WHO Global Clinical Platform
for COVID-19

Data for public health response

Clinical features and prognostic factors of COVID-19 in people living with HIV hospitalized with suspected or confirmed SARS-CoV-2 infection

15 JULY 2021

World Health Organization

WHO reference number: WHO/2019-nCoV/Clinical/HIV/2021.1

Contents

Acknowledgements

The WHO Heath Emergencies Programme coordinated the development of this report in collaboration with the Department of Global HIV, Hepatitis and STI Programmes COVID-19 Task Team.

This report was written by Dr Silvia Bertagnolio (World Health Organization, Department of Global HIV, STI, Hepatitis Programmes), in collaboration with Dr Soe Soe Thwin (World Health Organization, Department of Sexual and Reproductive Health and Research), Dr Ronaldo Silva (consultant, Department of Sexual and Reproductive Health and Research) and Dr Janet Diaz (World Health Organization, Department of Country Readiness Strengthening, Health Emergencies Programme).

The report benefited from the contribution of Dr Sairaman Nagarajan (consultant, World Health Organization), Flaminia Sabbatucci (Consultant, World Health Organization) and Mr Firdavs Kurbonov (Consultant, World Health Organization), the WHO regional advisors on clinical management (Dr John (Appiah, Dr Dina Pfeifer, Dr Chiori Kodama, Dr Ludovic Reveiz, Dr Pushpa Wijesinghe and Dr Joao Toledo), Dr Jacobus Preller (World Health Organization, Department of Country Readiness Strengthening, Health Emergencies Programme), Dr Pryanka Relan (World Health Organization, Department of Integrated Health Services), Dr Marta Lado (World Health Organization, Department of Country Readiness Strengthening, Health Emergencies Programme) and the Clinical Advisory Group: John Amuasi (Kwame Nkrumah University of Science and Technology, Ghana); Yaseen Arabi (King Saud University, Saudi Arabia); Shabin Ariff (Department of Paediatrics and Child Health, Ministry of Health, Pakistan); Lindsey Baden (Harvard Medical School, United States of America); Lucille Blumberg (National Institute for Communicable Diseases, South Africa); Paolo Bonfanti (Hospital San Gerardo, Monza, Italy); Bin Cao (China-Japan Friendship Hospital, China); Gail Carson (Centre for Tropical Medicine and Global Health, University of Oxford, United Kingdom of Great Britain and Northern Island); Robert Fowler (Sunnybrook Health Sciences Centre, Canada); Rashan Haniffa (University College Hospital, United Kingdom); Michael Hughes (Harvard TH Chan School of Public Health, United States of America); Michael Jacobs (Royal Free London NHS Foundation Trust, United Kingdom); Richard Kojan (ALIMA and University of Kinshasa, Democratic Republic of the Congo); Yee Sin Leo (National Centre of Infectious Diseases, Ministry of Health, Singapore); Pisake Lumbiganon (Khon Kaen University, Thailand); Flavia Machado (Federal University of São Paulo, Brazil); Sabue Mulangu (Institut National de Recherche Biomedical, Democratic Republic of the Congo); Roger Paredes (Departament de Salut, Generalitat de Catalunya, Spain); Natalia Pshyenshya (Rostov State Medical University, Russian Federation); Yinzhong Shen (Fudan University, China); Tim Uyeki (Centers for Disease Control and Prevention, United States of America); Lee Wallis (University of Cape Town, South Africa).

Sincere thanks to all the facilities and collaborators contributing individualized anonymized data of hospitalized patients with suspected or confirmed COVID-19 to the WHO Clinical Platform. The list of facilities that contributed to this analysis is provided in Annex.

Abbreviations

aHR	adjusted hazard ratio
aOR	adjusted odds ratio
ART	antiretroviral therapy
BMI	body mass index
CI	confidence interval
HIV	human immunodeficiency virus
SAP	statistical analysis plan
WHO	World Health Organization
PLHIV	people living with HIV

Background

Available published evidence on the impact of HIV infection on severity and mortality associated with COVID-19 is limited and conflicting, and analyses have been based primarily on small cohorts of individuals in specific settings (1-7).

A retrospective cohort study in the United Kingdom found that people living with HIV (PLHIV) appear to be at increased risk for mortality (8). A retrospective cohort study in the United States of America found that while PLHIV do not appear to be at increased risk of infection, they are at increased risk for poor outcomes (mainly owing to higher rates of severe disease requiring hospitalization). In this sample of patients, the risk of hospitalization increased with the progression of HIV disease (9). Data from South Africa showed HIV to be an independent risk factor for in-hospital mortality (10).

Data from meta-analyses are also inconsistent. One meta-analysis found that HIV infection was not associated with poor composite outcomes (11). However, two meta-analyses found that PLHIV had a moderately increased risk of mortality than compared with people without HIV (12, 13).

Additional evidence from larger datasets with a broader geographical representation is required to expand the understanding of the interplay between HIV and SARS-CoV2 co-infection and guide global discussion on optimal clinical care for PLHIV who are infected with SARS-CoV-2.

To expand the understanding of clinical characteristics and prognostic factors among patients hospitalized with suspected or confirmed COVID-19, and to inform optimal clinical management and interventions, the World Health Organization (WHO) has established the Global Clinical Platform, which is a secure web-based database including individual-level, anonymized clinical data of hospitalized patients with suspected or confirmed COVID-19 from health facilities across the globe. The WHO Global Clinical Platform is intended to provide Member States with a standardized clinical data collection system to characterize the natural history of COVID-19; identify risk factors for severe disease and poor outcomes; and describe treatment interventions and outcomes among adults, children, and subpopulations, including pregnant women and PLHIV.

Objectives of the analysis

This report describes the demographics, clinical presentation, clinical outcomes, and risk factors among PLHIV who have been hospitalized for suspected or confirmed COVID-19.

The specific objectives of the analysis were to:

- describe the clinical characteristics and outcomes of PLHIV hospitalized for COVID-19
- assess whether PLHIV hospitalized with COVID-19 were at increased risk of presenting with severe or critical illness at admission and were at increased risk of in-hospital death compared to individuals not infected with HIV
- assess risk factors associated with severe or critical illness at hospital admission and of in-hospital death among PLHIV hospitalized for COVID-19.

Methods

We conducted a preliminary analysis of anonymized patient-level clinical data submitted to the WHO Global Clinical Platform for COVID-19 between 1 January 2020 and 29 April 2021 by a mix of national registries and sentinel health facilities from 37 countries.

Data Collection Tools

Two options exist to contribute data to the WHO Clinical Platform: i) use of the WHO Case Report Form (CRF), which exists in both paper-based or electronic formats, and ii) data entered into a local system or database. For locally entered data, relevant variables were mapped and aligned to the WHO CRF data dictionary and transferred to the WHO Clinical Platform hosted on OpenClinica.

The WHO CRF contains a standardized set of variables, including demographics, severity, medications, comorbidities, and clinical outcomes (discharged alive to home, in-hospital mortality, transfer to another facility for further care, remaining in the hospital at the time of data entry and discharged to palliative care or hospice). The CRF is divided into three modules. Module1 is completed on the first day of inpatient admission to the healthcare facility, module 2 is completed daily during hospital stay for as many days as resources allow and module 3 is completed at the time of discharge or death. The CRF has been translated into Arabic, Chinese, English, French, Russian, Spanish and Portuguese.

Inclusion Criteria

All patients, regardless of age, with known HIV status and admitted to a hospital or health facility with laboratory-confirmed or suspected COVID-19 were included in the analysis.

Statistical Analysis

Descriptive and regression analyses were conducted to summarize demographic and clinical characteristics and to evaluate their association with HIV status, disease severity at hospital admission and in-hospital mortality. Records with missing data were excluded when determining distributions across outcome levels, and chi-square tests and student t-tests were used to assess the relationship between clinical characteristics and outcomes.

The two clinical outcomes of interest were **in-hospital mortality** (yes vs no) and **clinical severity**, defined as follows. Cases were defined as **severe or critical** if they met one or more of the following conditions at hospital admission: 1) SpO2: <90%; 2) respiratory rate: >30 breaths/minute in adults and children over 5 years old; 3) received extracorporeal membrane oxygenation (ECMO); 4) admitted to an Intensive Care Unit (ICU); 5) received an inotrope or vasopressor; and 6) received oxygen therapy or ventilation. Cases not meeting all the conditions described above, and those meeting the conditions below were described as **mild or moderate**: 1) SpO2: ≥90% without supplemental oxygen; 2) respiratory rate: ≤30 breaths/minute in adults and children over 5 years old, and 3) did not receive oxygen therapy or ventilation.

A logistic regression model using generalized estimating equations (GEE) was fitted to evaluate whether HIV infection was a risk for severe or critical illness at admission, and a proportional hazards model (that adjusted in variance estimation for clustering at the country level) was fitted to evaluate whether HIV infection was a risk factor for mortality. Age (≤65 years, >65 years), sex (male, female) with the binary indicator for HIV positive status (yes/no) were included in the model a priori.

Covariates were considered for inclusion in the model when >80% reported data was not highly correlated with other variables using a correlation matrix threshold of >0.8, and they were associated with both the outcome (severity or mortality) and exposure (HIV status) at $p<0.10$ level. After covariate selection, they were then retained in the final model if further found to be significant at $p<0.05$ level.

Based on the above criteria, the following underlying conditions were considered in the analysis: chronic cardiac disease, diabetes, hypertension, chronic pulmonary disease, tuberculosis, asthma and malignant neoplasms. A second model included categories of the number of underlying conditions or "comorbidity burden" (none, 1-2 underlying conditions, and ≥3 underlying conditions) to determine if the number of conditions, rather than the individual conditions themselves, had an impact on severe or critical illness and mortality.

A subgroup analysis stratifying mortality risk by WHO geographical region to determine the impact of WHO Region of origin on mortality was also conducted. Regression analysis was repeated in the restricted sample of PLHIV to evaluate risk factors for disease severity at admission (logistic model) and risk factors for mortality (proportional hazards model).

In a sensitivity analysis, the regression models were repeated, excluding individuals from South Africa, which represented the main data contributor and accounted for 94.6% of the data.

All analyses were conducted in SAS version 9.4 (Copyright (c) 2016 by SAS Institute Inc., Cary, North Carolina, United States of America) or R version 3.6.3 (R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria 2020, https://www.R-project.org) and maps were drawn using ARCGIS Pro Release 2.5.0 (Environmental Systems Research Institute (ESRI), 2020. Redlands, California, United States of America).