic testing will ensure the quality of data.
Local hospital protocols will be used to collect and handle specimens. Guidance on the collection of specimens from patients with emerging infections can be found on the WHO website.
Samples collected for routine and clinical monitoring are processed in local laboratories.
Samples collected for research purposes with be sent to local Biological Resource Centres that already process samples for the biobanking of ANRS protocols.

Virological analysis

Appropriate selection and timely collection of high-quality specimens, proper storage procedures and comprehensive diagnostic testing will ensure the quality of data.
Local hospital protocols will be used to collect and handle specimens. Guidance on the collection of specimens from patients with emerging infections can be found on the WHO website.
Virological analyses will be conducted in laboratories with BSL2 and BSL3 facilities.
1-viral load determination and kinetics using the protocol developed by the French National Reference Centre for respiratory viruses : intra and inter-host comparisons on serial samples and different sites including respiratory tract (naso-pharyngeal swab, Broncho-alveolar fluid), blood (plasma EDTA), tears or eye swabs, stool, saliva, urine, semen if possible, CSF or other samples if indicated. Viral load determination requires at least 300µl per sample.
*for ambulatory patients, sampling will be performed at inclusion and once a week until negativation,
*for hospitalized patients, sampling will n=be performed at inclusion, day3, 7 and once a week until negativation

2-identification of potential viral severity determinants by whole genome sequencing using high-throughput sequencing using protocols developed by the team "Environnement et Risques Infectieux". Comparisons of intra and inter-host sequences. NGS sequencing requires at least 500 µl per sample
NGS sequencing will be performed in samples from selected patients with contrasted outcomes

3-measure of mounted humoral immune response (humoral assays developments are ongoing)

4-Impact of the SARS-CoV-2 infection on latent infections or chronic underlying viral infections: viral load determination of CMV, EBV, (500 µl of whole blood EDTA) TTV, HBV if appropriate (1ml of plasma EDTA), using reagents routinely used for patients monitoring. Impact will be tested at day 1 -14 and Mo 3.

5-SARS-CoV-2 infection could lead to increased immune activation and thus reactivation of HIV from reservoir cells and potentially residual viremia [7]. We propose to study these points by the quantification of total HIV DNA, the quantification of intracellular HIV RNA transcripts and plasma HIV RNA at inclusion and 3 months later to analyze the evolution of these markers in comparaison with parameters of inflammation and immune markers
We have limited to 100 patients the analysis of the reservoir by the total HIV DNA marker and by the transcripts, in order to reduce the cost. Among them, 50 patients will be hospitalized and 50 will be followed up on an outpatient basis. This analysis will be realised by Véronique Avettant team at Cochin Institute.

Immunological analysis

Some recent publications about immunity and COVID-19 shown that SARS-CoV, MERS-CoV and SARS-CoV-2 interfere with the type 1 IFN response (which is delayed first and then hyperactive) and, on the other hand, causes hyper-inflammation (cytokine storm)[8, 9]. T cell immunity is also important to control the pathogenesis of coronaviruses infection but not yet well studied in SARS-CoV-2 infection. In SARS, paradoxical association has been reported between polyfunctional CD8 T cells and serious disease[8].

(1) In the work proposed here, we aim to: Characterise in peripheral blood the immune responses to infection and therapy over time including innate and acquired immune responses. Flux cytometry analyses will be performed to analyse, over time, immunological changes in the myeloid populations (monocytes, pDC, cDC1, cDC2) and in T CD4 and T CD8 lymphocytes (activation and exhaustion);
(2) Evaluate the impact of the COVID-19 disease on HIV immune responses. Functional assays (ICS) will be performed to characterize the HIV-specific immune responses in the patients with COVID-19;
(3) Characterise the COVID-19 specific T-cell immune responses in the patients. ICS will be performed using peptide pools spanning the Spike, Nucleocapsid, Envelope and/or Membrane Proteins (peptide pools are now available for these assays).

(4) Characterise in peripheral blood gene expression profiling by single-cell RNA sequencing (Chromium, 10x Genomics).

In this work, the immunological analyses will be conducted in a limited number of patients: 80 patients for the aims (1), (2) and (3) and 20 patients for the aim (4). We will analyse samples collected on day of inclusion and on day 20 +/- 3 days. Samples from other participants will be made available for complementary analyses. After the acute phase of infection, additional samplings are planned in patients. Biological samples (PBMCs) will be stored at the immunomonitoring laboratory UMR1184 for further analyses. Plasma samples collected during all the duration of the study will be also stored at the immunomonitoring laboratory for further analyses (biomarkers).

Coronavirus infection may increase the levels of residual inflammation in people living with HIV. If the levels measured in the plasma are higher following infection by the coronavirus there would potentially be a risk of increasing the size of the HIV reservoir (measurement by DNA) and residual replication (measurement by RNA).

7 ELIGIBILITY CRITERIA

7.1 Inclusion criteria

➢ Inclusion criteria for patients with COVID19

- Patient living with HIV (PLWHIV)
- Patient with confirmed infection with SARS-CoV-2 **since 1st January 2020** with and without criteria of hospitalisation.

➢ Inclusion criteria for the 20 patients without COVID19 (who will only realize the qualitative interview)

- Patient living with HIV (PLWHIV)
- Patient who did not have COVID-19

7.2 Exclusion criteria

➢ Exclusion criteria for patients with COVID19

- Confirmed diagnosis of another pathogen than SARS-CoV-2
- Refusal by participant, or appropriate representative.
- Being under guardianship or trusteeship mandate for future protection
- Participate to another study without consent of the promoter
- Patients less than 18 years old
- No Beneficiary or entitled to a social security scheme or state medical aid.

➢ Exclusion criteria for the 20 patients without COVID19 (who will only realize the qualitative interview)

- Refusal by participant, or appropriate representative.
- Being under guardianship or trusteeship mandate for future protection
- Participate to another study without consent of the promoter
- Patients less than 18 years old
- No Beneficiary or entitled to a social security scheme or state medical aid.

7.3 Recruitment procedure

Recruitment of participants will depend on the emergence and spread of the dynamic of the Covid19 epidemics in France, and among PLWHIV. We can't exclude a second epidemic phase, especially in several months and/or next year. Therefore, we plan to include up to 250 with COVID19 end 20 patients without COVID19 patients in one year, which would be a comfortable number to describe the clinical course and the factors associated with a more unfavourable evolution.

	Number of participants
Number patients COVID19 to be include	250
Number of additional patients no COVID19 to be include	20
Total of patients to be included	270
Number of centres	37
Enrolment period (months)	12
Number of participants/centre	7 to 20
Number of participants/centre/month	**1**

8 TERMINATION RULES

Several situations are possible

- Temporary discontinuation the investigator must document the reason for the arrest and its recovery in the source file of the subject and the CRF
- Premature discontinuation, but the participant remains enrolled in the study until the end of his/her participation: the investigator must document the reason

8.1 Criteria and procedure for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason..

- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead

- Patients enrolled to the study whose illness is subsequently confirmed to be the result of infection with a pathogen which is not relevant to the objectives of this study, and who have no indication or likelihood of co-infection with a relevant pathogen, will be withdrawn. No further follow-up will be conducted.

- The patient's will to withdraw from the study at any time must be respected
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- If a participant exits the study prematurely, his/her data may be used until the date of the withdrawal of his/her consent .

If a participant leaves the study prematurely or withdraws consent, any data collected prior to the date of premature discontinuation may still be used.

- The case report form must list the various reasons why the participant has discontinued the study:
  - ☐ Adverse reaction
  - ☐ Another medical issue
  - ☐ Personal reasons of the participant
  - ☐ Explicit withdrawal of consent

8.1.1 Procedures for replacing these participants,

Participants having prematurely discontinued the study are replaced and whether they are to be excluded from the analysis.

8.1.2 Full or partial discontinuation of the study

AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

In all cases in which a study is discontinued, the care options must be specified for participants currently enrolled in the study. Notably, it must be specified if the participants included in the study must be followed until the end of their participation, as set forth in the protocol.

9 VIGILANCE

"During this research, adverse events (serious and otherwise) do not need to be reported to the sponsor. The report must instead be made as part of the vigilance procedure applicable to the product or intervention under investigation (pharmacovigilance for a drug product; medical device vigilance for a medical device, etc.).

10 SPECIFIC STUDY COMMITTEES

10.1 Steering Committee

Composition: coordinating investigator, one or several other investigators, biostatistician, sponsor representatives appointed for this study.
Role: To define the overall structure of the study, coordinate information, determine the initial methodology and oversee the study.

- Committee members:
- Coordinating Investigator: Dr Antoine Chéret
- Responsible of the department of internal medicine of Bicêtre hospital : Pr Cécile Goujard
- Methodologist: Pr Laurence Meyer
- Responsible of the Clinical Research Unit (URC) : Pr Lamiae Grimaldi
- Project Manager (DRCI-URC): Fatoumata Waggeh
- Project Manager (DRCI-Siège): Akim Souag
- Scientific responsible for laboratory examinations : Dr Avettand Fenoël Véronique, Dr Delphine Dujardin, Dr Anne Marie Roque Afonso

10.2 Scientific Committee

Role: To define the purpose, draft the protocol, suggest modifications to the protocol during the study.

- Committee members:
- Coordinating Investigator: Dr Antoine Chéret
- Responsible of the department of internal medicine of Bicêtre hospital : Pr Cécile Goujard
- Methodologist: Pr Laurence Meyer
- Statistiacian : Alexandra Rouquette, Bruno Fallissard, Martin Duracinsky
- Project Manager (DRCI-URC): Fatoumata Waggeh
- Project Manager (DRCI-Siège): Akim Souag
- Responsible of the Clinical Research Unit (URC) : Pr Lamiae Grimaldi
- Scientific responsible for laboratory examinations : Dr Avettand Fenoël Véronique, Dr Delphine Dujardin, Dr Anne Marie Roque Afonso
- Pr Christine Rouzioux
- Marianne L'Henaff
- Dr Evgenia Krastinova
- Dr Dominique Salmon
- Dr PIALOUX Gilles
- Dr Jean-Paul Viard

11 DATA MANAGEMENT

11.1 Data collection procedures

Clinical and laboratory data will be collected throughout the acute illness period according to local resources. Priority at all times will be given to the collection of clinical information. Research data will be integrated as much as possible with information available from hospital and regulatory files. Clinical data will be collected locally with the relevant CRF for coivid-19.. The data will be anonymised at site and a study number issued.
When available, data collected by staff at each site will be submitted electronically to a protected online database. Anonymised data may be entered by local or study staff. The records kept will not include any information that allows patients to be identified. All data recorded in the framework of this study will be coded, using a unique study subject identification code. The study subject identification code will be the only patient identifier on any document related to the study, as well as in the electronic study database. For the Clinical Characterisation Protocol access to the data entry system will be protected by username and password. Username and password will be assigned during the registration process for individual Site Investigators.

11.2 Identification of data recorded directly in the CRFs which will be considered as source data

The self-administered questionnaires may be completed either in paper version by the patient (in this case the source document will be completed paper questionnaire) or entered directly into the eCRF (in this case the source data will be directly the eCRF)

11.3 Right to access data and source documents

11.3.1 Data access

In accordance with GCPs:

- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures.
- the investigators will ensure the persons in charge of monitoring, quality control and auditing the research have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force

11.3.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept by the investigator, or by the hospital in the case of a hospital medical file, for 15 years.

In the context of the study, the type of source document will be medical file, original biological examination results, summary from imaging examinations, etc.

11.3.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the *Code de la Santé Publique* (French Public Health Code) will take all necessary precautions to ensure the confidentiality of information relating to the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the *Code Pénal* [French Criminal Code]).
During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.
Under no circumstances shall the names and addresses of the participants involved be shown.
Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.4 Data processing and storage of research documents and data

11.4.1 Identification of the data processing manager and location(s)

Data will be collected by investigating centres teams, i.e clinical research technicians (TEC) and investigators.

Data management will be performed by of the URC APHP.PARIS-SACLAY

11.4.2 Data entry

Non-identifying data will be entered electronically via a web browser.

11.5 Data ownership

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

12 STATISTICAL ASPECTS

The statistical analyses will be carried out by URC APHP-Paris Saclay.

13 QUALITY CONTROL AND ASSURANCE

13.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centres.
For this purpose, the sponsor will define a strategy for opening the centers and may, if necessary, set up a quality control of the data.

13.1.1 Strategy for opening the centres

The strategy for opening the centres will be determined before the research begins.

13.1.2 Data quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the Clinical Research and Innovation Department.
The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate.

13.2 Case report forms

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.
When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The original of this document will be archived by the sponsor. The investigator must archive a copy of the authenticated document that was issued to the sponsor.

13.3 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.
These non-compliances will be managed in accordance with the sponsor's procedures.

13.4 Audit

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits. These audits and inspections cannot be refused on the grounds of medical secrecy.

An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The aim of the audit is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's audit requirements.
The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

13.5 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals). The CV must include any previous involvement in clinical research and related training.

Each investigator will commit to comply with legislation and to conduct the study in line with regulations, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing research participants and obtaining their consent

In accordance with Article L.1122-1-1 of the *Code de la Santé Publique* (French Public Health Code), no research involving human participants with minimal risks and burden can be carried out on a person without his/her freely given and informed consent, obtained expressly after the person has been given the information specified in Article L.1122-1 of the aforementioned Code.

A sufficient reflection period is given to the individual between the time when he or she is informed and when he or she signs the consent form.

The person's freely-given written informed consent [or a trustworthy person if se his not in a state to consent at the time of inclusion*]* will be obtained by the principal investigator, a physician representing the investigator or a qualified person before the person is enrolled on the study.

Consent forms will be provided in French. Each potential participant will be informed of the purpose, scope of the study, procedures involved, duration of follow-up, potential risks and any discomfort it may entail. Informed consent, by the patient or by a trustworthy person if se his not in a state to consent at the time of inclusion.
Illiterate participants will have the consent form read in the presence of a witness, who will sign to verify the accurate reading of the form and agreement of the participant. For participants who cannot understand the language of the available forms, verified translations will be made when possible. If it is not possible to prepare a translation in a required language, verbal translation of the document and the consent discussion (if required) will be used. In this case, the translator may act as the witness for consent and sign the consent form so that patients who cannot read the language of the forms are not excluded from this research.
In the case of adult participants who are unable to give informed consent due to mental or physical status (Article L1122-2 of the Code de la Santé Publique (French Public Health Code) , the wishes of the participant may be declared by an appropriate consultee according to the site policy on obtaining consent for medical procedures. If, during the course of the study, the participant's status changes such that they are able to consider consent independently, informed consent must be discussed and obtained.

A copy of the information note and consent form, signed and dated by the research participant [*any other person in the cases set forth by Articles L. 1122-1-1 to L. 1122-2 of the Code de la Santé Publique (French Public Health Code)]* and by the principal investigator, the physician representing the investigator, or qualified person will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent *[or consent from any other person in the cases set forth by Articles L. 1122-1-1 to L. 1122-2 of the Code de la Santé Publique (French Public Health Code)*] as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor

14.2 Prohibition from participating in another clinical study or exclusion period after the study, if applicable

Any exclusion period of participation after the participant has finished this study is defined in the context of this research.

The participant may not enrol in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study. (state what types of studies are permitted).

The participants can however participate in other non-interventional studies

14.3 Compensation for participants

14.3.1 Reimbursement of expenses **incurred**

Travelling costs for the M3 visit will be reimbursed to patients.

14.4 Legal obligations

Assistance Publique-Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article L.1121-1 of the Code de la Santé Publique (French Public Health Code). Assistance Publique-Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

14.5 Request for approval from the CPP (Research Ethics Committee)

Prior to starting the study, AP-HP, as sponsor, must obtain approval from the CPP (Research Ethics Committee) for its Minimal Risks and Burden research study, within the scope of the committee's authority and in accordance with in force legislation and regulatory requirements.

People who do not have social security affiliation or who are eligible may be included in the study. A derogation will be requested from the CPP for this.

14.6 Informing the ANSM

AP-HP will send the approval from the CPP (Research Ethics Committee) and the summary of the protocol to the ANSM for information.

14.7 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

The sponsor must obtain the authorisation of the CNIL (French Data Protection Agency) before implementing any data processing involving the data required to conduct the research.

14.8 Amendments to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain approval from the CPP (Research Ethics Committee) before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

14.9 Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the *Code de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year following the end of the study, i.e., the end of the participation of the last participant in the study

14.10 Archiving

Specific documents for a research involving human participants with Minimal Risks and Burden are to be archived by the investigator and the sponsor for 15 years following the end of the research.
This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- Study binders for the investigator and the sponsor, including (non-exhaustive list):
  - the successive versions of the protocol (identified by the version number and its date), and any appendices
  - decisions of the CPP (Research Ethics Committee)
  - any correspondence
  - the enrolment list or register
  - the appendices specific to the research
  - final study report
- Data collection documents

15 FUNDING AND INSURANCE

15.1 Funding sources

The funding source PHRC Hospital Funding for Clinical Research.

15.2 Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique - Hôpitaux de Paris (AP-HP) has taken out insurance with HDI - GLOBAL SE through BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article L.1121-10 of the Code de la Santé Publique (French Public Health Code).

16 PUBLICATION RULES

16.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant
- However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be "AP-HP"
- Each of these affiliations must be identified by an address and separated by a semicolon (;)
- The AP-HP institution must feature under the acronym "**AP-HP**" first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France

16.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

"The sponsor was Assistance Publique – Hôpitaux de Paris (Délégation à la Recherche Clinique et à l'Innovation)"

16.3 Mention of the financial backer in the acknowledgements of the text

"The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2020 (French Ministry of Health)"

This study has been registered on the website http://clinicaltrials.gov/ under number

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18 LIST OF ADDENDA

18.1 Addendum 1 : List of investigator

18.2 Addendum 2 : Post-traumatic stress disorder Checlist version DSM-5 Questionnaire

18.3 Addendum 3 : Interview Guide

18.4 Addendum 4 : French COVID-19 autoquestionaire HADS

18.5 Addendum 5 : Main clinical signs collected

18.6 Addendum 6 : PROQOL-VIH Questionnaire

18.7 Addendum 7 : HIV symptom index