Universitat Autònoma de Barcelona

HIV AND SARS-COV-2 CO-INFECTION: WHAT IS KNOWN SO FAR, EVOLVING PUBLIC HEALTH TRENDS, AND CLINICAL PERSPECTIVES

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Doctoral Program: Methodology of Biomedical Research and Public Health

Duration: January 2020 – September 2022

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to qualify as a Doctor of Medicine

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DEDICATION

"First your parents, they give you your life, but then they try to give you their life."

— Chuck Palahniuk

To my parents who never had the opportunity to complete even high school but have worked off their socks through the streets and markets of Koforidua, Ghana, to give me the opportunity to higher education.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank the Almighty God without whom none of these would have been possible.

I would like extend my appreciation to my thesis directors and tutor. Dr Juliana Reyes-Urueña has been my biggest source of support and encouragement. She was not only a supervisor but a friend. She makes me believe in myself and has instilled in me a desire to conduct quality research that can inform and transform policies. Dr Reyes-Urueña has been a mentor in the most candid sense and her guidance goes beyond what lies within these pages. Professor Jose M. Miro has provided thoughtful guidance to my PhD thesis journey. He is one of the most meticulous leaders in research and medicine I ever met. His timely comments have helped me significantly to refine my work. Dr Jordi Casabona gave me the opportunity to carry out my research in his team, provided enthusiastic support, and given me the chance to learn from his passionate experience in Public Health.

Thanks to the PISCIS Cohort study team, especially Dr Josep M. Llibre and Dr Aikaitz Imaz who provided me with wealthy ongoing support. Special thanks to my colleagues, family, and friends at the Centre for Epidemiological Studies on Sexually Transmitted Diseases and HIV/AIDS in Catalonia (CEEISCAT). I am forever indebted to Dr Andreu Bruguera, Dr Jorge Palacio, Ms. Yesika Diaz, Dr Alex Almuedo, and Dr Nana Aba Williams for their guidance and friendship. Dr Lucida Gibson-Cash, thank you for reading earlier versions of this dissertation and providing valuable feedback.

I would like to acknowledge my doctoral funding from the La Fundació La Marató de TV3 (2021) and the Fundació "La Caixa" (2020).

I appreciate my dear friends in Ghana and Barcelona. Your faith in me means a lot. Special thanks to Francisca, Sarah, Hannah, Angela, and Francis for being there for me throughout the entire process and reminding me of my goals whenever things got challenging. Shoutouts to my Ghana family here in Catalonia and the church, God bless you.

Finally, I want to thank my family for instilling in me the drive and dedication needed to complete this PhD. Anything good in me comes from you. Thanks for your unwavering support, Mom, Dad, Stephen, and Charles. I sincerely mean it when I say I could not have done it without you.

PREFACE

This thesis is presented as a compilation of publications according to the regulations approved by the Doctoral Committee of the Universitat Autònoma de Barcelona. It is comprised of five chapters. Chapter one, the introduction, provides a thorough review of existing literature regarding the impact of SARS-CoV-2 on HIV. Chapter two evaluates all the methods used to answer the research questions. Chapter three presents the results from the four articles. Article 1 compares SARS-CoV-2 testing, test positivity, and clinical outcomes between people living with HIV (PLWH) and the general HIV-negative population. Article 2 assesses the sociodemographic, clinical, and immunological risk factors of SARS-CoV-2 diagnosis and severe COVID-19 among PLWH. Additionally, it elaborates on the impact of CD4 count, viral load, and chronic comorbidities on the severity of HIV-SARS-CoV-2 co-infection. Article 3 assesses the association between tenofovir and SARS-CoV-2 outcomes among PLWH in matched groups of individuals receiving different regimens. Article 4 evaluates the SARS-CoV-2 vaccine coverage among people living with HIV in Catalonia, identifies the factors associated with low vaccine uptake, and compares COVID-19 outcomes among vaccinated PLWH and the unvaccinated. Chapter four, the discussion, discusses the key findings of the dissertation, implications of these findings, limitations, recommendations, and future research directions. And finally, chapter 5 outlines the main conclusions. All articles included in this thesis have been published.

The findings show that HIV itself might not be a risk factor for severe COVID-19 but sub-populations of PLWH like those with immune suppression, unsuppressed viraemia, comorbid conditions, migrants, and the aged have been more vulnerable to COVID-19. Regarding antiretrovirals, tenofovir was not associated with reduced SARS-CoV-2 diagnosis or associated hospitalisations and hence modification of preventive measures or management of COVID-19 among PLWH is not warranted until well-designed randomised controlled trials prove otherwise. Albeit similar rates compared to the general population, vaccination coverage was lower among some subgroups of PLWH like migrants, those with detectable viral load, higher CD4 levels, and previous SARS-CoV-2 infection. Ongoing vaccination campaigns should restrategise to effectively target these sub-populations.

The general conclusion of this thesis can confirm that progress has been made to advance the understanding of the impact of SARS-CoV-2 on PLWH, but much work remains to understand the burden in specific HIV sub-populations, develop effective therapies, ensure equal vaccine access for all, and assess the immune response to vaccinations.

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LIST OF ABBREVIATIONS

ABC/3TC	Abacavir lamivudine
AQuAS	Agency for Health Quality and Evaluation of Catalonia
ART	Antiretroviral therapy
BHIVA	British HIV Association
BMI	Body mass index
CEEISCAT	Centre for Epidemiological Studies on STIs and HIV/AIDS in Catalonia
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CVD	Cardiovascular disease
EMEA	European Medicines Agency
EuroMOMO	European Monitoring of Excess Mortality for Public Health Action
HAART	Highly active antiretroviral therapy
ICD-CM	International classification of diseases clinical modification
ICU	Intensive care unit
INI	Integrase inhibitors
IQR	Interquartile range
LMIC	Low-and middle-income countries
MERS	Middle East respiratory syndrome
MSM	Men who have sex with men
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
PADRIS	Public Data Analysis Program for Research and Innovation in Health
PEP	Post-exposure prophylaxis
PI	Protease inhibitors
PISCIS	Populational HIV Cohort from Catalonia and Balearic Islands
PLWH	People living with HIV
PrEP	Pre-exposure prophylaxis
PWID	People who inject drugs
RdRp	RNA dependent RNA polymerase
REC	Catalan Epidemiological Registry
rRT-PCR	Real-time reverse transcription polymerase chain reaction
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
SW	Sex workers
TAF/FTC	Tenofovir alafenamide/emtricitabine
TDF/FTC	Tenofovir disoproxil fumarate/emtricitabine
VACS	Veterans Aging Cohort Study
WHO	World Health Organization

ABSTRACT

Title

HIV and SARS-COV-2 co-infection: what is known so far, evolving public health trends, and clinical perspectives.

Background

The coronavirus disease 2019 (COVD-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has threatened health systems globally and led to unprecedented morbidity and mortality. The impact of SARS-CoV-2 infection in people living with HIV (PLWH) has been of particular concern because of their impaired immune status and the high burden of other determinants of health in this population. Existing population studies, case series, and cohort studies on this important topic involved mainly hospitalised patients, lacked the ability to sufficiently adjust for residual confounding, and studies regarding the possibility of using some anti-HIV agents have produced contradictory results. The general objectives of this PhD dissertation were to describe the impact of COVID-19 on PLWH including the clinical impact, the role of specific HIV markers and ART, and to assess SARS-CoV-2 vaccination and associated factors among PLWH.

Methodology

Study population

In articles 1-4, we leveraged the Populational HIV Cohort from Catalonia and the Balearic Islands (PISCIS) linked with the Analytical Data for Research and Innovation in Health Project of Catalonia (PADRIS). The PADRIS encompasses several official administrative public health databases to obtain information about chronic comorbidities, SARS-CoV-2 diagnosis, associated clinical outcomes, mortality, and COVID-19 vaccine reception.

In article 1, we used data on the general HIV-negative population aged ≥16 years obtained from the COVID-19 epidemiological monitoring registry via the Agency for Health and Quality Assessment of Catalonia (AQuAS).

Statistical analysis

- In article 1, we used the Z-test to compare testing, test positivity, hospitalisation, ICU admission, and mortality per 100 persons between PLWH and the general HIV-negative population.
- In article 2, we conducted a retrospective cohort study to evaluate SARS-CoV-2 diagnosis and severe outcomes among people living with HIV and univariable and multivariable Cox regression models to evaluate associated factors. We estimated the effect of immunosuppression on severe outcomes using Kaplan-Meier survival analysis.

- In article 3, we performed a propensity score-matched analysis among PLWH on different ART regimens. We further used adjusted Cox regression models to assess the association between tenofovir and SARS-CoV-2 outcomes.
- In article 4, we conducted a retrospective cohort study to assess SARS-CoV-2 vaccination coverage among PLWH in Catalonia and multivariable logistic regression model was used to assess the factors associated with under-vaccination.

Results

In article 1, PLWH tested less frequently for SARS-CoV-2 (27.1% vs. 30.3, p<0.001) had a higher test positivity (21.1% vs. 15.8%, p<0.001), similar hospitalisation rates (13.8% vs. 15.0% p=0.174) and ICU admission (0.9% vs. 1.7%, p=0.059)., and lower COVID-19 mortality compared to the general HIV-negative population (1.7% vs 3.6%, p=0.002).

In article 2, SARS-CoV-2 diagnosis was more common among migrants (adjusted hazard ratio [aHR] 1.55, 95% confidence interval [CI], 1.31–1.83), men who have sex with men (aHR 1.42; 95% CI, 1.09–1.86), and those with four or more chronic comorbidities (aHR 1.46; 95% CI, 1.09–1.97). Age at least 75 years (aHR 5.2; 95% CI 1.8–15.3), non-Spanish origin (aHR 2.1; 95% CI, 1.3–3.4), and neuropsychiatric (aHR 1.69; 95% CI, 1.07–2.69), autoimmune disease (aHR 1.92; 95% CI, 1.14–3.23), respiratory disease (aHR 1.84; 95% CI, 1.09–3.09), and metabolic disease (aHR 2.59; 95% CI, 1.59–4.23) chronic comorbidities were associated with increased risk of severe outcomes. A Kaplan-Meier estimator showed differences in the risk of severe outcomes according to CD4 cell count in patients with detectable HIV RNA (p=0.039) but no differences were observed in patients with undetectable HIV RNA (p=0.15).

In article 3, tenofovir alafenamide/emtricitabine (TAF/FTC) compared to abacavir/lamivudine (ABC/3TC) was not associated with reduced SARS-CoV-2 diagnosis (aHR 0.90; 95% CI, 0.78-1.04) or hospitalization (aHR 0.93; 95% CI, 0.60-1.43). When compared with ABC/3TC, TDF/FTC was not associated with reduced SARS-CoV-2 diagnosis (aHR 0.79; 95% CI, 0.60-1.04) or hospitalization (aHR 0.51; 95% CI, 0.15-1.70). TDF/FTC was not associated with reduced SARS-CoV-2 diagnosis (aHR 0.79; 95% CI, 0.60-1.04) or associated hospitalization (aHR 0.33; 95% CI, 0.10-1.07) compared with TAF/FTC.

In article 4, between December 27, 2020 and July 11, 2021, 9945 (66.6%) PLWH in our cohort received at least one dose of a SARS-CoV-2 vaccine. Non-Spanish origin (adjusted odds ratio [aOR] 0.64, 95% CI 0.59-0.70); CD4 cell count of 200-349 cells/μL (aOR 0.74, 95% CI 0.64 - 0.86) or 350-499 cells/μL (aOR 0.79, 95% CI 0.70 - 0.88); detectable plasma HIV RNA (aOR 0.61 95% CI 0.53-0.70); and previous SARS-CoV-2 diagnosis (aOR 0.58 95% CI 0.51-0.65) were associated with lower

vaccination coverage. SARS-CoV-2 diagnosis (437 [9.5%] vs. 323 [3.5%], p<0.001), associated hospitalisations (10 [2.3%] vs. 0 [0%], p<0.001), intensive care unit admissions (6 [1.4%] vs. 0 [0%], p<0.001), and deaths (10 [2.3%] vs. 0 [0%], P < .001) were higher among unvaccinated PLWH compared to the vaccinated.

Conclusions

This dissertation demonstrates that PLWH with comorbid conditions, unsuppressed HIV-RNA, and immune suppression could be at risk for worse COVID-19 outcomes and should be prioritised for COVID-19 risk reduction. Until well-designed randomized controlled trials reveal new evidence demonstrating a protective effect of tenofovir, clinical management of PLWH should not be modified. Our findings also show that SARS-CoV-2 vaccination could be beneficial for PLWH and therefore targeted public health strategies should be implemented to improve vaccine uptake in under-vaccinated groups. Additionally, this doctoral thesis throws more light on the fact that health inequalities are a major contributor to disease vulnerability with migrants affected more by SARS-CoV-2 in terms of diagnosis, severe outcomes, and under-vaccination. Although phenomenal progress has been made in understanding the impact of SARS-CoV-2 on PLWH, much work remains to understand the burden in specific HIV sub-populations, develop effective therapies, and ensure equal vaccination access to all.

Keywords: HIV; COVID-19; SARS-CoV-2; Tenofovir; vaccines; cohort studies.

RESUMEN

Título

Coinfección por VIH y SARS-COV-2: lo que se sabe hasta ahora, evolución de las tendencias de salud pública y perspectivas clínicas.

Antecedentes

La enfermedad por coronavirus 2019 (COVD-19) causada por el síndrome respiratorio agudo severo coronavirus 2 (SARS-CoV-2) ha amenazado los sistemas de salud a nivel mundial y ha provocado una morbilidad y mortalidad sin precedentes. El impacto de la infección por SARS-CoV-2 en las personas que viven con el VIH (PLWH) ha sido motivo de especial preocupación debido a su estado inmunitario deteriorado y la alta carga de otros determinantes de la salud en esta población. Los estudios de población, series de casos y estudios de cohortes existentes sobre este importante tema involucraron principalmente a pacientes hospitalizados, carecían de la capacidad de ajustar suficientemente los factores de confusión residuales y los estudios sobre la posibilidad de usar algunos agentes anti-VIH han producido resultados contradictorios. Los objetivos generales de esta tesis doctoral fueron describir el impacto de COVID-19 en las PLWH, incluido el impacto clínico, el papel de los marcadores específicos del VIH y el TAR, y evaluar la vacunación contra el SARS-CoV-2 y los factores asociados entre las PLWH.

Metodología

Poblaciónes de estudio

En los artículos 1-4, aprovechamos la Cohorte Poblacional de VIH de Cataluña y Baleares (PISCIS) vinculada con el Proyecto de Datos Analíticos para la Investigación y la Innovación en Salud de Cataluña (PADRIS). El PADRIS engloba varias bases de datos administrativas oficiales de salud pública para obtener información sobre comorbilidades crónicas, diagnóstico de SARS-CoV-2, resultados clínicos asociados, mortalidad y recepción de la vacuna COVID-19.

En el artículo 1, utilizamos datos de la población general seronegativa de edad ≥ 16 años obtenidos del registro de seguimiento epidemiológico de la COVID-19 a través de la Agencia de Evaluación de la Calidad y la Calidad de la Salud de Cataluña (AQuAS).

Análisis estadístico

- En el artículo 1, usamos la prueba Z para comparar las pruebas, la positividad de la prueba, la hospitalización, el ingreso en la UCI y la mortalidad por cada 100 personas entre las PLWH y la población general seronegativa al VIH.
- En el artículo 2, realizamos un estudio de cohorte retrospectivo para evaluar el diagnóstico de SARS-CoV-2 y los resultados graves entre las personas que viven con el VIH y modelos de regresión de Cox univariable y multivariable para evaluar los factores asociados.

Estimamos el efecto de la inmunosupresión en los resultados graves mediante el análisis de supervivencia de Kaplan-Meier.

- En el artículo 3, realizamos un análisis de puntuación de propensión entre PLWH en diferentes regímenes de TAR. Además, utilizamos modelos de regresión de Cox ajustados para evaluar la asociación entre los resultados de tenofovir y SARS-CoV-2.
- En el artículo 4, realizamos un estudio de cohortes retrospectivo para evaluar la cobertura de vacunación contra el SARS-CoV-2 entre las PVV en Cataluña y se utilizó un modelo de regresión logística multivariable para evaluar los factores asociados con la infravacunación.

Resultados

En el artículo 1, las PLWH que se hicieron la prueba de SARS-CoV-2 con menos frecuencia (27,1 % frente a 30,3, p<0,001) tuvieron una mayor positividad de la prueba (21,1 % frente a 15,8 %, p<0,001), tasas de hospitalización similares (13,8 % frente a .15,0 % p=0,174) e ingreso en UCI (0,9 % frente a 1,7 %, p=0,059), y menor mortalidad por COVID-19 en comparación con la población general seronegativa (1,7 % frente a 3,6 %, p=0,002).

En el artículo 2, el diagnóstico de SARS-CoV-2 fue más común entre los migrantes (hazard ratio ajustado [aHR] 1,55, intervalo de confianza [IC] del 95 %, 1,31–1,83), hombres que tienen sexo con hombres (aHR 1,42; IC del 95 % , 1,09–1,86) y aquellos con cuatro o más comorbilidades crónicas (HRa 1,46; IC 95 %, 1,09–1,97). Edad de al menos 75 años (HRa 5,2; IC 95 % 1,8–15,3), origen no español (HRa 2,1; IC 95 %, 1,3–3,4) y neuropsiquiátrico (HRa 1,69; IC 95 %, 1,07–2,69), autoinmune (aHR 1,92; IC 95 %, 1,14–3,23), enfermedad respiratoria (aHR 1,84; IC 95 %, 1,09–3,09) y enfermedad metabólica (aHR 2,59; IC 95 %, 1,59–4,23), las comorbilidades crónicas se asociaron con un aumento riesgo de resultados severos. Un estimador de Kaplan-Meier mostró diferencias en el riesgo de resultados graves según el recuento de células CD4 en pacientes con ARN del VIH detectable (p=0,039), pero no se observaron diferencias en pacientes con ARN del VIH indetectable (p=0,15).

En el artículo 3, tenofovir alafenamida/emtricitabina (TAF/FTC) en comparación con abacavir/lamivudina (ABC/3TC) no se asoció con un diagnóstico reducido de SARS-CoV-2 (aHR 0,90; IC del 95 %, 0,78-1,04) u hospitalización (aHR 0,93; IC 95%, 0,60-1,43). En comparación con ABC/3TC, TDF/FTC no se asoció con un diagnóstico de SARS-CoV-2 reducido (aHR 0,79; IC del 95 %, 0,60-1,04) ni hospitalización (aHR 0,51; IC del 95 %, 0,15-1,70). TDF/FTC no se asoció con un diagnóstico reducido de SARS-CoV-2 (aHR 0,79; IC del 95 %, 0,60-1,04) u hospitalización asociada (aHR 0,33; IC del 95 %, 0,10-1,07) en comparación con TAF/FTC.

En el artículo 4, entre el 27 de diciembre de 2020 y el 11 de julio de 2021, 9945 (66,6%) PLWH de nuestra cohorte recibieron al menos una dosis de una vacuna contra el SARS-CoV-2. origen no español (odds ratio ajustado [aOR] 0,64, IC 95% 0,59-0,70); Recuento de células CD4 de 200-349 células/µL (aOR 0,74, IC del 95 % 0,64 - 0,86) o 350-499 células/µL (aOR 0,79, IC del 95 % 0,70 - 0,88); ARN de VIH detectable en plasma (aOR 0,61, IC del 95%: 0,53-0,70); y el diagnóstico previo de SARS-CoV-2 (aOR 0,58 IC 95% 0,51-0,65) se asociaron con una menor cobertura de vacunación. Diagnóstico de SARS-CoV-2 (437 [9,5 %] frente a 323 [3,5 %], p<0,001), hospitalizaciones asociadas (10 [2,3 %] frente a 0 [0 %], p<0,001), ingresos en unidades de cuidados intensivos (6 [1,4 %] frente a 0 [0 %], p<0,001) y las muertes (10 [2,3 %] frente a 0 [0 %], P < 0,001) fueron mayores entre las PLWH no vacunadas en comparación con las vacunadas.

Conclusiones

Esta disertación demuestra que las PVV con condiciones comórbidas, ARN-VIH no suprimido e inmunosupresión podrían estar en riesgo de peores resultados de COVID-19 y deben priorizarse para la reducción del riesgo de COVID-19. Hasta que los ensayos controlados aleatorios bien diseñados revelen nueva evidencia que demuestre un efecto protector de tenofovir, el manejo clínico de las PVV no debe modificarse. Nuestros hallazgos también muestran que la vacunación contra el SARS-CoV-2 podría ser beneficiosa para las PVV y, por lo tanto, se deben implementar estrategias de salud pública específicas para mejorar la aceptación de la vacuna en los grupos insuficientemente vacunados. Además, esta tesis doctoral arroja más luz sobre el hecho de que las desigualdades en salud son un factor importante que contribuye a la vulnerabilidad a las enfermedades, ya que los migrantes se ven más afectados por el SARS-CoV-2 en términos de diagnóstico, resultados graves y falta de vacunación. Aunque se ha logrado un progreso fenomenal en la comprensión del impacto del SARS-CoV-2 en las PVV, queda mucho trabajo por hacer para comprender la carga en subpoblaciones específicas del VIH, desarrollar terapias efectivas y garantizar la igualdad de acceso a la vacunación para todos.

Palabras clave: VIH; COVID-19; SARS-CoV-2; tenofovir; vacunas; estudios de cohortes.

RESUM

Títol

Coinfecció pel VIH i SARS-COV-2: el que es coneix fins ara, tendències en evolució de la salut pública i perspectives clíniques.

Antecedents

La malaltia del coronavirus 2019 (COVD-19) causada pel coronavirus 2 (SARS-CoV-2) de la síndrome respiratòria aguda severa ha amenaçat els sistemes sanitaris a nivell mundial i ha provocat una morbiditat i mortalitat sense precedents. L'impacte de la infecció per SARS-CoV-2 en les persones que viuen amb el VIH (PLWH) ha estat especialment preocupant a causa del seu estat immune deteriorat i l'alta càrrega d'altres determinants de la salut en aquesta població. Els estudis de població existents, les sèries de casos i els estudis de cohorts sobre aquest important tema van implicar principalment pacients hospitalitzats, no tenien la capacitat d'ajustar-se prou per a la confusió residual i els estudis sobre la possibilitat d'utilitzar alguns agents anti-VIH han produït resultats contradictoris. Els objectius generals d'aquesta tesi doctoral eren descriure l'impacte de la COVID-19 en les PVVS, inclòs l'impacte clínic, el paper dels marcadors específics del VIH i la TAR, i avaluar la vacunació contra el SARS-CoV-2 i els factors associats entre les PVVS.

Metodologia

Estudi de poblacions

En els articles 1-4, s'aprofita la Cohort Població VIH de Catalunya i les Illes Balears (PISCIS) vinculada al Projecte de Dades Analítiques per a la Recerca i la Innovació en Salut de Catalunya (PADRIS). El PADRIS inclou diverses bases de dades administratives oficials de salut pública per obtenir informació sobre comorbiditats cròniques, diagnòstic de SARS-CoV-2, resultats clínics associats, mortalitat i recepció de la vacuna contra la COVID-19.

A l'article 1 s'han utilitzat dades de la població general seronegativa ≥16 anys obtingudes del registre de seguiment epidemiològic de la COVID-19 a través de l'Agència d'Avaluació de Qualitat i Salut de Catalunya (AQuAS).

Anàlisi estadística

- A l'article 1, hem utilitzat la prova Z per comparar la prova, la positivitat de la prova, l'hospitalització, l'ingrés a la UCI i la mortalitat per 100 persones entre les PVVS i la població general seronegativa.
- A l'article 2, vam realitzar un estudi de cohort retrospectiu per avaluar el diagnòstic de SARS-CoV-2 i els resultats greus entre persones que viuen amb el VIH i models de regressió de Cox univariables i multivariables per avaluar els factors associats. Es va estimar l'efecte de la

immunosupressió sobre els resultats greus mitjançant l'anàlisi de supervivència de Kaplan-Meier.

- A l'article 3, es va realitzar una anàlisi de la puntuació de propensió entre les PVVS en diferents règims de TARV. A més, vam utilitzar models de regressió de Cox ajustats per avaluar l'associació entre tenofovir i resultats SARS-CoV-2.
- A l'article 4 es va realitzar un estudi de cohort retrospectiu per avaluar la cobertura de vacunació SARS-CoV-2 entre les PVVS a Catalunya i es va utilitzar un model de regressió logística multivariable per avaluar els factors associats a la subvacunació.

Resultats

A l'article 1, les PVVS es van provar amb menys freqüència per SARS-CoV-2 (27,1% vs. 30,3, p<0,001) van tenir una positivitat més alta (21,1% vs. 15,8%, p<0,001), taxes d'hospitalització similars (13,8% vs. 15,0% p=0,174) i ingrés a la UCI (0,9% vs. 1,7%, p=0,059), i menor mortalitat per COVID-19 en comparació amb la població general seronegativa (1,7% vs 3,6%, p=0,002).

A l'article 2, el diagnòstic de SARS-CoV-2 era més comú entre els migrants (ràtio de risc ajustat [aHR] 1,55, interval de confiança [IC] del 95%, 1,31–1,83), homes que tenen relacions sexuals amb homes (aHR 1,42; IC del 95% , 1,09–1,86), i aquells amb quatre o més comorbiditats cròniques (aHR 1,46; IC del 95%, 1,09–1,97). Edat almenys 75 anys (aHR 5,2; 95% IC 1,8-15,3), origen no espanyol (aHR 2,1; 95% IC, 1,3-3,4) i neuropsiquiàtric (aHR 1,69; 95% IC, 1,07-2,69), autoimmune La malaltia (aHR 1,92; 95% IC, 1,14-3,23), la malaltia respiratòria (aHR 1,84; 95% IC, 1,09-3,09) i la malaltia metabòlica (aHR 2,59; 95% IC, 1,59-4,23) es van associar amb un augment de les comorbiditats cròniques. risc de resultats greus. Un estimador de Kaplan-Meier va mostrar diferències en el risc de resultats greus segons el recompte de cèl·lules CD4 en pacients amb ARN del VIH detectable (p=0,039), però no es van observar diferències en pacients amb ARN del VIH indetectable (p=0,15).

A l'article 3, tenofovir alafenamida/emtricitabina (TAF/FTC) en comparació amb abacavir/lamivudina (ABC/3TC) no es va associar amb un diagnòstic reduït de SARS-CoV-2 (aHR 0,90; IC del 95%, 0,78-1,04) ni hospitalització (aHR). 0,93; IC del 95%, 0,60-1,43). En comparació amb ABC/3TC, TDF/FTC no es va associar amb un diagnòstic reduït de SARS-CoV-2 (aHR 0,79; IC 95%, 0,60-1,04) ni hospitalització (aHR 0,51; IC 95%, 0,15-1,70). El TDF/FTC no es va associar amb un diagnòstic reduït de SARS-CoV-2 (aHR 0,79; IC del 95%, 0,60-1,04) ni hospitalització associada (aHR 0,33; IC del 95%, 0,10-1,07) en comparació amb TAF/FTC.

A l'article 4, entre el 27 de desembre de 2020 i l'11 de juliol de 2021, 9945 (66,6%) PVVS de la nostra cohort van rebre almenys una dosi de la vacuna SARS-CoV-2. Origen no espanyol (odds ratio ajustat [aOR] 0,64, IC 95% 0,59-0,70); Recompte de cèl·lules CD4 de 200-349 cèl·lules/μL (aOR 0,74, IC

del 95% 0,64 - 0,86) o 350-499 cèl·lules/μL (aOR 0,79, IC del 95% 0,70 - 0,88); ARN del VIH en plasma detectable (aOR 0,61 IC 95% 0,53-0,70); i el diagnòstic previ de SARS-CoV-2 (aOR 0,58 95% CI 0,51-0,65) es va associar amb una cobertura de vacunació més baixa. Diagnòstic de SARS-CoV-2 (437 [9,5%] vs. 323 [3,5%], p<0,001), hospitalitzacions associades (10 [2,3%] vs. 0 [0%], p<0,001), ingressos a la unitat de cures intensives (6 [1,4%] vs. 0 [0%], p<0,001) i les morts (10 [2,3%] vs. 0 [0%], P <0,001) van ser més elevades entre les PVVS no vacunades en comparació amb les vacunades.

Conclusions

Aquesta tesi demostra que les PVV amb condicions comòrbides, ARN del VIH no suprimit i supressió immune podrien estar en risc de pitjors resultats de COVID-19 i s'haurien de prioritzar per a la reducció del risc de COVID-19. Fins que els assaigs controlats aleatoris ben dissenyats no revelin noves proves que demostrin un efecte protector del tenofovir, no s'ha de modificar la gestió clínica de les PVV. Les nostres troballes també mostren que la vacunació contra el SARS-CoV-2 podria ser beneficiosa per a les PVV i, per tant, s'han d'implementar estratègies de salut pública dirigides per millorar l'absorció de la vacuna en grups poc vacunats. A més, aquesta tesi doctoral posa més llum sobre el fet que les desigualtats en salut són un factor important en la vulnerabilitat a la malaltia amb els migrants més afectats pel SARS-CoV-2 en termes de diagnòstic, resultats greus i infravacunació. Tot i que s'ha fet un progrés fenomenal en la comprensió de l'impacte del SARS-CoV-2 sobre les PVV, queda molta feina per entendre la càrrega de subpoblacions específiques del VIH, desenvolupar teràpies efectives i garantir l'accés igualitari a la vacunació per tothom.

Paraules clau: VIH; COVID-19; SARS-CoV-2; Tenofovir; vacunes; estudis de cohorts.

1. INTRODUCTION

The introductory chapter introduces and describes: 1) the interplay between HIV and SARS-CoV-2 from a public health perspective; 2) the complex relationship between HIV and SARS-CoV-2; 3) the effect of HIV on susceptibility to SARS-CoV-2 infection and severe COVID-19 outcomes; 4) the factors associated with COVID-19 severity among in people living with HIV (PLWH); 5) the potential impact of antiretroviral therapy (ART) on SARS-CoV-2 infection and COVID-19 outcomes, and 6) SARS-CoV-2 vaccination among PLWH. The chapter also elaborates on the Populational HIV Cohort from Catalonia and Balearic Islands – PISCIS and the Public Data Analysis Program for Research and Innovation in Health – PADRIS, which provide the foundation of this thesis in answering the research questions. Finally, the chapter presents the relevance, justification, and objectives of this dissertation.

1.1. Background

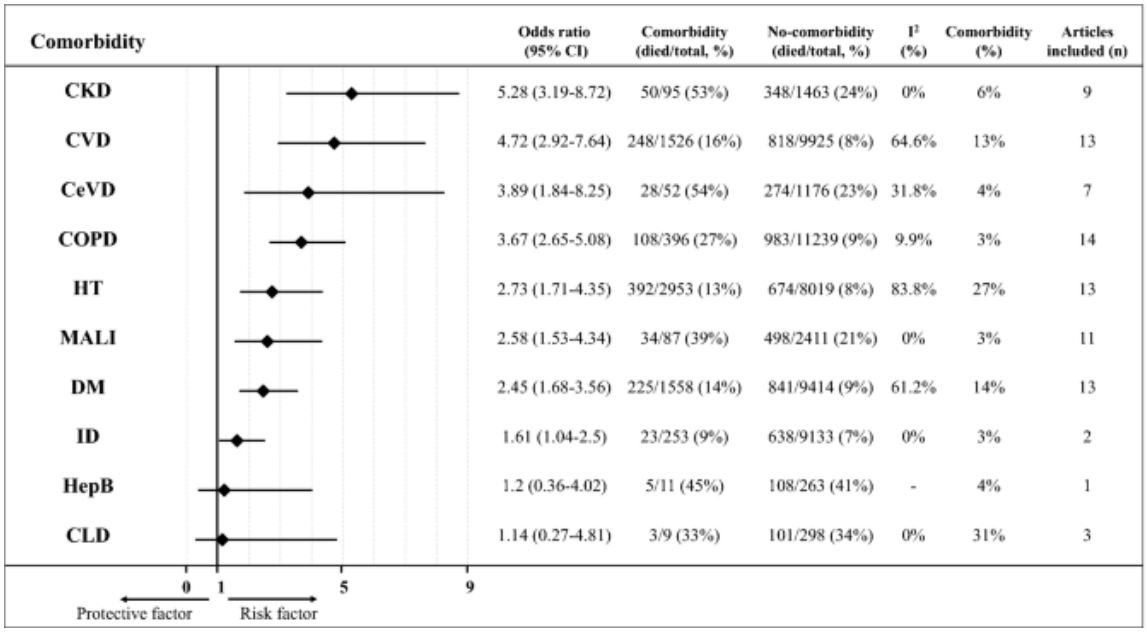
1.1.1. HIV and SARS-CoV-2: dealing with two pandemics

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly emerged as a major challenge to public health. It was first reported in Wuhan, China after a series of pneumonia cases of unknown etiology appeared in Wuhan, Hubei, China, in December 2019 [1] and was subsequently declared a pandemic by the World Health Organization (WHO) on March 12, 2020 [2]. The COVID-19 pandemic which has threatened the world's economy and disrupted every aspect of modern life has led to overwhelming morbidity and mortality throughout the world [3]. More worrying is the continued emergence of new variants of SARS-CoV-2 with higher transmissibility and reduction in the protection provided by neutralizing monoclonal antibodies and vaccination [4–6].

The current pandemic has interacted with existing health challenges including communicable and non-communicable diseases influencing the effect of COVID-19 on health outcomes [7]. Additionally, the vulnerability to COVID-19 has been higher among socio-economic and culturally disadvantaged populations [7]. The syndemic nature of this threat emphasizes the need for an approach that addresses the existing social and economic disparities and ensures that policy responses are needed to ensure that the COVID-19 pandemic does not exacerbate health inequalities [8,9].

While the clinical spectrum of COVID-19 remains varying with the majority of infected persons showing no to mild symptoms, some infected persons develop severe disease requiring hospitalization or management at the intensive care unit (ICU) [10]. Existing evidence shows that the severity of COVID-19 depends largely on older age and underlying chronic comorbidities such as hypertension, diabetes, renal disease, obesity, cardiovascular disease (CVD), malignancies, and chronic respiratory disease [11–14].

Figure 1. The impact of comorbidities on the disease course of COVID-19.



Summary figure for odds ratios (OR) with 95% confidence interval (95% CI) of mortality for different comorbidities. CKD chronic kidney disease, CVD cardiovascular disease, CeVD cerebrovascular disease, COPD chronic obstructive pulmonary disease, HT hypertension, MALI malignancy, DM diabetes mellitus, ID immunodeficiency, HepB Hepatitis B, CLD chronic liver disease.

Source: [14]

The baffling question during the early days of the pandemic was whether HIV was a risk factor for SARS-CoV-2 infection and severe clinical outcomes. Initial reports showed no increased risk of death among HIV/SARS-CoV-2 co-infected patients but larger studies demonstrated a higher risk of mortality among people living with HIV (PLWH) [15–18]. Particularly, accumulating evidence shows that those with unsuppressed HIV viremia and advanced immunosuppression could be more vulnerable to severe COVID-19 [19–21].

As a response to the pandemic, governments reacted in different ways and implemented different measures requiring societal restrictions to mitigate SARS-CoV-2 transmission. These measures inadvertently hampered key HIV/AIDS services worldwide. Over the past half a century, massive strides have been made in the HIV/AIDS response. The WHO have set the 90-90-90 target which aims at ensuring that 90% of PLWH know their status, 90% of positive persons are on antiretroviral therapy (ART), and 90% of those on ART achieve viral suppression [22]. Large scale self-quarantines, nationwide lockdowns, and channelling of health system resources into fighting the COVID-19 pandemic have presented multifaceted challenges to the HIV response and could undo the achievements made so far.

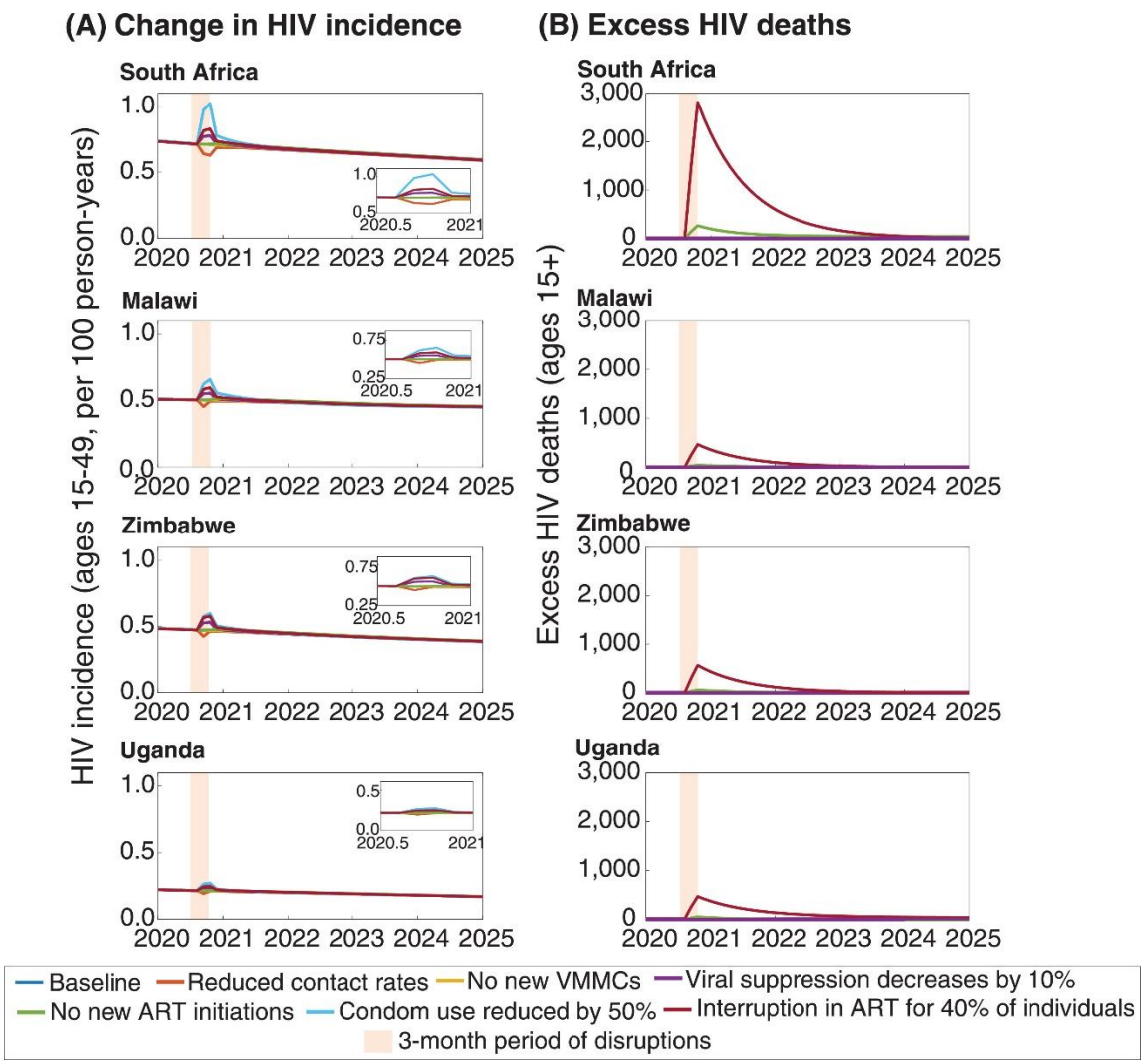
Learning from the history of pandemics and infectious disease outbreaks, the influenza pandemic of 1918 continued to affect the health outcomes of the population many years after the pandemic due to the negative influence on health systems and disruptions in care for chronic diseases [23–26]. Also, during the Ebola outbreak in West Africa, care for chronic diseases including HIV was interrupted. The outbreak limited HIV testing services [27] and access to ART [27–29] in the countries affected. Similarly, during the ongoing COVID-19 pandemic, access to key HIV services including routine testing, timely linkage to care, ART continuation, pre-exposure prophylaxis (PrEP) for HIV high-risk populations, harm reduction services for people who inject drugs (PWID), and social services for PLWH [30–34] have been restricted and could result in major setbacks towards ending HIV [35].

At the heights of the current COVID-19 pandemic, a report from Boston, USA, showed a 72% reduction in PrEP initiations, a 278% increase in refill lapses, and an 18% overall decrease in PrEP usage [36]. A PrEP program in South Africa reported over two-fold increased odds of a missed visit with no reports of change in sexual activity among recipients [37]. The COVID-19 pandemic has also resulted in a reduced HIV post-exposure prophylaxis (PEP) prescription with a reported 80% decrease in London [38] and 66% decrease in Melbourne [39] during the first month after the implementation of lockdown measures. A modeling study estimated that in low-and middle-income countries (LMICs) where the HIV burden is highest, there could be a 10% increase in HIV-related deaths in the next five years due to the COVID-19 pandemic [40]. In the light of further possible disruptions, the WHO and UNAIDS have worked together to provide strategies to ensure the continued provision of preventive and testing services and an uninterrupted HIV care continuum as we battle COVID-19 [38,41,42].

Lessons from the HIV pandemic have glaringly shaped the public health strategies employed to curb the COVID-19 pandemic. Contact tracing programs developed during the heights of the HIV epidemic have been revisited and repurposed to combat COVID-19 [43–45]. Recommendations on providing testing services with no or minimal financial barriers to high-risk communities as part of measures for the HIV response have been expanded to the current COVID-19 pandemic [44]. Both HIV and COVID-19 prevention strategies have focused on individual and socio-ecological aspects to reduce infection risk and improve clinical outcomes [43,44].

Many health systems, even those in high-income countries, have been overwhelmed by the COVID-19 pandemic and this has clearly impacted the HIV response. As COVID-19 continues to engulf the globe, it is crucial to develop clinical and public health solutions that juxtapose both HIV and COVID-19 pandemics. An effective response to these two pandemics requires collective and concerted efforts from policymakers, scientists, medical practitioners, industry, and community-based organisations to expedite research and implementation of evidence-based interventions that adequately address and contain both HIV and COVID-19 pandemics.

Figure 2. The impact of interruptions to HIV services during the COVID-19 pandemic.



Source: [46]

1.1.2. Relationship between HIV and SARS-CoV-2

Currently available data do not establish a definite interplay between HIV and SARS-CoV-2 [47]. Data from two previous 21st-century coronavirus epidemics, the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), showed relatively low infection rates and mild disease severity among PLWH [48].

The clinical course and outcomes for both HIV and SARS-CoV-2 depend on a drastic reduction of CD4+ T cell counts. In both infections, immune activation, direct attacks on CD4 cells, and redistribution of CD4 lead to CD4 lymphopenia [49]. Approximately 80% of SARS-CoV-2 acutely infected patients present with lymphopenia [50–57]. Lymphopenia when accompanied by suppression of B helper cells

and cytotoxic T cell function is a signal of poor COVID-19 prognosis [50,52,54,56–63]. There are indications that lymphopenia delays the clearance of SARS-CoV-2 allowing a cytokine storm and resulting in organ dysfunction [2,51,52,60,63–65]. In the case of HIV, the acute phase of the infection is characterized by a significant drop in peripheral CD4+ T cell counts which gradually declines during the chronic phase resulting in the development of AIDS [66]. Antiretrovirals are able to suppress the replication of HIV but systemic immune activation persists in PLWH after long-term reception of ART [66].

Considering that CD4 cell count plays a key role in both infections, comparing T cell responses taking into account host characteristics and hyper-inflammatory responses could provide important insights about HIV and SARS-CoV-2 co-infection. Nonetheless, no extra reduction in CD4 levels was observed in HIV/SARS-CoV-2 co-infected patients [67].

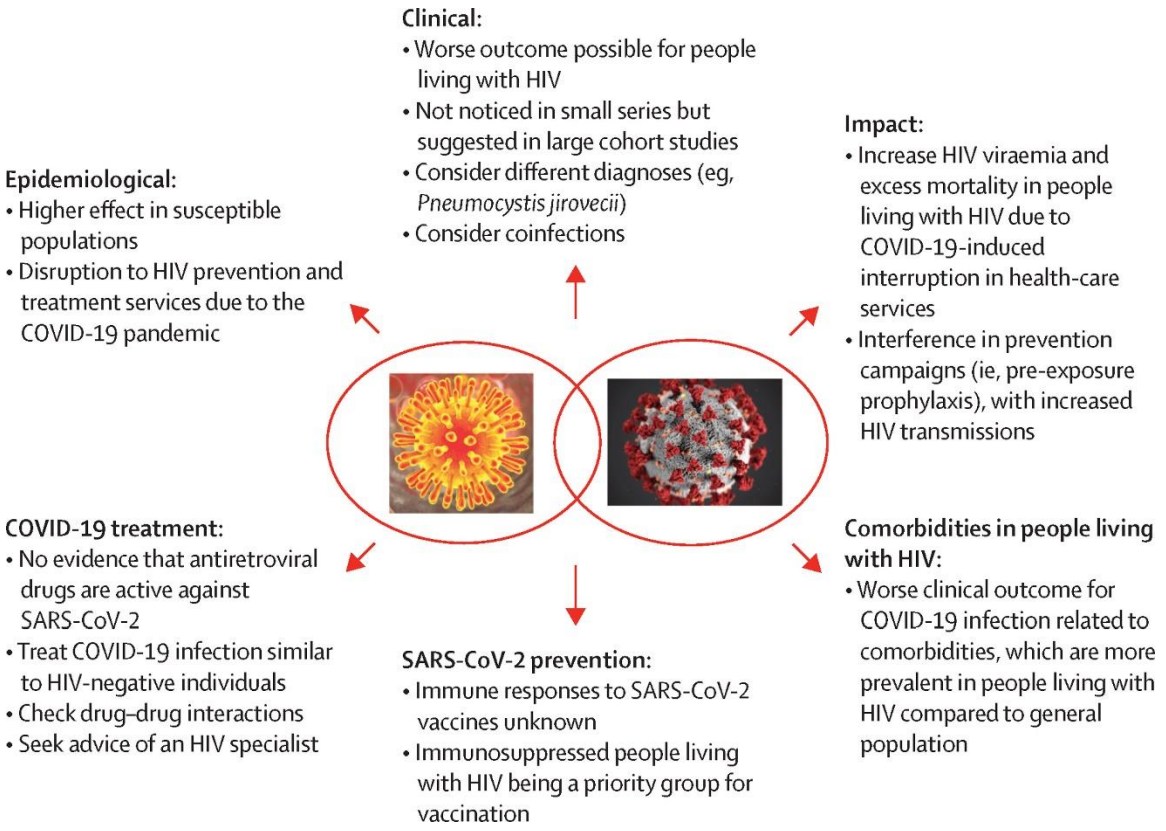
The relationship between SARS-CoV-2 and HIV remains unclear and it is affected by other factors including the presence of residual chronic inflammation, CD4 cell count, age of the host, reception of ART, and existence of comorbidities. The interplay between HIV and SARS-CoV-2 is suggested to be dependent on the interactions between these factors [66].

1.1.3. Impact of HIV on susceptibility to SARS-CoV-2 infection and severe COVID-19 outcomes

Early data from the first wave in Spain reported a lower incidence of SARS-CoV-2 among PLWH compared to the general HIV-negative population [68]. In a prospective cohort study of 5,683 PLWH in Barcelona, the observed standardised infection rate was 62% lower than in the general population [69]. Subsequently, a multicentre cohort involving 77,590 PLWH on ART reported a lower age- and sex-standardized incidence of SARS-CoV-2 infection compared to the general population (30.0 per 10,000 vs 41.7 per 10,000) [68]. When healthcare workers were excluded from the general population sample, the incidence estimates were similar in the two populations (30.0 per 10,000 vs 33.0 per 10,000) [68].

Contrary to these reports, a study from France which compared SARS-CoV-2 attack rates between PLWH and HIV-negative individuals on PrEP, found similar risks of symptomatic COVID-19 in both populations [70]. In Wuhan, China, similar SARS-CoV-2 incidence rates were observed among PLWH (0.38%, 95% CI: 0.24% – 0.53%) and the general population (0.45%, 95% CI: 0.45% - 0.46%) [71].

Figure 3. Interaction of the HIV and SARS-CoV-2 pandemics and unanswered questions.



Source: [47]

In the largest HIV cohort in the USA, the Veterans Aging Cohort Study (VACS), PLWH experienced higher testing rates compared to HIV-negative individuals, but test positivity rates were similar in the two populations (9.7% in PLWH vs 10.1% in HIV-negative individuals) [72]. A more recent study involving 2,988 HIV/SARS-CoV-2 co-infected patients in New York found similar rates of SARS-CoV-2 diagnosis among PLWH and the HIV-negative population [20]. In San Francisco, susceptibility to SARS-CoV-2 in the first 6 months of the pandemic was significantly higher among PLWH (4.5%) than in those without HIV (3.5%) (p=0.00004) [73].

In earlier case reports, PLWH on ART with suppressed viremia and higher CD4 cell counts reported mild diseases with high rates of recovery [74–85]. Due to the mild disease course observed, some researchers postulated that immunosuppression or the reception of ART could be protective against SARS-CoV-2 infection or severe COVID-19 outcomes [86].

Different studies have reported that once PLWH acquire SARS-CoV-2, the rate of hospital admissions is higher compared to the general HIV-negative population [12,64–66]. In the study by Tesoriero et al [20], hospitalisation rates were significantly higher among PLWH (8.28 per 1000) compared to HIV-negative persons (3.15 per 1000; standardized rate ratio [sRR] 1.38, 95% CI, 1.29 – 1.47). In another study propensity score-matched for sex, race, body mass index (BMI), diabetes, hypertension, chronic lung

disease, chronic kidney disease (CKD), and nicotine dependence, higher hospitalisation rates were observed among PLWH (19.3%) compared to HIV-negative individuals (11.4%; risk ratio [RR] 1.70, 95% CI 1.21-2.38) [88]. Similarly, Braunstein et al [87] found higher a proportion of PLWH hospitalised for COVID-19 compared to the general population of New York (42% vs 26%). Admissions to the ICU were also higher among PLWH (5%) in this study compared to those without HIV (3%) [87]. A poorer prognosis was also found in a retrospective cohort study involving 4,613 COVID-19 patients of which 100 were HIV-positive [90]. The risk of intubation was higher among PLWH compared to HIV-negative individuals (adjusted hazard ratio [aHR] 1.73, 95% CI 1.12-2.67; p = 0.01) [90]. Similar results were found in the study from Miyashita et al [91] where the risk of intubation was higher among PLWH <50 years (relative risk 2.97, 95% CI, 1.29 – 6.84). This study, however found no significant differences among other age groups [91]. On the contrary, Garetti et al [18] found no significant differences in ICU admission risk between PLWH and HIV-negative persons after adjusting for sex, age, ethnicity, baseline date, intermediate/probable COVID-19 acquisition in the hospital, and comorbidities (odds ratio [OR] 1.22, 95% CI, 0.80 – 1.87; p=0.35). The observed higher hospitalisation and ICU admission rates among PLWH might not be due to HIV itself but the fact that PLWH have characteristics common with people who experience poor outcomes from COVID-19.

In the first half-year of the pandemic, two meta-analyses found no significant association between HIV and COVID-19-related deaths [92,93]. Ssentongo et al reported that HIV was not significantly associated with an increased risk of COVID-19 mortality (RR = 0.88, 95% CI 0.34–2.31) [93]. The sample size in this analysis was however small involving only three studies published between December 1, 2019, and July 9, 2020 [93]. Sarkar et al subsequently reported another meta-analysis involving 7 studies dating up to September 3, 2020, and also found no significant association between HIV and COVID-19 mortality (RR = 0.99, 95% CI 0.82–1.19) [92]. The weakness in this study from Sarkar et al s similar to the previous one including only seven studies.

In a very large retrospective cohort study, Khrishnan Bhaskaran and colleagues [94] analysed COVID-19 mortality among PLWH in the OpenSAFELY primary care database of 17.3 million adults in the United Kingdom (UK). The risk of COVID-19 deaths was higher among the 27,480 PLWH (representing 0.16% of the study population) compared to the general population (adjusted hazard ratio [aHR] 2.59, 95% CI 1.74–3.84; p<0.0001). This study was limited by the lack of SARS-CoV-2 testing in the UK as of the time of the study, under-representation of London in the study population (which harbours about 50% of all UK HIV cases), and missing data for ethnicity. Geretti et al in an analysis of hospitalised COVID-19 patients also found an increased risk of mortality among HIV-positive patients (aHR 1.69, 95% CI 1.15–2.48; p=0.008) [18]. The risk of mortality increased when the analysis was restricted to persons less than 60 years old (aHR 2.87; 95% CI 1.70–4.84; P < 0.001) [18]. This study lacked data to adjust for

socioeconomic deprivation and important HIV parameters like ART history, plasma HIV-RNA load, and CD4 cell count [18].

The Department of Health of Western Cape, South Africa, conducted a study from 1 March to 9 June 2020 on 223,080 SARS-CoV-2 infected patients [17]. Among patients aged <50 years, COVID-19 mortality was higher among PLWH compared to the general HIV-negative population (39% vs 13%) [17]. After adjusting for age, sex, and comorbidities, the risk of COVD-19 deaths was higher among PLWH (aHR 2.14, 95% CI 1.70-2.70). This study could however be limited by unmeasured confounding including socioeconomic levels and unrecorded comorbidities. Similar results were observed in the study by Braunstein et al [87] where higher mortality was reported among PLWH compared to HIV-negative persons (13% vs 8%).

In the study by Tesoriero and colleagues [20] involving 2,988 HIV-positive persons, after standardization, PLWH experienced an elevated mortality rate compared to those living without HIV, per population (sRR, 1.30 [95% CI, 1.13-1.48]) but among hospitalized patients, the mortality rates were similar (sRR, 0.96 [95% CI, 0.83-1.09]). Hadi et al conducted a cohort study involving a total of 50,167 patients diagnosed with COVID-19 (404 HIV-positives and 49, 763 negatives) [88]. At 30-days from COVID-19 diagnosis, higher mortality was observed among PLWH (4.95% vs 3.2%, risk ratio 1.55, 95% CI 1.01-2.39) in the unmatched analysis [88]. After matching for sex, race, BMI, diabetes, hypertension, chronic lung diseases, CKD, and nicotine dependence, no significant differences in mortality were found (5.0% vs 3.7%, risk ratio 1.33, 95% CI 0.69% -2.57%) [88]. This points out the fact that the differences in sociodemographic characteristics and chronic comorbidities between PLWH and the general HIV-negative population could be driving the observed higher mortality among HIV-positive individuals.

1.1.4. Risk factors for COVID-19 severity among people living with HIV

Due to the unsettled position regarding the susceptibility of PLWH to poor COVID-19 outcomes [95], there is keen interest from the HIV scientific community to establish sociodemographic and clinical characteristics, as well as specific HIV markers such as CD4 cell counts, HIV RNA viral load, and disease stage are associated with severe outcomes from an HIV/SARS-CoV-2 co-infection. There are several factors that increase the risk of PLWH to severe COVID-19 outcomes. PLWH are aging and have increase rates of smoking, alcoholism, comorbidities, and obesity [96].

Different studies have consistently found the presence of chronic comorbidities like hypertension, diabetes, CVD, and cancers to be associated with severe COVID-19 outcomes [97]. A meta-analysis highlighted the high prevalence of comorbidities among PLWH who developed severe COVID-19 underscoring the key role of comorbidities in poor COVID-19 outcomes among PLWH [98]. In Madrid,

Spain, Vizcarra *et al* [89] observed no significant differences in CD4 cell counts between the 51 PLWH with SARS-CoV-2 infection and the 1299 PLWH without SARS-CoV-2. The prevalence of comorbidities assessed was higher among HIV/SARS-CoV-2 co-infected patients (63%) compared to PLWH with a SARS-CoV-2 infection [89]. Inciarte *et al* [69] in a cohort of 5,683 PLWH in Barcelona, Spain, found no HIV-associated factor associated with COVID-19 severity. In this study, the median CD4 cell count was 624 cells/ml among PLWH and 662 cells/ml to HIV-negative persons [69].

Compared to PLWH with a CD4 count >500 cells/μl, HIV-positive persons with CD4 counts of 200–499 cells/μl experienced a 29% increase in hospitalisation rates, and those with <200 cells/μl experienced a 69% increase in hospitalisation rates in New York [20]. An 11% and 26% increase in mortality were observed among PLWH with CD4 counts of 200–499 cells/μl, and those with <200 cells/μl respectively [20]. Hoffman *et al* [19] in a pooled analysis involving PLWH from three European countries found elevated mortality among PLWH with CD4 count <350 cells/μl (OR 2.85, 95% CI 1.26–6.44) compared to those with higher values. Dandachi *et al* [99] reported an increased hospitalisation and mortality among PLWH with lower CD4 cell count (<200 cells/mm^3). The study also identified older age, chronic lung disease, and hypertension as risk factors for severe outcomes [99].

Additionally, the acquisition of infectious diseases and clinical outcomes are influenced by social factors [100]. During the H1N1 influenza pandemic of 2009 for example, poorer clinical outcomes were observed among socioeconomically deprived individuals, migrant and ethnic minority groups, and people with unfavourable workplace policies [101–103]. Increased rates of SARS-CoV-2 diagnosis, associated hospital admissions, and deaths have been recorded in communities with low socioeconomic status and high proportions of racialized individuals [104]. In the UK, Hastie et al [105] evaluated Biobank data of 348,598 people found higher odd of SARS-CoV-2 test positivity among Black and South Asian individuals compared to Whites after controlling for socioeconomic, lifestyle, and health-related factors (Black: OR = 4.30, 95% CI: 2.92–6.31, p<0.001; South Asian: OR = 2.42, 95% CI = 1.50–3.93, p<0.001). Subsequently, another study from the UK found similar results reporting higher test positivity among Black compared to White adults in multivariable analysis (OR = 4.75, 95% CI = 2.65–8.51) [106]. In a retrospective cohort study involving 14,036 adults of which 1,052 were positive for COVID-19, non-Hispanic Black-identifying participants had higher odds of hospitalization compared to non-Hispanic White-identifying participants after adjusting for potential confounders (OR = 2.67, 95% CI: 1.30–5.47, p<0.01) [107]. Higher risk of infection and poorer clinical outcomes have also been reported for people in closed settings like prisons, homeless shelters, and facilities providing long-term care for people with physical and mental disbabilities[108,109].

In the PLWH population, racial and ethnic minorities have faced more vulnerabilities to COVID-19. The study by Bhaskaran and colleagues [94] reported a higher association between HIV and COVID-19 among people of Black ethnicity (HR 4.31, 95% CI 4.2–7.65) than in non-Black individuals (HR 1.84,

1.03–3.26). In the study from Sachdev et al [73] that reported a higher susceptibility of SARS-CoV-2 infection among PLWH (4.5%) compared to HIV-negative individuals (3.5%) (p=0.00004), only 55% of PLWH had stable housing highlighting the fact that the variations in the incidence of SARS-CoV-2 among PLWH are heavily impacted by social determinants of health which influence exposure to SARS-CoV-2 and not by virtue of the HIV infection itself.

1.1.5. Therapeutic options for COVID-19

Current evidence shows that the majority of SARS-CoV-2 infected individuals experience only mild to moderate illness [110]. There are still 5-10% who suffer severe disease course and sometimes death warranting the need to find strategies to control and cure the infection [110]. Public health professionals, researchers, clinicians, and governments across the globe have therefore been challenged to find short- and long-term solutions to curb the current COVID-19 pandemic.

Currently (February 16, 2022), the EMA has authorized five vaccines for use against SARS-CoV-2 in the European Union (EU) [111] but, specific and effective pharmacotherapy for SARS-CoV-2 is still unsettled. Also, it is unknown if the available vaccines can provide long-term protection against SARS-CoV-2 with variants emerging that could escape vaccine-induced immunity [112–114]. Therefore, there is an urgent need to find other therapeutic alternatives.

Despite the urgent need, the development of new safe, and effective therapies for emerging infectious diseases is usually a lengthy and expensive process. Drug repurposing has therefore been explored as a potential opportunity to identify viable therapeutic options with known safety profiles, complications, and side effects [115,116]. Different pharmacological agents have been postulated as potential treatments for COVID-19. Considered options include antivirals, steroids, chloroquine, hydroxychloroquine, and biological therapies like the use of convalescent plasma and monoclonal antibodies [117]. In the early phases of the pandemic, remdesivir was pursued as a treatment option because of its wide range of antiviral activity including its use against the Ebola virus [118–120]. In a recent study molnupiravir, a drug originally developed against the influenza virus, reduced the risk of COVID-19-associated hospitalisations and mortality with the producers seeking authorisation for use as the first oral antiviral medicine for COVID-19 [121].

In the early phases of the pandemic, some researchers suggested that the lower or similar COVID-19 outcomes observed among PLWH compared to the general HIV-negative population could be a result of the protection from some ART regimes [122]. Type 1 aspartate protease inhibitor, lopinavir/ritonavir (LPV/r), was studied because it exhibited positive clinical activity against other coronaviruses [123]. At the peak of the pandemic in Spain, treatment of some HIV/SARS-CoV-2 co-infected patients was amended to include LPV/r because of expected anti-SARS-CoV-2 effects [89]. However, no clear clinical

benefits could be established in recent randomized control trials testing the efficacy of LPV/r against COVID-19 [124,125].

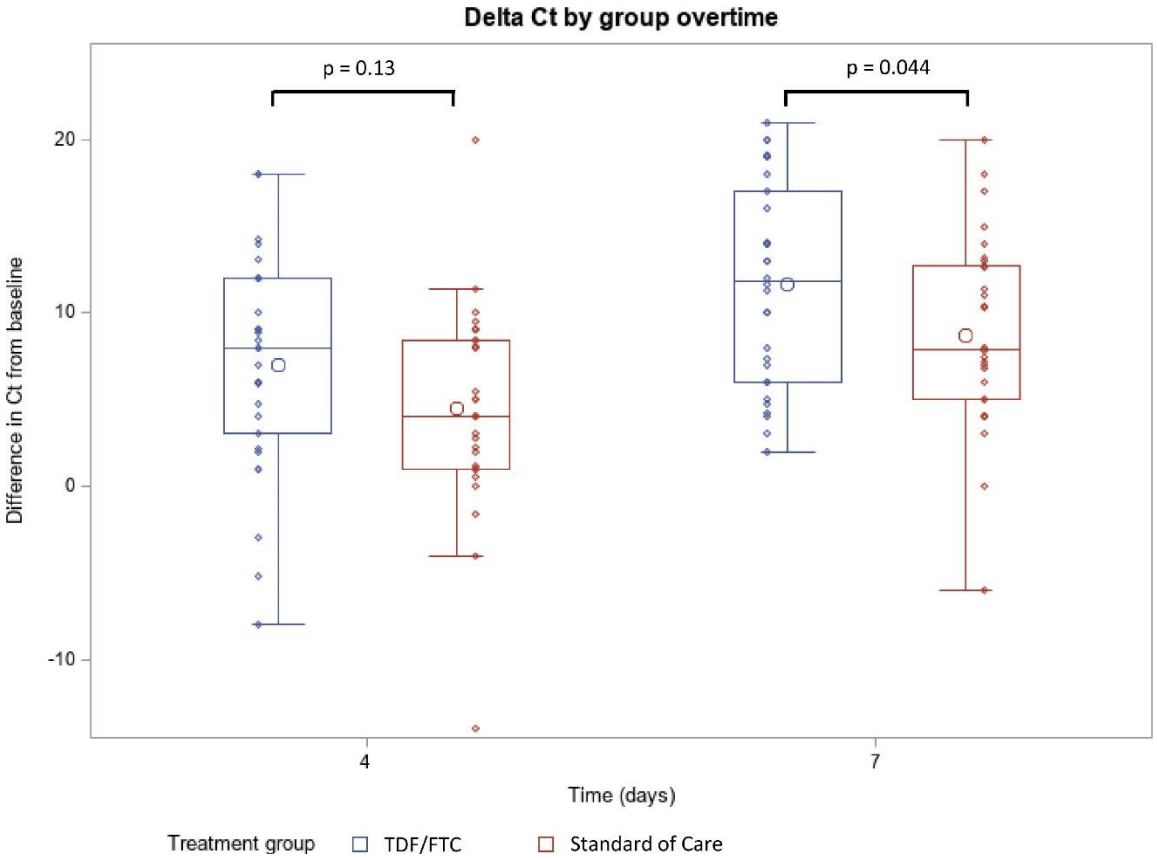
Some studies have reported associations between tenofovir (as its prodrug tenofovir disoproxil fumarate, TDF) and SARS-CoV-2 outcomes among PLWH. Three relatively large observational studies found lower risks of SARS-CoV-2 seropositivity [126], diagnosis [68,127], associated hospitalisations [68,127], and deaths [17,68,127] among PLWH receiving TDF/emtricitabine (TDF/FTC).

In the country-wide study of PLWH on ART from del Amo et al [68,127], confirmed SAR-CoV-2 was lower among TDF/FTC users compared to PLWH receiving other regimens. When the analysis was adjusted for age, SARS-CoV-2 diagnosis (rate ratio 0.44; 95% CI 0.27–0.70) and associated hospitalisations (rate ratio 0.53, 95% CI 0.27–0.97) remained lower among TDF/FTC users compared to those on TAF/FTC [68,127]. TDF/FTC recipients, however are likely to be healthier with fewer comorbidities like CVD and CKD [128–130] which have been identified as risk factors for severe COVID-19. In Western Cape, South Africa, the risk of COVID-19 death for PLWH on TDF/FTC was lower (aHR 0.41, 95% CI 0.21–0.78) compared to those receiving abacavir or zidovudine after adjusting for renal disease, viral suppression, and antiretroviral treatment duration [17]. Zidovudine use, however could be a result of a prior virologic failure or the presence of tuberculosis, both of which were not adjusted for in this study. A cohort study among Hepatitis B virus (HBV) patients in Spain also reported better COVID-19 clinical outcomes for TDF/FTC users compared to entecavir users [131]. In this study, the prevalence of chronic comorbidities was lower among patients receiving TDF/FTC and could have influenced the results. The protective effect of TDF/FTC is backed by molecular docking studies that showed that tenofovir could inhibit SARS-CoV-2 RdRp [122,132,133] and the activity expressed in animal models [134] and in-vivo studies [122].

Contrarily, a study assessed the protective effects of tenofovir against SARS-CoV-2 infection among HIV-negative individuals and reported a higher SARS-CoV-2 seroprevalence among PrEP (tenofovir) users compared to persons not receiving tenofovir (15.5% vs 9.2%, P=0.026) [135]. The study found no statistically significant differences in terms of COVID-19 clinical manifestations between users of PrEP (TDF/FTC or TAF/FTC) and the control group [135]. Similarly, the PREVENIR-ANRS and SAPRIS-Sero study from France also showed no reduction in SARS-CoV-2 seroprevalence among TDF/FTC PrEP users [136].

The discrepancy between the two prodrugs of tenofovir (TAF/FTC and TDF/FTC) leading to mixed results is unexplained and deserves further research. Given the limited resources to develop potential antivirals and the rapidly changing COVID-19 situation, understanding the preventive and protective effects of tenofovir is very relevant in finding solutions to curb the pandemic.

Figure 4. Effect of Tenofovir Disoproxil Fumarate and Emtricitabine on nasopharyngeal SARS-CoV-2 viral load burden amongst outpatients with COVID-19.



Variation of Ct RT-PCR for SARS-CoV-2 in fresh nasopharyngeal samples by study visit according to allocated groups. The length of the box represents the interquartile range (IQR, the distance between the 25th and 75th percentiles). The horizontal line and the larger circle within the box are the median and the arithmetic mean, respectively. The upper and lower whiskers mark the more extreme observations within 1.5(IQR) above the 75th percentiles and within 1.5(IQR) below the 25th percentiles, respectively.

Source: [137]

1.1.6. SARS-CoV-2 vaccination among people living with HIV

Data from the WHO Global Clinical Platform involving data from 37 countries indicates that HIV is an independent risk factor for severe COVID-19 presentation at hospital admission and in-hospital mortality [138]. Also, PLWH with unsuppressed HIV-RNA, lower CD4 cell count, and/or not receiving ART could experience a dysregulated immune response to SARS-CoV-2 infection [139,140]. Thirdly, PLWH are more likely to have chronic comorbidities and they experience them at a younger age compared to the HIV-negative population [141] and this increases their risk of severe outcomes from a SARS-CoV-2 infection. PLWH are also disproportionately affected by socioeconomic determinants of health which elevates their risk of COVID-19 [97]. Lastly, HIV is common among blacks and ethnic minority groups who have been identified to have higher risks of SARS-CoV-2 infection and severe COVID-19 [142]. It

has therefore become crucial to implement measures to prevent PLWH from getting infected with SARS-CoV-2.

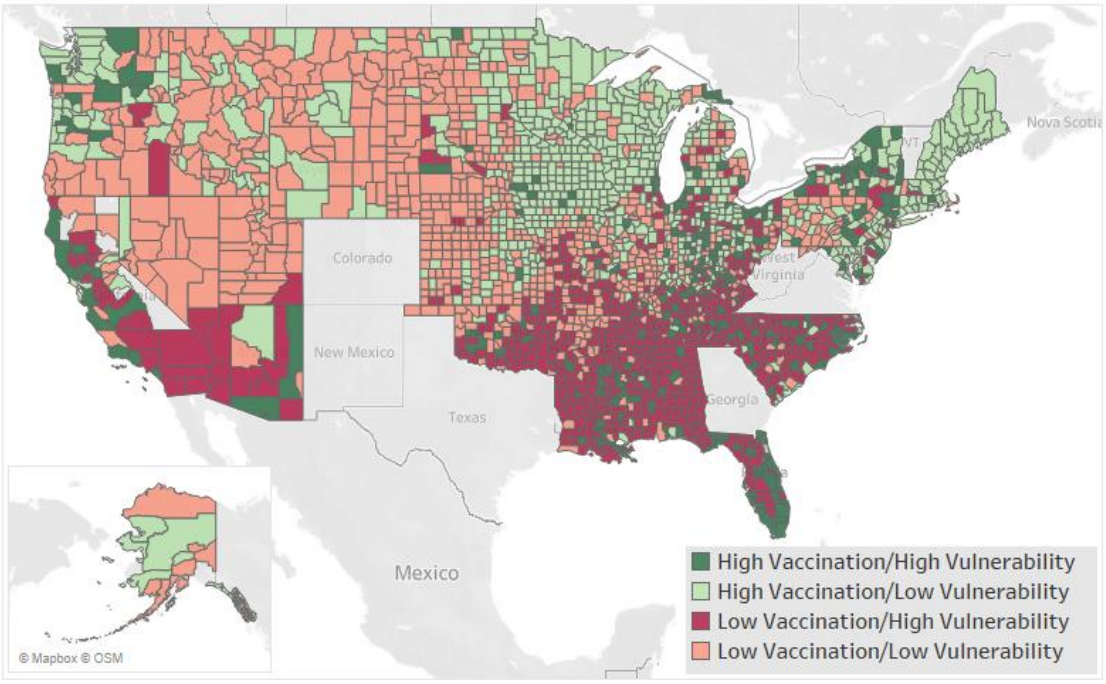
The development and equitable distribution of vaccines against SARS-CoV-2 present a golden opportunity to finally beat the current pandemic. A simulation experiment showed that with a vaccine efficacy of 80%, 75% coverage could help end the COVID-19 pandemic without further restrictions [143]. The European Medicines Agency (EMEA) has approved five vaccines for use in the European countries as of February 16, 2022 [111]. There are the Comirnaty developed by BioNTech and Pfizer; Janssen vaccine from Janssen-Cilag International NV; Nuvaxovid produced by Novavax CZ; Spikevax from Moderna Biotech Spain S.L.; and Vaxzevria developed by AstraZeneca AB/Oxford [111].

The initial immune responses to most vaccines are impaired in PLWH [144,145]. More specifically, defects in humoral and cellular immunity of HIV-positive patients lead to ineffective immune responses to vaccinations, and antibody levels post-immunization decay more rapidly in this population compared to HIV-negative counterparts [146,147]. The poor immune response from PLWH has been attributed to an alteration in antigen-specific antibody generation, poor generation of immunological memory, and/or loss of quantitative and functional T and B memory cells [148]. The advent of the highly active ART has resulted in suppressed viral replication and partial improvement of immune function including response to vaccines [149].

A number of PLWH were included in the vaccine trials for some of the globally widely-accepted vaccines. The Pfizer study included 196 HIV-positive persons but a sub-analysis of this population was not specifically shared prior to their authorization [150]. In the phase III trials of the Oxford/AstraZeneca COVID-19 vaccine study, 157 PLWH were recruited to participate [151]. Again, vaccine efficacy for PLWH in this study was not published before approval of the vaccine [151]. The Moderna study included 176 PLWH of which one (out of 76) in the placebo arm and zero (out of 80) in the vaccine arm contracted COVID-19 [152]. The Janssen vaccine included the highest number of PLWH – 1218 [153]. Four PLWHA who received the placebo and two who received Janssen vaccine contacted SARS-CoV-2 [153]. The overall vaccine efficacy observed in the Novavax study was 49.4% [154]. When the 201 PLWH (6% of the trial population) were excluded from the study, however the efficacy improved (60%) [154]. There are currently no safety concerns regarding the available SARS-CoV-2 vaccines for use among PLWH and the WHO and British HIV Association (BHIVA) recommend them for use among PLWH regardless of CD4+ T cell count [155,156]. The elevated vulnerability of PLWH to poorer COVID-19 outcomes makes them a priority group for SARS-CoV-2 vaccination.

A study that assessed the association between community vulnerability and SARS-CoV-2 vaccination till May 25, 2021, found lower vaccination rates among communities with increased vulnerability to COVID-19 [157]. Such factors should be given high consideration to ensure equitable vaccination uptake in high-risk populations as high vaccine uptake will be critical to achieving individual and population immunity.

Figure 5. County-level map depicting COVID community vulternability index scores and COVID-19 vaccination rates among populations aged 18+ (n = 2415 counties) in the United States.



Vaccination data include fully-vaccinated populations through May 25th, 2021 from https://covid.cdc.gov/covid-data-tracker/#vaccinations. Population denominators align with numbers utilized by the Centers for Disease Control based on Vintage 2019 Census Tables found at https://www.census.gov/programs-surveys/popest/data/tables.2019.html. COVID-19 Community Vulnerability Indices come from precisionforcovid.org/ccvi. "High" indicates quintile 4 or 5, and "Low" indicates quntile 1, 2, or 3.
Source: [157]

1.2. Gaps in literature

Critical gaps exist regarding the impact of SARS-CoV-2 in PLWH in terms of the biological interaction, susceptibility of PLWH to SARS-CoV-2, the clinical impact of SARS-CoV-2 on specific PLWH sub-populations, potential protection from some antiretrovirals, and the immune response of PLWH to SARS-CoV-2 vaccinations.

Earlier studies that were published on SARS-CoV-2 infection among PLWH showed no clear evidence of a higher infection rate and poorer disease course compared to HIV-negative individuals [12,69,70,78,85,86,89,158–163]. These studies were however largely case series with smaller sample sizes and reported SARS-CoV-2 among younger HIV patients compared to HIV-negative patients hospitalised for COVID-19 [12,69,70,78,85,86,89,158–163]. The fact that they predominantly included hospitalised patients means that the real impact of COVID-19 among HIV-infected individuals could be underestimated. Also, smaller sample sizes make it difficult to determine if the reported outcomes are generally true for the PLWH population.

Larger studies that subsequently reported severe clinical outcomes for PLWH infected with SARS-CoV-2 compared to the general HIV-negative population have been limited by a lack of adjustment for HIV-related variables including ART, viral load, and CD4 cell count [18,94]. Abnormal humoral and T-cell–mediated immune responses associated with HIV infection could escalate the susceptibility of PLWH to other infections [164] and therefore adequate adjustment for these variables is crucial. The study from South Africa [17] adjusted for these factors but important baseline patients' characteristics could differ from PLWH living in Europe including age, chronic comorbidities, and prevalence of tuberculosis [17]. Obesity and socioeconomic status were also not captured in this study [17]. Existing findings show that both obesity [165] and low socioeconomic levels [166] are associated with poor COVID-19 outcomes, making the control for these variables relevant.

Current evidence demonstrates that chronic comorbid conditions like hypertension, diabetes, CVD, and chronic lung diseases are associated with severe outcomes from COVID-19 whilst the role of specific HIV surrogate markers remains unclear [160,167]. There is therefore the need for continued research with quality data that allows adjustment for potential confounders to reduce the uncertainties regarding HIV and SARS-CoV-2 co-infection.

Data regarding the impact of tenofovir on SARS-CoV-2 is conflicting. Reports from in vitro studies have been contradictory. One in vitro study [168] exhibited antiviral activity against SARS-CoV-2 whilst two others showed no activity [169,170]. Large observational studies from South Africa and Spain have suggested that TDF could be protective against SARS-CoV-2 infection and prevent severe disease. These studies had limitations such as the inability to adjust for comorbidities in the study from Spain [68,127]

and the study from South Africa did not adjust for prior virologic failure of tuberculosis associated with zidovudine use [171]. There is currently no justification to switch the current ART regimen of PLWH. There is however a need for comprehensive data to understand the association between tenofovir exposure and SARS-CoV-2 infection and severe COVID-19.

HIV-positive persons, especially those with immune suppression and chronic comorbidities could be at an increased risk of poor outcomes from COVID-19 and hence the general recommendation of prioritising PLWH for SARS-CoV-2 vaccination [155]. The SARS-CoV-2 vaccines present an opportunity to beat the COVID-19 pandemic which has resulted in overwhelming morbidity and mortality. Even though data on the effectiveness and safety is limited, none of the currently available SARS-CoV-2 vaccines are contraindicated for use in PLWH. Monitoring the coverage of vaccination and identifying sub-populations under-vaccinated will help authorities to timely devise strategies to vaccinate inadequately vaccinated groups. The lack of knowledge regarding specific and vital aspects of HIV and SARS-CoV-2 infection is a matter of concern considering the potential vulnerability of PLWH and the unpredictability of the current pandemic.

1.3. Justification

To precisely understand the biological, clinical, and social interplay between HIV and SAS-CoV-2 requires more robust evidence than currently available. As of the end of the year 2020, there were approximately 38 million people globally living with HIV with 73% accessing ART [172] and COVID-19 has infected over 420 million people resulting in close to six million deaths as of February 23, 2022 [3]. In Europe, more than 50% of the 2.3 million PLWH are 50 years old or older and individuals >50 years old contribute to half of the newly diagnosed cases [173]. In general, these factors illustrate an aging HIV population who are at an increased risk of comorbid conditions. The compounding effect of an aging population, chronic diseases, HIV, and a SARS-CoV-2 co-infection though complex could be aggravating and warrants further investigation on the susceptibility of PLWH to SARS-CoV-2 infection.

Although initial reports suggested that immune suppression could be protective against severe disease and prevent the development of a cytokine storm in the case of an HIV/SARS-CoV-2 co-infection, there are signs of low CD4 cell count increasing the risk of severe outcomes. With current reports contradictory, establishing the effect of lower CD4 cell counts and detectable HIV RNA on severe COVID-19 requires well-designed studies from large HIV cohorts. Understanding if PLWH with advanced immune deficiency or unsuppressed viral loads will assist in answering questions about whether these subpopulations should be managed differently to prevent potential clinical progression of COVID-19.

Tenofovir, an antiretroviral medication has been proposed as a potential treatment for COVID-19. The evidence on the effect of tenofovir on infection acquisition and disease progression is however conflicting. Alteration of ART regimens of PLWH has been regarded unjustified as existing studies show important limitations and found equivocal results [47]. With the uncertainty of long-term protection from available SARS-CoV-2 vaccines, specific pharmacological remedies for SARS-CoV2 is vital and hence the potential repurposing of tenofovir for SARS-CoV-2 should be investigated in well-designed studies. Also, repurposing tenofovir for SARS-CoV-2 prevention and treatment of COVID-19 would reduce the time and costs related to new drug discoveries. Additionally, the safety profiles of tenofovir are already known in humans.

Equitable access to SARS-CoV-2 vaccines among PLWH will help protect this potentially vulnerable population. PLWH have shown hesitancy to receive other vaccines and are burdened by socioeconomic determinants that could limit vaccine access to this population. Vaccine deployment programs among PLWH should be strategic to meet the needs of the high-risk subpopulations and groups with limited access to healthcare.

These represents relevant knowledge gaps which need to be addressed to make significant progress in understanding the impact and intersection of SARS-CoV-2 and HIV. The knowledge generated will help to understand if PLWH need additional protective measures for COVID-19 due to increased susceptibility and if specific populations need to be prioritised in COVID-19 control programs and clinical mamangement. There is also the need to explore the potential impact of antiretrovirals and possibly understand if there switching ART regimens should be considered. With key health insitutions worldwide recommending that PLWH are prioritised for SARS-CoV-2 vaccinations, it will be important to monitor vaccination uptake among PLWH and timely identify sub-groups with lower uptake to restrategize public health policies on the vaccination roll-out.

1.4. Hypothesis

- Hypothesis 1: We hypothesized that the rate of testing and test positivity for SARS-CoV-2 will be similar between PLWH and the general population.

- Hypothesis 2: We hypothesized that COVID-19 clinical outcomes among PLWH with HIV viral suppression, higher CD4 cell count and on ART will be similar to the general HIV-negative population. We hypothesized that PLWH with advanced immunodefiecincy (low CD4 cell count) and those not recieving ART will suffer severe COVID-19 clinical outcomes.

- Hypothesis 3: We hypothesized that tenofovir (as TDF or TAF) will be protetive against SARS-CoV-2 diagnosis and clinical severity compared to other ART regimens among PLWH.

- Hypothesis 4: We hypothesized that vaccination coverage among PLWH will be similar to the general HIV negative population and COVID-19 vaccination will offer similar protection to the observed in the general population.

1.5. Aim and objectives

1.5.1. Aim

The purpose of this doctoral thesis is to describe the impact of COVID-19 on PLWH including the clinical impact, role of specific HIV markers and ART, and to assess SARS-CoV-2 vaccination and associated factors among PLWH in the European context.

1.5.2. General and specific objectives

The general objectives will be met by a number of specific objectives.

General objective 1: To compare SARS-CoV-2 outcomes between PLWH and the general HIV-negative population of Catalonia, Spain.

Specific objectives

1.1. Explore the frequency of SARS-CoV-2 testing between PLWH and the general HIV-negative population in Catalonia, Spain.
1.2. Compare SARS-CoV-2 diagnosis between PLWH and the general HIV-negative population.
1.3. Contrast hospitalisation, ICU admission, and mortality between PLWH and the general HIV-negative population.

General objective 2: To assess the factors associated with SARS-CoV-2 diagnosis and severe outcomes among PLWH.

Specific objectives

2.1. Describe the sociodemographic and clinical characteristics of PLWH infected with SARS-CoV-2 infection.
2.2. Identify the risk factors associated with SARS-CoV-2 diagnosis and diseases severity among PLWH.
2.3. Estimate the effect of immunosuppression and unsuppressed viremia on severe COVID-19 outcomes.
2.4. Evaluate the impact of chronic comorbidities on SARS-CoV-2 diagnosis and severe outcomes among PLWH.

General objective 3: To evaluate the effect of tenofovir as either TAF/FTC or TDF/FTC against SARS-CoV-2 infection and associated clinical outcomes among PLWH.

Specific objectives

3.1. Describe the sociodemographic and clinical characteristics including comorbid conditions of PLWH receiving TAF/FTC, TDF/FTC, and ABC/3TC.

3.2. Investigate the association between TAF/FTC and TDF/FTC exposure against SARS-CoV-2 infection.

3.3. Evaluate the association between TAF/FTC and TDF/FTC and severe COVID-19 among PLWH.

General objective 4: To assess the SARS-CoV-2 vaccination coverage among PLWH in Catalonia, Spain, and determine the factors associated with under-vaccination.

Specific objectives

4.1. Describe the SARS-CoV-2 vaccination coverage, distribution and trend among PLWH in Catalonia, Spain.

4.2. Identify sociodemographic, clinical, and epidemiological factors associated with low vaccination uptake among PLWH.

4.3. Compare SARS-CoV-2 diagnosis and associated clinical outcomes among vaccinated and unvaccinated PLWH.

These four main objectives will be met through the specific objectives of four main articles:

- **Article 1. Population-based assessment of SARS-CoV-2 infection among people living with HIV and the general population of Catalonia (March–December, 2020).** In line with objective 1.1, 1.2, and 1.3, this article aims to understand the susceptibility of SARS-CoV-2 among PLWH comparing with the general population. The study compares SARS-CoV-2 testing, test positivity, hospitalisation, ICU admission, and mortality between PLWH and the general HIV-negative population of Catalonia, Spain.

- **Article 2. Sociodemographic, clinical, and immunological factors associated with SARS-CoV-2 diagnosis and severe COVID-19 outcomes in people living with HIV: a retrospective cohort study.** In line with objective 2.1, 2.2, 2.3, and 2.4, this article aims to describe the sociodemographic, immunological, and clinical characteristics associated with SARS-CoV-2 diagnosis and COVID-19 outcomes among PLWH in Catalonia (Spain), and assessed the risk factors of worse disease prognosis using a multicentre population-based cohort of PLWH.

- **Article 3. Impact of tenofovir on SARS-CoV-2 infection and severe outcomes among people living with HIV: a propensity score matched study.** In line with objective 3.1, 3.2, and 3.3, the study aimes to evaluate the association between TAF/FTC and TDF/FTC exposure against SARS-CoV-2 infection and severe COVID-19 among PLWH mitigating the limitations in existing studies by adjusting adequately for baseline potential confounders.

- **Article 4. SARS-CoV-2 vaccination coverage and factors associated with low uptake in a cohort of people living with HIV.** In line with obhective 4.1, 4.2, and 4.3, this article aims to assess the SARS-CoV-2 vaccination coverage among PLWH in Catalonia, Spain, to describe the distribution, and identify sociodemographic, clinical, and epidemiological factors associated with low vaccination uptake. Additionally, the study aims to compare SARS-CoV-2 diagnosis and associated clinical outcomes among vaccinated and unvaccinated PLWH without a previous SARS-CoV-2 infection.

2. METHODOLOGY

This chapter provides an overview of the diverse methods and approaches used in the four main articles presented in this thesis dissertation, the main data sources, and the study setting.

2.1. Data sources

2.1.1. The PISCIS Cohort

The Populational HIV Cohort from Catalonia and Balearic Islands – PISCIS, is an observational, prospective, ongoing, population-based, and multicentre study that follows PLWH in care in Catalonia and the Balearic Islands, Spain. The cohort was established in 1998 with the objectives of standardising patient data across participating hospitals, describing the sociodemographic, clinical, and epidemiological characteristics of new HIV diagnoses, their evolution, and natural history, as well as assessing the patterns of use and effectiveness of ART.

A three-phase plan led to the commencement of the cohort; 1) the creation and dissemination of patient data management software, 2) the validation of the software through the collection of retrospective data between 1998 and 2000; and 3) the prospective data collection from 2000. An invitation to participate in the project was sent to the Regional Catalan Hospitals network that already participated in the HIV/AIDS Working Group of Catalonia. Subsequently, this invitation was extended to other regional hospitals in Catalonia and the Balearic Islands.

An initial 10 hospitals constituted the cohort with the Centre for Epidemiological Studies on Sexually Transmitted Infections and HIV/AIDS in Catalonia (CEEISCAT) steering its coordination and data management. The study received ethical approval from the Germans Trias i Pujol University Hospital's Clinical Research Ethics Committee, reference number EO-11-108. Data collection was also approved by the ethics committees of all participating hospitals.

Reporting of newly diagnosed HIV cases was mandatory in Catalonia since 1987. However, between 2001 -2010, reporting of new cases was made voluntary. On May 25, 2010, a decree (Decree 67/2010) was passed re-establishing the mandatory reporting of new HIV cases and becoming a part of the epidemiological surveillance system of Catalonia (SUVEC) [174].

All newly diagnosed HIV patients of ≥16 years are recruited at their first visit to any of the 18 participating centres. Currently, about 800 new participants join the cohort each year. It is estimated that the cohort represents approximately 84% and 60% of all PLWH in Catalonia and the Balearic Islands respectively. Annually, the coordinating centre receives data of all patients participating in the cohort and undergoes robust quality control, data harmonisation, and statistical analyses.

The PISCIS framework has contributed essentially to topics of high interest in HIV science and public health including important studies on highly active antiretroviral therapy (HAART) [175–179], HIV co-infections [180–182], predictors of HIV progression [179], HIV care continuum [183], the impact of HIV on vulnerable populations [184], and estimating HIV undiagnosed population of Catalonia [185]. PISCIS has also contributed to multiple international cohorts conducting innovative HIV research in ART initiation timing [186,187], ART response and effectiveness [188–190], patient prognosis and mortality [188,191], AIDS-defining and non-AIDS-defining illnesses [192,193], the significance of immunological and virologic responses [194], and HIV drug resistance and virologic failure [195]. PISCIS welcomes physicians and HIV units interested in collaborating and detailed information about the project can be found via the website http://www.pisciscohort.org/.

2.1.2. The PADRIS program

The Public Data Analysis Program for Research and Innovation in Health – PADRIS, is an initiative of the Department of Health of the Catalonian Government. The operation of the program is coordinated by the Agency for Health Quality and Evaluation of Catalonia (AQuAS) [196]. The aim of the program is to promote and facilitate research and innovation in the field of health through the reuse of comprehensive public healthcare service data generated in Catalonia following all established legal and ethical protocols [196].

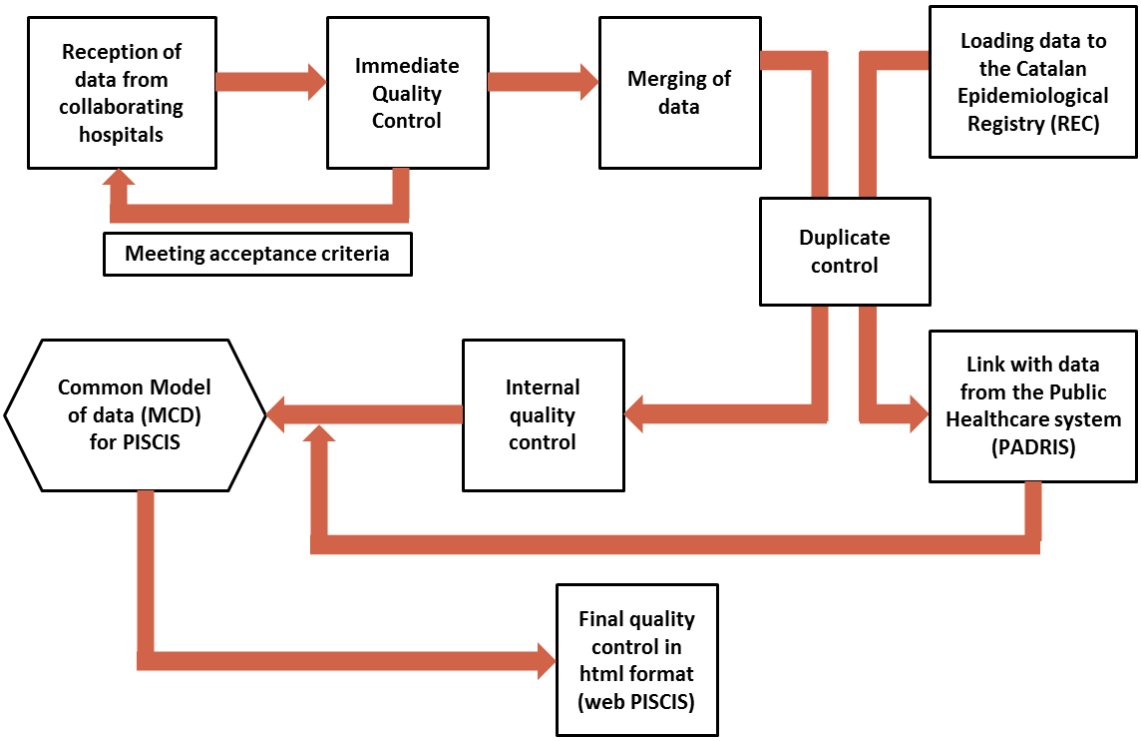
PADRIS enables researchers to utilize the data produced by the project to maximize research capacity and improve the health of the population. The program has several governing bodies that ensure compliance with the ethical principles of the scientific projects carried out. The structure is made up of the Research Ethics Committee, the AQuAS Board of Directors, and the Advisory Board, as well as the Supervisory and Operations Committees [196]. Data is anonymised and deidentified to eliminate any potential data that could identify patients before being handed over to research teams. The PADRIS registry has an automated validation system and external audits are carried out on its operations regularly [196].

The program systematically collects patient-level information on sociodemographic, clinical, and epidemiological features, and extensive use of the overall Catalan public health system. Healthcare-related data collected longitudinally across several databases via the PADRIS program includes information on primary care visits, hospital admissions, pharmacy prescriptions, laboratory, and diagnostic tests, emergency room use, outpatient visits to the specialists, visits to nursing facilities, and any engagement with the public healthcare system. More information about the PADRIS program is available here: https://aquas.gencat.cat/ca/ambits/analitica-dades/padris/ .

2.1.3. Study setting

This dissertation relied on data from three key sources; the PISCIS cohort, the PADRIS, and the COVID-19 epidemiological monitoring registry of Catalonia. For article two, we used data from the PISCIS cohort and the COVID-19 epidemiological monitoring registry of Catalonia. For articles three, four, and five we used data from the PISCIS cohort linked with the PADRIS. The linkage process is described in the diagram below.

Figure 6. Diagram showing the reception of data from PISCIS cohort collaborating hospitals, data treatments, and linkage with PADRIS.



Data is received from all the PISCIS collaborating hospitals. The data undergoes immediate quality control based on pre-defined criteria such as a minimum of 90% of patients should have values for recent (not longer than six months) CD4 cell count, viral load, and antiretroviral therapy. All hospitals are also expected to upload data on all patients into the Catalan Epidemioloical registry (REC). We merge our data with that of the REC to augment our data and reduce the amount of missing values. Data is then screened and duplicates are eliminated. The data set further undergoes an internal quality and is linked with data from the PADRIS to create the PISCIS common data model. The PISCIS common data model undergoes final quality control and is made available in HTML format. Abbreviations: PADRIS, Public Data Analysis for Health Research and Innovation Program of Catalonia.

2.2. Research Methods

2.2.1. Two proportion Z-test

This method was employed in article 1.

The two-proportion Z-test is a statistical hypothesis test used to evaluate differences or similarities between two proportions [197]. Z-test is performed when the two samples are completely independent and the null hypothesis is that the two samples or populations are equal. To be able to compute Z-statistics, three conditions must be met [197]:

1) The two populations must be normal or approximately normal,
2) Samples must be randomly selected from the two populations,
3) The two proportions being tested must be independent.

In the event that these conditions are not met, other tests must be considered [197]. The advantage of the two-sample z-test is the ability to compute it without prior knowledge of the standard deviation of the populations [197]. The two steps involved in computing the Z-test are [197]:

1) Calculating the standard error of the difference between the two populations.
2) Calculating the z-statistic by dividing the difference between the two proportions by the standard error of the difference.

When the z-statistic is greater than or equal to the significance level, a conclusion can be made that a difference exists between the two proportions being compared, and thus, we can reject the null hypothesis [197].

The formula for the two-sample Z-test for proportions

$$z = \frac{\hat{p}_1 - \hat{p}_2}{\sqrt{\hat{p}(1-\hat{p})\left(\frac{1}{n_1}+\frac{1}{n_2}\right)}}$$

Where, p1-hat is the proportion of the 1st sample; p2-hat is the proportion of the 2nd sample; n1 is number of data samples in the 1st sample; n2 is number of data samples in the 2nd sample; and p-hat is mean of both the samples.

2.2.2. Cox proportional hazard regression

This method was used in articles 2 and 3.

Sir David Cox first introduced the Cox proportional hazards model in 1972 to estimate the effects of different covariates influencing the times of the failures of a system [198]. The model has gone on to be broadly used in biomedical research typically to investigate the association between the survival time of subjects and one or more predictor variables [198,199]. The Cox proportional-hazards regression model is employed in time-to-event clinical investigations with many known covariates that could potentially affect the outcome [200]. The model allows us to determine how specific factors affect the rate of a particular outcome.

The model is calculated by a hazard function denoted by **h(t)**. In short, the function is a risk of having an outcome at time t estimated as [200]:

$$\mathbf{h(t)=h_0(t)\times exp(b_1x_1+b_2x_2+...+b_px_p)}$$

where, *t* represents the survival time; $\boldsymbol{h(t)}$ is the hazard function determined by a set of p covariates $\boldsymbol{(x_1,x_2,...,x_p)}$; the coefficients $\boldsymbol{(b_1,b_2,...,b_p)}$ measure the effect size of the covariates; the term $\boldsymbol{h_0}$ is the baseline hazard. It corresponds to the value of the hazard if all the $\boldsymbol{x_i}$ is equal to zero. The **'t'** in **h(t)** depicts that the hazard may vary over time.

A hazard ratio equal to 1, shows there is no effect; above 1 indicates a covariate that is positively associated with the event probability, and thus negatively associated with the length of survival, and below 1 shows that a covariate is negatively associated with the event probability [200].

In estimating Cox proportional hazards models, a fundamental assumption that all hazards are proportional is made. This implies that the relative hazard is constant over time with varying covariate levels [200]. Different approaches can be used to test the proportional hazards assumption. The Kaplan-Meier curves and the scaled Schoenfeld residuals plots can be assessed visually [201]. A violation of the proportional hazards assumption could result in biased effect estimates in Cox regression analysis [201]. When there is a violation of the proportional hazards assumption, time-dependent coefficients [202], Schemper's weighted model [203], or a restricted mean survival time [204] are methods that could be used to deal with the violation.

In time-to-event regression analysis, it is important to address the presence of collinearity or multicollinearity between covariates that is when there is a correlation between predictor variables (or independent variables), such that they express a linear relationship in a regression model [205,206]. When this occurs, the predictor variables cannot independently predict the value of the dependent variable. To determine the presence of collinearity or multicollinearity, the variance inflation factor (VIF) is calculated [205,206]. The VIF quantifies the extent of correlation between one predictor and the other predictors

in a model. The degree of correlation in linear regression can be calculated as the R-squared statistic of the regression where the predictor of interest is predicted by all the other predictor variables. The VIF is calculated with the formula [205,206]:

$$VIF = \frac{1}{1 - R^2}$$

If the resulting value is 1, t means there is no correlation between the variables. The greater the value, the higher the correlation [205,206]. A VIF of 5 is usually considered moderate while 10 is regarded as very high [205,206]. To resolve issues of collinearity or multicollinearity in regression analysis, highly correlated independent variables could be removed from the model; independent variables could be linearly combined, or perform a principal components analysis or partial least squares regression to deal with highly correlated variables [205,206].

2.2.3. Kaplan-Meier analysis

This method was used in article 2.

The Kaplan-Meier survival curve describes the probability of surviving in a defined duration of time while considering the time in many small intervals [207]. In Kaplan-Meier survival analysis, three assumptions are made. Firstly, it is assumed that every subject that is censored has the same survival chances as those who are continued to be followed [208]. Secondly, the survival probability for subjects recruited at different times in the follow-up period is assumed to be the same [208]. And thirdly, it is assumed that all events occur at a specified time [208]. The Kaplan-Meier estimate is also referred to as "the product limit estimate". The process involves calculating the probability that an event will occur at a certain point in time and computing these probabilities to get a final estimate. The survival probability of any subject at a particular point in time is calculated by:

$$S_t = \frac{\text{Number of subjects living at the start} - \text{Number of subjects died}}{\text{Number of subjects living at the start}}$$

For each specific time interval, the survival probability is determined by dividing the number of surviving subjects by the number of subjects at risk. Subjects who die, drop out, or are lost to follow-up are not do not contribute to the number of subjects at risk and are censored and not counted in the denominator. Survival curves can be compared using the log-rank test and Cox proportion hazard test [209].

2.2.4. Propensity score-matching

This method was used in article 3.

Propensity scores estimate the effect of receiving treatment of treatments or other interventions by accounting for the covariates that predict receiving the treatment when random assignments to subjects are not feasible: $e_i = Pr(Zi = 1|Xi)$ [210]. The propensity score is a balancing score dependent on the similar or equal distribution of covariates between treated and untreated subjects [210]. Typically, the score is determined through a logistic regression model where the treatment status is regressed on observed covariates. Other methods such as boosting [211], recursive partitioning [211], random forests [212], and neural networks [212] could potentially be used to estimate the propensity scores.

Propensity score matching (PSM) is defined as the pairing of treatment and control subjects with similar propensity scores and other covariates, and the removal of all unmatched subjects [210]. Fundamentally, the PSM is used to compare two populations but could be used in cases of more than two groups [213]. In observational studies, an analysis of a propensity scre-matched simple is comparable to randomised control trials (RCT) with the possibility to compare outcomes between treated and untreated groups. There is a possibility of residual confounding in baseline covariates and adjusted regression analysis can be used to increase the precision and improve statistical power [214]. Similarly, results from PSM can be improved using additional matching of other covariates or adjusted regression analysis [215,216].

2.2.5. Logistic regression analysis

This method was used in article 5.

Logistic regression analysis is a statistical technique to evaluate the relationship between various predictor variables (either categorical or continuous) and an outcome that is binary (dichotomous). It was first used by Cornfield et al in the early 1960s [217]. The main edge logistic regression analysis has over the Mantel-Haenszel OR is its possibility to use continuous explanatory variables and the ability to compute more than two explanatory variables simultaneously [218]. The logistic regression models the chance that an outcome is based on the subject's characteristics. The logarithm of the chance is modeled in the formula:

$$\log \pi \, (1 - \pi = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots \beta_m X_m) \text{ [219]}$$

where π indicates the probability of an event, β_i is the regression coefficient associated with the reference group, and the x_i is associated with the explanatory variables. The reference group, β_0, represents subjects presenting the reference level of each and every variable X_1...m. Logistic regression analysis, like other

statistical approaches used in epidemiological studies, has some assumptions. First, the dependent variable is dichotomous [218]. Secondly, multicollinearity between the predictor variables should completely be avoided [218]. Thirdly, the independent variables should be linearly related to the log odds [218]. And finally, logistic regression analysis is fairly suitable for large sample sizes [218]. The larger the sample, the more reliable the results.

2.3. Statistical analysis

2.3.1. Article 1

We conducted a cross-sectional study leveraging data from the PISCIS cohort of PLWH in Catalonia (Spain). Aggregated data on the SARS-COV-2 testing, test positivity, related hospitalisation, ICU admission, and death for the general HIV-negative population within the same study period for individuals aged ≥16 years was obtained from COVID-19 epidemiological monitoring registry via the Agency for Health and Quality Assessment of Catalonia (AQuAS). We excluded PLWH from the general population before the analysis. We calculated SARS-CoV-2 test positivity per the proportion of the population that tested for SARS-CoV-2. Among SARS-CoV-2 positive cases, we determined the rates per 100 persons of hospitalisation, ICU admission, and mortality. We used the Z-test to compare testing, test positivity, hospitalisation, ICU admission, and mortality between the two populations. We presented our findings using the onion plots concept.

2.3.2. Article 2

We conducted an observational retrospective cohort study using the PISCIS cohort of PLWH in Catalonia, Spain between March 1, 2020 and December 15, 2020. Patient numbers were depicted in a flowchart. Categorical variables were expressed as counts and percentages and continuous variables were expressed as medians and interquartile ranges (IQR). Proportions for categorical variables were compared using the $\chi 2$ or Fisher's exact test where appropriate. Continuous variables were compared using the Mann-Whitney U test.

Univariable and multivariable Cox proportional hazards regression models were estimated to identify risk factors associated with SARS-CoV-2 diagnosis and severe COVID-19, providing hazard ratios (HR) and adjusted hazard ratios (aHR) with 95% confidence intervals (95% CI). We calculated the Schoenfeld residuals for each regression variable to see if each variable independently satisfies the assumptions of the Cox model (Figure 7) and made sure no variables exhibited multicollinearity (Table 1) or correlation (Table 2).

We assessed the impact of immunosuppression on severe outcomes stratifying by unsuppressed and suppressed plasma HIV viral load, using survival analysis techniques. We reported the survival probability during the study period using the Kaplan–Meier estimator. We censored patients who did not experience a severe outcome by the end of the follow-up period. The differences between the curves were assessed using the log-rank test. Statistical significance was set at a *P*-value of <0.05 (2-sided).

Table 1. Evualtion of variance inflation factor (VIF) of all variables using the rms package in R.

	SARS-CoV-2 diagnosis		Severe COVID-19 outcomes	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Sex (male)	1	6,414771	1	3,56623
Age - 40-64	1,099936	1,280296	1,689316	1,917725
Age - 65-74	1,076809	1,23092	1,467236	1,736728
Age - ≥75	1,026841	1,159477	1,294904	1,687872
Place of Birth - Outside Spain	1	1,097682	1	1,147007
Socialeconomic deprivation - Mild	1,102294	1,134731	1,075556	1,12522
Socialeconomic deprivation - Moderate/severe	1,102294	1,1952	1,075556	1,18302
HIV transmission group - female homo/hetero/bisexual	1,883244	7,50108	1,769764	4,379618
HIV transmission group - PWID	1,5378	1,729577	1,922328	2,317876
HIV transmission group - MSM	2,429238	2,641269	2,364769	2,547738
HIV transmission group - Others	1,428454	1,545984	1,398058	1,472003
CD4 T-cell count - <200	1,010795	1,080254	3,295943	3,85788
CD4 T-cell count - 200-500	1,010795	1,053781	3,295943	4,057348
Plasma HIV-RNA - detectable	1	1,050397	1	1,100773
Bakcbone ART - TAF	4,799077	4,847104	4,265625	5,416442
Bakcbone ART - TDF	2,050212	1,975447	2,008681	2,353352
Bakcbone ART - ABC+3TC	4,518226	4,584842	3,888888	4,870552
Number of comorbidities - 1	1,29418	1,327239	4,139769	4,193891
Number of comorbidities - 2	1,252088	1,337336	3,91455	3,997017
Number of comorbidities - 3	1,156116	1,264007	4,24661	4,544029
Number of comorbidities - 4 or more	1,193116	1,512377	5,333893	5,81974

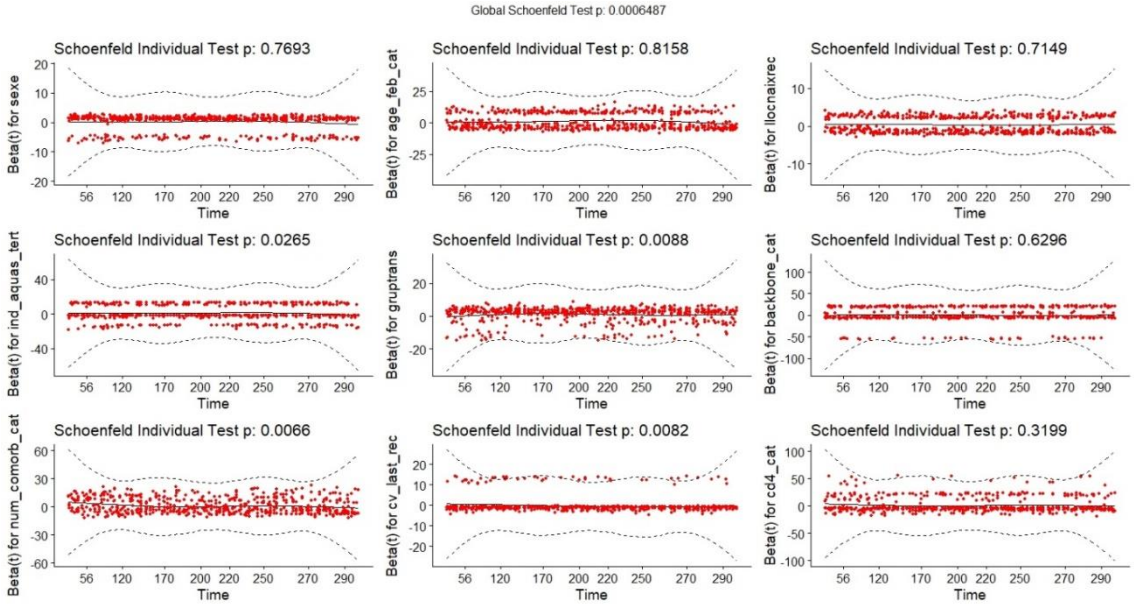
Abbreviations: PWID, people who inject drugs; MSM, men who have sex with men; ART, antiretroviral therapy; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ABC, abacavir; 3TC, lamivudine.

Table 2. Evualtion of correlation of all variables using the hector package (Heterogeneous Correlation Matrix) in R.

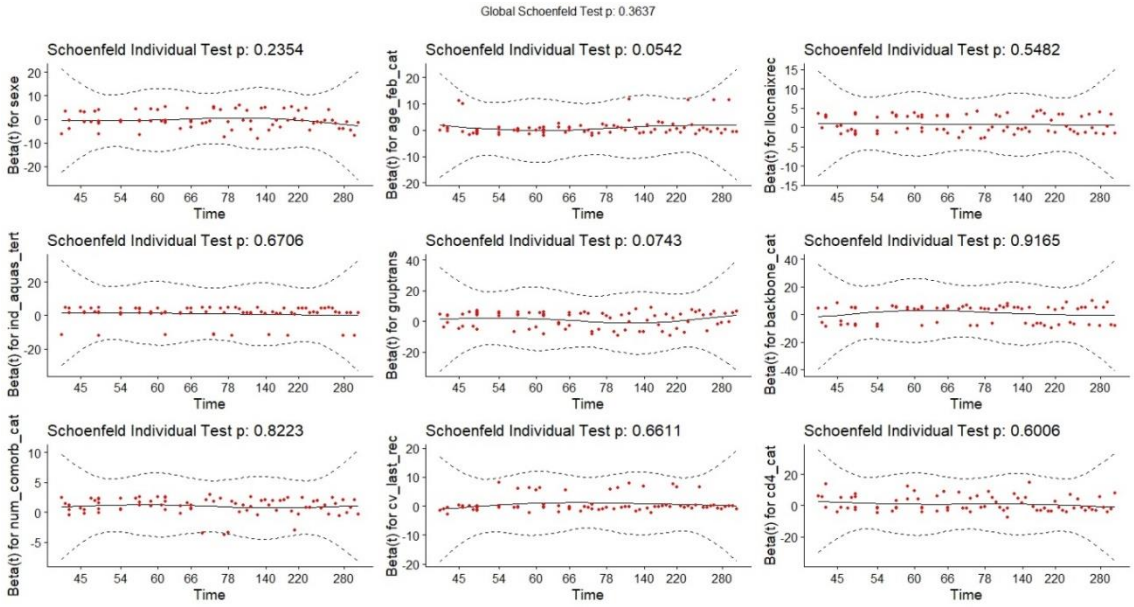
	Sex	Age	Country of origin	Socioeconomic deprivation	HIV transmission group	CD4 count	HIV-RNA viral load	Backbone ART	Number of comorbidities
Sex	1	-0,10213	-0,00079	-0,23352	0,38113	-0,06459	-0,05807	-0,03419	-0,17775
Age	-0,10213	1	-0,2998	0,07051	-0,21153	0,15245	-0,14452	0,04666	0,48579
Country of origin	-0,00079	-0,2998	1	-0,08877	0,07306	0,03005	0,1181	-0,01378	-0,29637
Socioeconomic deprivation	-0,23352	0,07051	-0,08877	1	-0,20578	0,06614	0,0115	0,05688	0,15014
HIV transmission group	0,38113	-0,21153	0,07306	-0,20578	1	-0,11807	-0,0168	-0,00329	-0,16369
CD4 count	-0,06459	0,15245	0,03005	0,06614	-0,11807	1	0,24882	0,0021	0,15265
HIV-RNA viral load	-0,05807	-0,14452	0,1181	0,0115	-0,0168	0,24882	1	-0,04419	-0,01422
Backbone_ART	-0,03419	0,04666	-0,01378	0,05688	-0,00329	0,0021	-0,04419	1	0,0641
Number of comorbidities	-0,17775	0,48579	-0,29637	0,15014	-0,16369	0,15265	-0,01422	0,0641	1

Figure 7. Shoenfeld analysis of Hazard proportionality for Cox models of a) SARS-CoV-2 diagnosis b) severe COVID-19 outcomes.

A)



B)



2.3.3. Article 3

We performed a retrospective study using data from the PISCIS. We divided the study population in three groups according to nucleos(t)ide reverse transcriptase inhibitor (NRTI) exposure: i) TAF/FTC; ii) TDF/FTC; and iii) abacavir/lamivudine (ABC/3TC).

Continuous variables are presented as median with interquartile ranges (IQR) and frequencies with percentages for categorical variables. Proportions for categorical variables were compared using the $\chi 2$ or Fisher's exact test where appropriate. Continuous variables were compared using the Kruskal Wallis test. We performed four rounds of propensity-score matching for TAF/FTC vs ABC/3TC and a single round for TDF/FTC vs ABC/3TC and TAF/FTC vs TDF/FTC using nearest neighbour algorithms with a calliper width of 0.1 of the pooled standard deviations to ensure that key baseline characteristics of the groups were adequately balanced. We matched patients by sex, age, plasma HIV-RNA (detectable and undetectable), and number of comorbidities (none, one, two, three, four or more).

We did three separate propensity score matching in a ratio 1:1 for TAF/FTC versus ABC/3TC, and 1:3 for TDF/FTC versus ABC/3TC, and TDF/FTC versus TAF/FTC. To evaluate the effect of ART regimens on SARS-CoV-2 diagnosis and severe outcomes, we used Cox regression models and provided adjusted (aHR) and unadjusted hazard ratios (uHR) along with their 95% confidence intervals (95% CI). In multivariable models performed to remove residual confounding bias,[220] we adjusted for the factors that were significantly different after propensity score matching. We adjusted for country of origin, socioeconomic status, CD4 count (continuous variable), time in years on ART, CD4/CD8 ratio, diabetes, chronic kidney disease, and metabolic disease.

In multivariable analysis, we removed time since HIV diagnosis due to collinearity with time in years on ART (Table 3). Missing values were reported in the corresponding tables; records with missing values for adjustment covariates were excluded in adjusted analyses, as they were few and not expected to affect estimates significantly. A 2-sided P value less than 0.05 was considered statistically significant.

Table 3. Evaluation of variance inflation factors (VIF) of all variables using the rms package in R (Article 3).

	SARS-CoV-2 diagnosis			**Hospitalisation**		
	TAF vs ABC	**TDF vs ABC**	**TDF vs TAF**	**TAF vs ABC**	**TDF vs ABC**	**TDF vs TAF**
Country of birth	1.025	1.031	1.031	1.022	1.039	1.035
Socioeconomic deprivaton	1.004	1.004	1.004	1.003	1.010	1.009
Hypertension	1.068	1.080	1.043	1.099	1.154	1.065
Chronic kidney disease	1.038	1.065	1.027	1.078	1.135	1.060
Metabolic disease	1.064	1.055	1.034	1.076	1.088	1.055
CD4 count	1.359	1.021	1.027	1.382	1.298	1.426
Duration on ART	1.109	1.122	1.079	1.108	1.166	1.088
CD4/CD8 ratio	1.354	1.014	1.017	1.367	1.286	1.408

Abbreviations: SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; ART, antiretroviral therapy; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ABC, abacavir; 3TC, lamivudine.

2.3.4. Article 4

We conducted a retrospective study leveraging the unique dataset of the PISCIS cohort linked with the PADRIS. We described the baseline characteristics of the vaccinated and unvaccinated groups using proportions. We presented descriptive statistics as median and interquartile ranges (IQR) for continuous variables and frequencies for categorical variables. Proportions for categorical variables were compared using the $\chi 2$ or Fisher's exact test where appropriate. Continuous variables were compared using the Mann-Whitney U test. We used univariable and multivariable logistic regression models to assess the factors associated with vaccination coverage. In the multivariable model, we adjusted for sex, age, country of origin, socioeconomic deprivation, HIV-exposure group, CD4 levels, plasma HIV RNA, number of chronic comorbidities, and previous SARS-CoV-2 diagnosis. We calculated odds ratios (OR) with 95% confidence intervals (CI) to assess the strength of association. We compared SARS-CoV-2 diagnosis among vaccinated and unvaccinated PLWH without a previous SARS-CoV-2 diagnosis. Among those with confirmed SARS-CoV-2 diagnosis, we compared associated hospital admissions, ICU admissions, and death between the two groups. Level of significance of *P* was set at <0.05.

2.4. Ethics statement

The PISCIS cohort study was approved by the Ethics Committee of the Germans Trias i Pujol University Hospital, Badalona, Spain (EO-11-108). All data collection was also approved by the ethics committees of participating hospitals. Patient-level information obtained from PADRIS were anonymized and deidentified before the analysis. All cohort studies in this thesis followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines [221]. The planning, conduct, and reporting of studies were in line with the Declaration of Helsinki, as revised in 2013 [222].

3. RESULTS

The main four articles that form part of this thesis dissertation are as follows:

- Article 1. Population-based assessment of SARS-CoV-2 infection among people living with HIV and the general population of Catalonia (March–December, 2020). Enfermedades Infecciosas y Microbiología Clínica. 2022 Mar 3.

- Article 2. Sociodemographic, clinical, and immunological factors associated with SARS-CoV-2 diagnosis and severe COVID-19 outcomes in people living with HIV: a retrospective cohort study. The Lancet HIV. 2021 Nov 1;8(11):e701-10

- Article 3. Impact of tenofovir on SARS-CoV-2 infection and severe outcomes among people living with HIV: a propensity score matched study. J Antimicrob Chemother. 2022 Jun 9:dkac177. doi: 10.1093/jac/dkac177.

- Article 4. SARS-CoV-2 vaccination coverage and factors associated with low uptake in a cohort of people living with HIV. Microorganisms. 2022 Aug 18;10(8):1666. doi: 10.3390/microorganisms10081666.

Article 1

Population-based assessment of SARS-CoV-2 infection among people living with HIV and the general population of Catalonia (March – December, 2020)

Article I

Population-based assessment of SARS-CoV-2 infection among people living with HIV and the general population of Catalonia (March – December, 2020)

Daniel K. Nomah[1,2,3], Yesika Díaz[1,3], Rosa M. Vivanco-Hidalgo[4], Jordi Casabona[1,2,3,5], Jose M. Miro[6*] and Juliana Reyes-Urueña[1,3,5*] and the COVID-19- PISCIS research group.

Enfermedades Infecciosas y Microbiología Clínica. 2022 Mar 3.

Summary

In this study, we compared SARS-CoV-2 testing, test positivity, hospitalization, ICU, and mortality rates between PLWH and the general HIV-negative population in Catalonia, Spain in the furst year of the pandemic in Spain (March – December, 2020).

At the early stages of the COVID-19 pandemic, it ws unclear if COVID-19 affected people living with HIV more than the general HIV-negative population as a definitive interaction between SARS-CoV-2 and HIV was yet to be established. Studies which had attempted to compare the incidence and severity of SARS-CoV-2 were mianly used hospitalized patients or did not report the testing patterns. Both scenarios however could leasd to biased reports and make it challenging to understand the impact of COVID-19 among PLWH. People living with HIV across Europe are ageing and hence have are more affected my comorbidities. These two factors have been proven to be associated with poor clinical outcomes from COVID-19 making it crucial to understand the impact of SARS-CoV-2 among PLWH. HIV-infected persons are expected to be tested more for SARS-CoV-2 due to their potential vulnerability but reports on this matter are contractridictory. Whilst, reports on vulnerability of this population to COOVID-19 outcomes has also been unequivocal with soime studies suggesting that immunosuppression and reception of antiretrovirals could be protective against sever COVID-19.

We therefore compared SARS-CoV-2 testing, test positivity, hospitalisation, intensive care unit (ICU) admission, and mortality between PLWH and the general HIV-negative population of Catalonia, Spain from March 1 to December 15, 2020. We used acute SARS-CoV-2 infections confirmed by real-time reverse transcription polymerase chain reaction (rRT-PCR) test or rapid antigen test (RAT).

PLWH in our population were predominantly male (81.7%) with a median age of 47.6 years. More than half of PLWH were MSM (52.9%) and 34.8% were of non-Spanish origin. Median CD4 count was 692.5 cells/mm3 and 81.9% had undetectable plasma HIV-RNA (≤50 copies/ml). Regarding treatment, 94.1% of PLWH were on ART with majority receiving tenofovir (57.4%). SARS-CoV-2 testing was lower among PLWH 3,556/13,142 (27.06%) compared to the general HIV-negative population 1,954,902/6,446,672 (30.32%) ($p<0.001$) but test positivity was higher among PLWH (21.06% vs. 15.82%, $p<0.001$). We observed no significant differences between PLWH and the general population in terms of hospitalisation (13.75% vs. 14.97% $p=0.174$) and ICU admission (0.93% vs. 1.66%, $p=0.059$). Among positive cases, we found a lower mortality rate among PLWH compared to the general population (1.74% vs 3.64%, $p=0.002$).

In conclusion, PLWH tested less frequently for SARS-CoV-2, had a higher test positivity, similar ICU admission and hospitalisation rates, and lower SARS-CoV-2-associated mortality compared to the general HIV-negative population.

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EIMC-2559; No. of Pages 4
ARTICLE IN PRESS

Enfermedades Infecciosas y Microbiología Clínica xxx (xxxx) xxx–xxx

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Brief report

Population-based assessment of SARS-CoV-2 infection among people living with HIV and the general population of Catalonia (March–December, 2020)

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ARTICLE INFO

Article history:
Received 1 December 2021
Accepted 15 February 2022
Available online xxx

Keywords:
SARS-CoV-2
COVID-19
HIV
AIDS
Epidemiological surveillance

ABSTRACT

Introduction: It is unclear if SARS-CoV-2 has affected people living with HIV (PLWH) more.
Methods: We compared SARS-CoV-2 testing, test positivity, hospitalisation, intensive care unit (ICU) admission, and mortality between PLWH and the general HIV-negative population of Catalonia, Spain from March 1 to December 15, 2020.
Results: SARS-CoV-2 testing was lower among PLWH 3556/13,142 (27.06%) compared to the general HIV-negative population 1,954,902/6,446,672 (30.32%) ($p < 0.001$) but test positivity was higher among PLWH (21.06% vs. 15.82%, $p < 0.001$). We observed no significant differences between PLWH and the general population in terms of hospitalisation (13.75% vs. 14.97%, $p = 0.174$) and ICU admission (0.93% vs. 1.66%, $p = 0.059$). Among positive cases, we found a lower mortality rate among PLWH compared to the general population (1.74% vs 3.64%, $p = 0.002$).
Conclusion: PLWH tested less frequently for SARS-CoV-2, had a higher test positivity, similar ICU admission and hospitalisation rates, and lower SARS-CoV-2-associated mortality compared to the general HIV-negative population.

Evaluación poblacional de la infección por SARS-CoV-2 entre personas que viven con el VIH y la población general de Cataluña (marzo-diciembre de 2020)

Palabras clave:
SARS-CoV-2
COVID-19
VIH
Sida
Vigilancia epidemiológica

RESUMEN

Introducción: No está claro si el SARS-CoV-2 ha afectado más a las personas que viven con VIH (PVV).
Métodos: Se compararon los test realizados de SARS-CoV-2, la positividad de la prueba, la hospitalización, los ingresos en la unidad de cuidados intensivos (UCI), las tasas de mortalidad entre PVV y la población general de Cataluña desde el 1 de marzo hasta el 15 de diciembre de 2020.
Resultados: Los test realizados de SARS-CoV-2 fueron menos entre PVV 3.556/13.142 (27.06%) comparado con la población general de Cataluña 1.954.902/6.446.672 (30,32%) ($p < 0,001$), pero la positividad de la prueba de SARS-CoV-2 fue mayor entre las PVV (21,06 vs. 15,82%; $p < 0,001$). No se observaron diferencias estadísticamente significativas entre PVV y la población general en cuanto a hospitalizaciones (13,75 vs. 14,97%; $p = 0,174$) e ingresos en la UCI (0,93 vs. 1,66%; $p = 0,059$). Entre los casos positivos, se encontró una menor tasa de mortalidad entre las PVV en comparación con la población general (1,74 vs. 3,64%; $p = 0,002$).

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https://doi.org/10.1016/j.eimc.2022.02.006

Please cite this article as: D.K. Nomah, Y. Díaz, R.M. Vivanco-Hidalgo et al., Population-based assessment of SARS-CoV-2 infection among people living with HIV and the general population of Catalonia (March–December, 2020), Enferm Infecc Microbiol Clin., https://doi.org/10.1016/j.eimc.2022.02.006

Conclusiones: Las PVV fueron testadas menos frecuentemente por SARS-CoV-2 que la población general, tuvieron una tasa de positividad más elevada, tasas similares de hospitalización e ingresos en la UCI, y menos mortalidad asociada al SARS-CoV-2.

Introduction

It is unclear if the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected people living with HIV (PLWH) more.[1] Current data on testing and incidence of SARS-CoV-2 in this population is conflicting.[2,3] Intuitively, PLWH should have more opportunities to test for SARS-CoV-2 because this population is considered a high-risk group. However, PLWH had limited access to healthcare and were not routinely tested for SARS-CoV-2 during the current pandemic.[4] Testing in Spain was based on the presence of signs and symptoms of coronavirus disease 2019 (COVID-19), chronic comorbidities, older age, and contact tracing.[4]

Initial studies demonstrated no vivid evidence of poorer disease course among PLWH infected with SARS-CoV-2 compared to HIV-negative individuals.[5] As more data become available, large studies have reported poorer outcomes for HIV/SARS-CoV-2 co-infected persons.[5] Older age and the presence of underlying chronic conditions like hypertension, diabetes, cardiovascular disease, obesity, and chronic respiratory diseases have been linked with severe COVID-19 outcomes.[1] With PLWH in Europe aging and disproportionately affected by comorbidities,[6] they could experience poorer prognosis than HIV-negative individuals. The potential enhanced susceptibility of PLWH to SARS-CoV-2 and severe outcomes from the co-infection has become a matter of concern.[7]

We compared SARS-CoV-2 testing, test positivity, hospitalisation, intensive care unit (ICU) admission, and mortality between PLWH and the general HIV-negative population of Catalonia, Spain.

Methods

We conducted a cross-sectional study leveraging data from the PISCIS cohort of PLWH in Catalonia (Spain). PISCIS is a prospective, multicentre, observational, population-based cohort that monitors hospital utilisation, reception of antiretroviral therapy (ART), and clinical status of approximately 80% of all PLWH aged ≥ 16 years in Catalonia since January 1, 1998. PISCIS data was linked with data from public health care system and disease surveillance registries through the Public Data Analysis for Health Research and Innovation Project of Catalonia (PADRIS)[8] to obtain data on SARS-CoV-2 testing and associated outcomes. This work was conducted according to the Declaration of Helsinki as revised in 2013. The PISCIS cohort study has been approved by the Institutional Review Board of Germans Trias i Pujol Hospital, Badalona, Spain (EO-11-108). Patient information obtained from PADRIS was anonymized and deidentified before the analysis.

Aggregated data on the SARS-COV-2 testing, test positivity, related hospitalisation, ICU admission, and death for the general HIV-negative population within the same study period for individuals aged ≥ 16 years was obtained from COVID-19 epidemiological monitoring registry via the Agency for Health and Quality Assessment of Catalonia (AQuAS).

The study period was from March 1, 2020 to December 15, 2020. We used acute SARS-CoV-2 infections confirmed by real-time reverse transcription polymerase chain reaction (rRT-PCR) test or rapid antigen test (RAT). We excluded PLWH from the general population before the analysis.

We calculated SARS-CoV-2 test positivity per the proportion of the population that tested for SARS-CoV-2. Among SARS-CoV-2 positive cases, we determined the rates per 100 persons of hospitalisation, ICU admission, and mortality.

We used the *Z*-test to compare testing, test positivity, hospitalisation, ICU admission, and mortality between the two populations. We presented our findings using the onion plots concept.

Results

PLWH in our population were predominantly male (81.7%) with a median age of 47.6 years. More than half of PLWH were men who have sex with men (MSM) (52.9%) and 34.8% were of non-Spanish origin. Median CD4 count was 692.5 cells/mm^3 and 81.9% had undetectable plasma HIV-RNA (≤50 copies/ml). Regarding treatment, 94.1% of PLWH were on ART with majority receiving tenofovir (57.4%). PLWH had been diagnosed with HIV for a median duration of 12.0 years and 34.2% were without chronic comorbidities (Table 1).

SARS-CoV-2 testing was lower among PLWH 3556/13,142 (27.06%) compared to the general HIV-negative population 1,954,902/6,446,672 (30.32%) ($p < 0.001$). SARS-CoV-2 test positivity was however higher among PLWH 749/3556 (21.06%, 95% confidence interval [95% CI]: 19.72–22.40) compared to the general population 309,359/1,954,902 (15.82%, 95% CI: 15.76–15.87) ($p < 0.001$). We observed no significant differences between PLWH and the general population in terms of hospitalisation [103/749 (13.75%, 95% CI: 11.29–16.22) vs 46,318/309,359 (14.97%, 95% CI: 14.85–15.10) ($p = 0.174$)] and ICU admission [7/749 (0.93%, 95% CI: 0.25–1.62) vs 5140/309,359 (1.66%, 95% CI: 1.62–1.71 $p = 0.059$)]. Among positive cases, we found a lower mortality rate among PLWH 13/749 (1.74%, 95% CI: 0.80–2.67) compared to the general population 11,272/3,093,599 (3.64%, 95% CI: 3.58–3.71) ($p = 0.002$) (Fig. 1).

Discussion

In our population-based assessment, SARS-CoV-2 testing was lower among PLWH with higher test positivity compared to the general HIV-negative population. In terms of hospitalisation and ICU admission, no significant differences were observed between the two groups. Mortality was lower among PLWH compared to the general population.

A large study from the USA reported higher testing rates among PLWH compared to HIV-negative individuals.[3] The findings of our population-based assessment found otherwise. HIV-positive persons were not prioritised for SARS-CoV-2 testing in Spain.[4] During the early days of the pandemic, testing was based on presenting signs and symptoms, comorbidities, age, and contact tracing.[4] The fact that PLWH are not prioritized for SARS-CoV-2 testing could mask the real picture of the pandemic in this population. Testing is imperative because it helps to timely identify positive cases including asymptomatic and mildly symptomatic persons and isolate to control spread or initiate early treatment to avoid severe clinical outcomes.

Contrary to other studies that have reported a similar or lower[9,10] SARS-CoV-2 incidence among PLWH, our assessment

Table 1
Characteristics of HIV-positive individuals with and without SARS-CoV-2 diagnosis in Catalonia, Spain.

Characteristic	People living with HIV (PLWH) No. (%)			*p* value
	All (*n* = 13,142)	SARS-CoV-2 negative (*n* = 12,393)	SARS-CoV-2 positive (*n* = 749)	
Sex				
Male	10,739 (81.7)	10,121 (81.7)	618 (82.5)	0.59
Female	2402 (18.3)	2271 (18.3)	131 (17.5)	
Missing	1 (0.01)	1 (0.01)	0 (0)	
Age, median (IQR), y	47.6 (39.6–54.9)	47.8 (39.8–55.0)	43.5 (37.0–52.7)	<0.001
Country of origin				<0.001
Spain	8564 (65.2)	8162 (65.9)	402 (53.7)	
Outside Spain	4576 (34.8)	4229 (34.1)	347 (46.3)	
Unknown	2 (0.02)	2 (0.02)	0 (0)	
HIV transmission route				<0.001
PWID	1876 (14.3)	1817 (14.7)	59 (7.9)	
MSM	6870 (52.3)	6425 (51.8)	445 (59.4)	
Male heterosexual	1768 (13.5)	1680 (13.6)	88 (11.8)	
Female hetero/homo/bisexual	1714 (13.0)	1609 (13.0)	105 (14.0)	
Other	787 (6.0)	741 (6.0)	46 (6.1)	
Missing	127 (1.0)	121 (1.0)	6 (0.8)	
Years since HIV diagnosis, median (IQR)	12.0 (7.0–18.7)	12.1 (7.1–18.9)	10.3 (6.1–15.7)	<0.001
Recent CD4 count (cells/mm^3), median (IQR)	692.5 (500.0–917.0)	692.0 (500.0–917.0)	695.5 (483.5–912.3)	0.65
CD4/CD8 ratio, median (IQR)	0.9 (0.6–1.2)	0.9 (0.6–1.2)	0.9 (0.6–1.2)	0.26
HIV-RNA(recent)[a]				0.19
Detectable	1068 (8.1)	1017 (8.2)	51 (6.8)	
Undetectable	10,758 (81.8)	10,136 (81.8)	622 (83.0)	
Missing	1316 (10.0)	1240 (10.0)	76 (10.2)	
Chronic comorbidities				
Number of chronic comorbidities				0.83
0	4489 (34.2)	4231 (34.1)	258 (34.5)	
1	3434 (26.1)	3247 (26.2)	187 (25.0)	
2	2244 (17.1)	2106 (17.0)	138 (18.4)	
3	1325 (10.1)	1253 (10.1)	72 (9.6)	
≥ 4	1650 (12.6)	1556 (12.6)	94 (12.6)	
Years on ART, median (IQR)	9.4 (5.1–15.0)	9.5 (5.1–15.2)	7.8 (4.6–12.9)	<0.001
Backbone ART				0.79
TAF	6606 (50.2)	6215 (50.2)	391 (52.2)	
TDF	939 (7.2)	891 (7.2)	48 (6.4)	
ABC + 3TC	3820 (29.1)	3594 (29.0)	226 (30.2)	
Other	670 (5.1)	630 (5.1)	40 (5.3)	
Missing	1107 (8.4)	1063 (8.6)	44 (5.9)	

Abbreviations: SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; IQR, interquartile range; PWID, people who inject drugs; MSM, men who have sex with men; ART, antiretroviral therapy; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ABC, abacavir; 3TC, lamivudine.

[a] Undetectable HIV/RNA plasma viral load was defined as values ≤50 copies/ml.

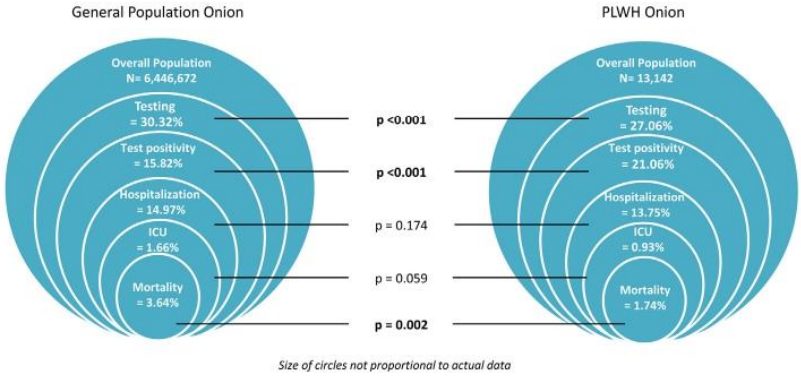

Fig. 1. Diagram comparing testing, test positivity, and clinical outcomes of Coronavirus disease 2019 (COVID-19) between PLWH and in the general population of Catalonia (Spain) from March 1, 2020 to December 15, 2020. *Abbreviations*: PLWH: People living with HIV. ICU: intensive care unit. Rates are provided per 100 persons. Testing is the percentage (%) of the overall population. Hospitalisation, ICU, and mortality are given per 100 persons per number of SARS-CoV-2 infected persons. Z-test was used to compare testing, test positivity, hospitalisation, ICU admission, and mortality between the two populations.

found a higher test positivity in this group. The previously reported lower incidence was attributed to sheltering of PLWH due to perceived vulnerability.[11] Besides sheltering, some studies have suggested that the low SARS-CoV-2 infection rates in this population is due to the potential protection from ART.[12] The therapeutic effects of these anti-HIV agents against SARS-CoV-2 is however inconclusive.[12] PLWH are disproportionately affected by social determinants including low socioeconomic levels and non-Spanish origin which have been associated with increased SARS-CoV-2 diagnosis in Spain and could partly explain higher test positivity among PLWH.[13,14]

We found similar rates of COVID-19-associated hospitalisation and ICU admission with lower mortality among PLWH. Earlier studies reported no increased risks of severe outcomes from SARS-CoV-2 infection among PLWH compared to HIV-negative individuals.[5] However, subsequent relatively larger studies showed higher risk of death among PLWH infected with COVID-19.[5] The variation in the impact of HIV on COVID-19 outcomes could be explained by the differences in severe COVID-19 risk factors present in the study populations. The fact that PLWH are disproportionately affected by other heath determinants for worse COVID-19 outcomes makes it uncertain to access the excess risk of HIV on COVID-19.

Our analysis is limited by our inability to adjust for potential confounders including age and chronic comorbidities due to its ecological design as these factors could evidently impact COVID-19 outcomes. A matched analysis adjusted for these factors will be vital to understand the observed differences. Secondly, our analysis involves only individuals engaged in the public health system of Catalonia. Individuals who tested for SARS-CoV-2 in private health facilities, pharmacies, and outside Catalonia would not be captured in the PADRIS records. However, we do not expect this to qualitatively affect the results of our study as the first phases of the pandemic was handled by the public healthcare system with restricted movements to other regions and countries. Finally, we could be underestimating the SARS-CoV-2 diagnosis rates because we only included laboratory confirmed (rRT-PCR or RAT) acute infections in the analysis and moreover, only symptomatic individuals were offered testing at the beginning of the pandemic in Spain.

In summary, PLWH tested less frequently for SARS-CoV-2 infection than the general population, had a higher positivity rate, and similar rates of hospitalisation and ICU admission. Overall, SARS-CoV-2-associated mortality was lower among PLWH. Public health strategies should be employed to increase SARS-CoV-2 testing coverage among PLWH and further studies will be needed to understand the susceptibility of this population to SARS-CoV-2.

Funding

This work was supported by the Fundació “la Caixa” [grant name: COVIHCAT]. The funder had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Conflicts of interest

J.M.M. reported receiving a personal 80:20 research grant from Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, during 2017–21. For the remaining authors none was declared.

Acknowledgements

We thank the Public Data Analysis for Health Research and Innovation Program of Catalonia (PADRIS) and all healthcare workers from the PISCIS cohort collaborating hospitals for their support.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.eimc.2022.02.006.

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Article 2

Sociodemographic, clinical, and immunological factors associated with SARS-CoV-2 diagnosis and severe COVID-19 outcomes in people living with HIV: a retrospective cohort study

Article II

Sociodemographic, clinical, and immunological factors associated with SARS-CoV-2 diagnosis and severe COVID-19 outcomes in people living with HIV: a retrospective cohort study

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The Lancet HIV. 2021 Nov 1;8(11):e701-10

Summary

COVID-19 continues to cause enourmous morbidity and mortality globally. The pandemic has overwhelmed healthcare systems in both low and high-income countries and has stretched available health resources. During the early stages of the pandemic, it was unclear if PLWH were at an increased risk of associated morbidity and mortality. This was a major concern because of the impaired immune status of PLWH. Some studies suggested the contrary. Earlier studies suggested that detectable HIV viremia and low CD4 cell count in PLWH could reduce COVID-19-associated immune dysregulation and diminish the development of a cytokine storm hence, minimizing disease severity. Characterisation of PLWH therefore imperative to prioritise vaccination strategy and clinical management for sub-populations at increased risk of severe COVID-19 clinical outcomes. The existing evidence before this study was sparse and inconsistent and could not inform definite public health interventions. The study, therefore, aimed to characterize COVID-19 among people living with HIV, identify the factors associated with a SARS-CoV-2 diagnosis and severe clinical outcomes, and understand the impact of advanced or uncontrolled HIV on the co-infection.

We leveraged the PISCIS cohort linked with the PADRIS to conduct a retrospective cohort study between March 1 to December 15, 2020. We employed Cox proportional hazard regression models to identify the factors associated with SARS-CoV-2 diagnosis and severe COVID-19 outcomes. To understand the impact of immunosuppression and detectable viremia on severe outcomes, we used survival analysis techniques.

During the study period, 749/13,142 (5·7%) PLWH were diagnosed with SARS-CoV-2. One-hundred and three (13·8%) were hospitalized, 7 (0·9%) were admitted to the ICU and 13 (1·7%) died. Among co-infected patients, 618 (82·5%) were male and their median age (IQR) was 43·5 (37·0-52·7) years. Five hundred and twenty-nine (70·9%) co-infected patients had CD4 count ≥500 cells per μL and 622 (83·0%) had HIV viral suppression. Non-Spanish origin (aHR 1·55 [95% CI 1·31-1·83]), being MSM (aHR 1·42 [95% CI 1·09-1·86]), and having ≥4 chronic comorbidities (aHR 1·46 [95% CI 1·09-1·97]) were associated with an increased risk of SARS-CoV-2 diagnosis. Being a PWID (aHR 0·66 [95% CI 0·44-0·98]) and aged 40-64 years (aHR 0·70 [95% CI 0·58-0·85]) were negatively associated with SARS-CoV-2 diagnosis in adjusted analysis. Age at least 75 years (5·2, 1·8–15·3), non-Spanish origin (2·1, 1·3–3·4), and neuropsychiatric (1·69, 1·07–2·69), autoimmune disease (1·92, 1·14–3·23), respiratory disease (1·84, 1·09–3·09), and metabolic disease (2·59, 1·59–4·23) chronic comorbidities were associated with increased risk of severe outcomes.

Kaplan-Meier survival analysis revealed that, compared with higher CD4 cell counts, CD4 <200 cells per μL was significantly associated with severe COVID-19 outcomes during the study period (P = 0·001). A detectable HIV-RNA was also associated with severe COVID-19 outcomes (P =0·029). We then performed Kaplan-Meier survival analysis stratifying patients into detectable and undetectable HIV-

RNA. We found differences in the risk of severe outcomes according to CD4 levels in patients with detectable HIV-RNA (P=0·039) but no differences were observed in patients with undetectable HIV-RNA (P=0·15).

In this cohort study of PLWH in care in Catalonia, Spain, SARS-CoV-2 diagnosis was more common among migrants, those with ≥4 chronic comorbidities and MSM. Among PLWH with COVID-19, those with CD4 count <200 cells per μL, detectable plasma HIV viral load, older age, non-Spanish origin, and neuropsychiatric, autoimmune, respiratory, and metabolic disease had a higher risk of severe outcomes. Notably, CD4 count <200 cells per μL was not associated with severe outcomes among patients with HIV virologic suppression. Our findings suggest that PLWH with detectable HIV viraemia, chronic comorbidities and subpopulations like the aged and migrants could be more susceptible to severe outcomes from COVID-19 and should be prioritized in clinical management and considered a target group for SARS-CoV-2 vaccination programs.

Sociodemographic, clinical, and immunological factors associated with SARS-CoV-2 diagnosis and severe COVID-19 outcomes in people living with HIV: a retrospective cohort study

Daniel K Nomah, Juliana Reyes-Urueña*, Yesika Díaz, Sergio Moreno, Jordi Aceiton, Andreu Bruguera, Rosa M Vivanco-Hidalgo, Josep M Llibre, Pere Domingo, Vicenç Falcó, Arkaitz Imaz, Cristina Cortés, Lluís Force, Emili Letang, Ingrid Vilaró, Jordi Casabona, Jose M Miro, and the PISCIS study group*

Summary

Background Factors affecting outcomes of SARS-CoV-2 infection in people living with HIV are unclear. We assessed the factors associated with SARS-CoV-2 diagnosis and severe outcomes among people living with HIV.

Methods We did a retrospective cohort study using data from the PISCIS cohort of people with HIV in Catalonia (Spain) between March 1 and Dec 15, 2020. We linked PISCIS data with integrated health-care, clinical, and surveillance registries through the Public Data Analysis for Health Research and Innovation Program of Catalonia (PADRIS) to obtain data on SARS-CoV-2 diagnosis, chronic comorbidities, as well as clinical and mortality outcomes. Participants were aged at least 16 years in care at 16 hospitals in Catalonia. Factors associated with SARS-CoV-2 diagnoses and severe outcomes were assessed using univariable and multivariable Cox regression models. We estimated the effect of immunosuppression on severe outcomes (hospital admission for >24 h with dyspnoea, tachypnoea, hypoxaemia, asphyxia, or hyperventilation; or death) using Kaplan-Meier survival analysis.

Findings We linked 20 847 (72·8%) of 28 666 participants in the PISCIS cohort with PADRIS data; 13 142 people had HIV. 749 (5·7%) people with HIV were diagnosed with SARS-CoV-2: their median age was 43·5 years (IQR 37·0–52·7), 131 (17·5%) were female, and 618 (82·5%) were male. 103 people with HIV (13·8%) were hospitalised, seven (0·9%) admitted to intensive care, and 13 (1·7%) died. SARS-CoV-2 diagnosis was more common among migrants (adjusted hazard ratio 1·55, 95% CI 1·31–1·83), men who have sex with men (1·42, 1·09–1·86), and those with four or more chronic comorbidities (1·46, 1·09–1·97). Age at least 75 years (5·2, 1·8–15·3), non-Spanish origin (2·1, 1·3–3·4), and neuropsychiatric (1·69, 1·07–2·69), autoimmune disease (1·92, 1·14–3·23), respiratory disease (1·84, 1·09–3·09), and metabolic disease (2·59, 1·59–4·23) chronic comorbidities were associated with increased risk of severe outcomes. A Kaplan-Meier estimator showed differences in the risk of severe outcomes according to CD4 cell count in patients with detectable HIV RNA (p=0·039) but no differences were observed in patients with undetectable HIV RNA (p=0·15).

Interpretation People living with HIV with detectable HIV viraemia, chronic comorbidities, and some subpopulations could be at increased risk of severe outcomes from COVID-19. These groups should be prioritised in clinical management and SARS-CoV-2 vaccination programmes.

Funding Fundació "la Caixa".

Lancet HIV 2021; 8: e701–10

Published Online October 13, 2021 https://doi.org/10.1016/S2352-3018(21)00240-X

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For the Catalan translation of the Summary see Online for appendix 1

For the Spanish translation of the Summary see Online for appendix 2

For the Russian translation of the Summary see Online for appendix 3

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Introduction

At the beginning of the COVID-19 pandemic, people living with HIV, particularly those with low CD4 cell count, detectable HIV RNA viral load, chronic comorbidities, and not receiving antiretroviral therapy (ART), were speculated to be at an increased risk of severe disease from the co-infection.[1–3] The first published case series and cohort studies on the incidence of COVID-19 or adverse outcomes among people with HIV, however, showed contradictory results and remains a matter of debate.[4] In fact, reports suggested that high HIV viraemia and low CD4 cell count might restrict COVID-19-associated immune dysregulation and diminish the development of a cytokine storm, hence, minimising disease severity.[5] The potential protection from some anti-HIV agents has also been postulated by different studies.[6] The therapeutic effects of these medications against COVID-19 are, however, inconclusive.[6]

Nevertheless, a report from the WHO Global Clinical Platform for COVID-19 involving 37 countries indicated that HIV is an independent risk factor for severe or critical presentation at hospital admission and in-hospital mortality.[7] This finding is similar to those from the UK[8] and South Africa,[9] reporting increased mortality risk for patients co-infected with HIV and SARS-CoV-2.

The potential effect of immunosuppression and unsuppressed HIV RNA on severe COVID-19 outcomes

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Research in context

Evidence before this study

We searched PubMed, Embase, MEDLINE, medRxiv, and Google Scholar using the search terms "SARS-CoV-2" or "COVID-19" or "coronavirus disease 2019" and "HIV" or "AIDS" or "human immunodeficiency virus" from Jan 1 to Oct 30, 2020, without language restrictions. The published data was inconclusive regarding an increased risk of people living with HIV to SARS-CoV-2 infection. The largest cohort study of SARS-CoV-2 infection among people with HIV in Europe (77 590 people with HIV) found a higher incidence than in the general population (3·7 per 10 000 *vs* 2·1 per 10 000). Factors associated with SARS-CoV-2 diagnoses have not, however, been assessed in large cohort studies of people with HIV. Three large studies subsequently suggested an increased incidence of severe COVID-19 outcomes for people with HIV. There were, however, common limitations, such as an inadequate adjustment for potentially confounding variables including socioeconomic factors, comorbidities, and immunological markers (CD4 cell count and plasma HIV RNA viral load). Whether immunosuppression and unsuppressed HIV viraemia are associated with severe COVID-19 outcomes is unknown. In a large study from South Africa, lower CD4 cell count was associated with higher mortality, but CD4 cell count was only measured during the presence of SARSCoV-2 co-infection and could be misleading.

Added value of the study

In this observational cohort study, we investigated SARS-CoV-2 diagnosis and severe outcomes in a cohort of people with HIV. To the best of our knowledge, this study of 749 people with HIV with SARS-CoV-2 co-infection is the largest in Europe. 103 (13·8%) co-infected patients were hospitalised and 13 (1·7%) died. All SARS-CoV-2 diagnoses were laboratory confirmed. SARS-Cov-2 diagnoses were increased among migrants, men who have sex with men (MSM), and those with four or more comorbidities. Being aged 75 years or older, of non-Spanish origin, with chronic comorbidities, and detectable HIV viraemia were associated with severe COVID-19.

Implications of all the available evidence

Our findings are incongruous with those of previous studies, which observed reduced SARS-CoV-2 diagnosis rates among people with HIV. Factors such as non-Spanish origin, multimorbidity, and MSM were associated with SARS-CoV-2 diagnosis, and studies are needed to further explore this association. Our results also show that subpopulations (eg, migrants, people aged 75 years or older, and people with HIV with chronic comorbidities and unsuppressed HIV RNA viral load) could be at increased risk of severe COVID-19 outcomes and should be prioritised in terms of clinical management and SARS-CoV-2 vaccination programmes.

has become a matter of concern.[10] A pooled analysis of a combined group of 175 patients with both HIV and SARS-CoV-2 from Germany, Italy, and Spain identified an association between low CD4 count (<350 cells per µL) and severe COVID-19 (adjusted odds ratio 2·85, 95% CI 1·26–6·44; p=0·01).[11] In this study, a lower nadir CD4 cell count was associated with increased mortality risk.[11] The study from South Africa reported a similar increased risk of mortality for co-infected patients with CD4 counts less than 200 cells per µL.[9] This study did not, however, capture data on socioeconomic status and obesity, both of which can be associated with increased mortality. Little is known about the effect of detectable HIV viral load on patients with severe COVID-19. An analysis by Tesoriero and colleagues in New York (NY, USA) showed that co-infected patients with detectable HIV viraemia were 30% more likely to be hospitalised, compared with those not living with an HIV diagnosis.[12]

Moreover, COVID-19 might cause more adverse outcomes among people with HIV because of the increasing prevalence of comorbidities such as diabetes, chronic obstructive pulmonary disease, and chronic kidney disease in this population.[13] The high presence of overlapping social determinants of health such as low socioeconomic status, sex, gender, racial and minority ethnic groups, and mental health burden might also contribute to more severe outcomes of COVID-19 among people with HIV.[14]

The existing controversy on the effect of SARS-CoV-2 on people with HIV is partly a result of study limitations, including inadequate sample sizes and an absence of data on key variables that potentially confound results (eg, socioeconomic factors, CD4 cell count, plasma HIV RNA concentrations, ART, and chronic comorbidities). Large population-based studies are imperative to assess whether people with HIV or subpopulations thereof are at increased risk of SARS-CoV-2 infection and severe COVID-19 disease after adjusting for potential confounders. Additional studies are also crucially needed to investigate whether immunosuppression and detectable HIV RNA are associated with severe COVID-19. To date, data available are inconclusive on these matters.[10]

In this study, we aimed to describe the sociodemographic and clinical characteristics associated with SARS-CoV-2 diagnosis and COVID-19 outcomes among people living with HIV in Catalonia (Spain), and assess the risk factors for severe disease prognosis in a multicentre population-based cohort of people with HIV (Populational HIV Cohort from Catalonia and Balearic Islands [PISCIS]).

Methods

Study design and population

We did an observational retrospective cohort study using the PISCIS cohort of people with HIV in Catalonia, Spain, between March 1 and Dec 15, 2020. The design of the PISCIS cohort has been described elsewhere.[15]

Briefly, PISCIS is a population-based cohort of people with HIV aged at least 16 years in care at 16 hospitals in Catalonia. The cohort has collected sociodemographic and clinical data since Jan 1, 1998.

We linked PISCIS data with integrated health-care, clinical, and surveillance registries through the Public Data Analysis for Health Research and Innovation Program of Catalonia (PADRIS) to obtain data on SARS-CoV-2 diagnosis, chronic comorbidities, as well as clinical and mortality outcomes (appendix 4 p 1). PADRIS encompasses patient-level information on overall public health-care usage including primary, emergency, outpatient, and inpatient care, laboratory and diagnostic tests, pharmacy, and disease surveillance registries.[16] We excluded patients who were recorded dead before Feb 1, 2020.

The study was done in accordance with the Declaration of Helsinki and adhered to existing legislation on data protection. The PISCIS cohort study has been approved by the Institutional Review Board of Germans Trias i Pujol Hospital, Badalona, Spain. All participating patients have signed informed consent forms. Patient information obtained from PADRIS was anonymised and de-identified before analysis.

Procedures

SARS-CoV-2 diagnoses, hospital admissions, and mortality were assessed among people with HIV in the PISCIS-PADRIS cohort. SARS-CoV-2 diagnosis was defined by a nucleic acid amplification test or antigen detection from respiratory samples, or antibodies detection according to the Spanish Ministry of Health guidelines.[17]

Severe COVID-19 outcome was defined as hospitalisation (admission for >24 h with any of the following signs: dyspnoea, tachypnoea, hypoxaemia, asphyxia, or hyperventilation), admission to an intensive care unit (ICU), or death.

See Online for appendix 4

We extracted the most recent data on sociodemographic characteristics (age, sex, country of origin, and socioeconomic status), HIV-associated variables, chronic comorbidities, SARS-CoV-2 diagnosis, hospitalisation, and mortality. The HIV-associated variables analysed were years since diagnosis; transmission group (people who inject drugs [PWID]; men who have sex with men [MSM]; male heterosexual; female homosexual, heterosexual, or bisexual); years on ART; current ART; most recent CD4 count (<200 cells per µL, 200–499 cells per µL, or ≥500 cells per µL), and HIV RNA viral load (detectable and undetectable). Undetectable plasma viral load was defined as HIV RNA of 50 copies per mL or lower. Immunosuppression was defined as CD4 count of less than 200 cells per µL.

We used the International Classification of Diseases (ICD), ninth and tenth revisions, to extract chronic comorbidities. The ICD classification system was modified

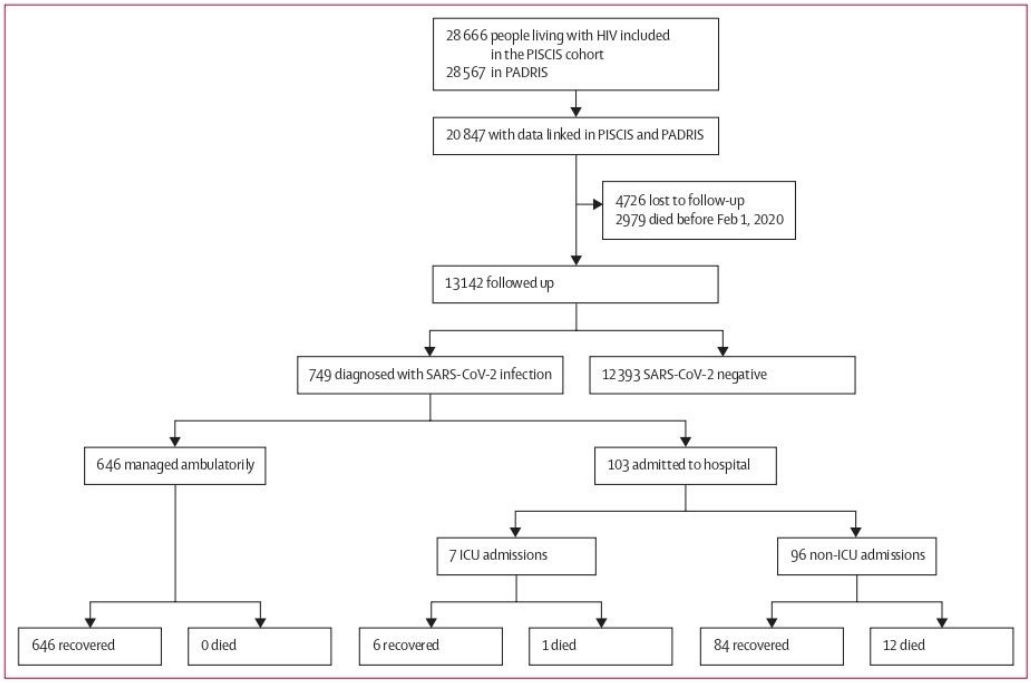

Figure 1: **Patient flow diagram**
ICU=intensive care unit. PADRIS=Public Data Analysis for Health Research and Innovation Program of Catalonia.

	People living with HIV (n=13 142)	SARS-CoV-2 negative (n=12393)	SARS-CoV-2 positive (n=749)	Hospital admission (n=103)	Death (n=13)
Sex*					
Male	10 739 (81·7%)	10 121 (81·7%)	618 (82·5%)	81 (78·6%)	10 (76·9%)
Female	2402 (18·3%)	2271 (18·2%)	131 (17·5%)	22 (21·4%)	3 (23·1%)
Unknown	1 (<1%)	1 (<1%)	0	0	0
Age, years†					
Median (IQR)	47·6 (39·6–54·9)	47·8 (39·8–55·0)	43·5 (37·0–52·7)	52·3 (43·4–59·8)	60·2 (53·6–67·5)
16–39	3442 (26·2%)	3181 (25·7%)	261 (34·9%)	16 (15·5%)	1 (7·7%)
40–64	8870 (67·5%)	8426 (68·0%)	444 (59·3%)	71 (68·9%)	7 (53·9%)
65–74	643 (4·9%)	610 (4·9%)	33 (4·4%)	10 (9·7%)	3 (23·1%)
≥75	187 (1·4%)	176 (1·4%)	11 (1·5%)	6 (5·8%)	2 (15·4%)
Place of birth‡					
Spain	8564 (65·2%)	8162 (65·9%)	402 (53·7%)	59 (57·3%)	11 (84·6%)
Outside Spain	4576 (34·8%)	4229 (34·1%)	347 (46·3%)	44 (42·7%)	2 (15·4%)
Unknown	2 (<0·1%)	2 (<0·1%)	0	0	0
Socioeconomic status					
Least deprived	6377 (48·5%)	6004 (48·5%)	373 (49·8%)	54 (52·4%)	5 (38·5%)
Mildly deprived	2523 (19·2%)	2409 (19·4%)	114 (15·2%)	12 (11·7%)	3 (23·1%)
Most deprived	3941 (30·0%)	3696 (29·8%)	245 (32·7%)	34 (33·0%)	5 (38·5%)
Missing	301 (2·3%)	284 (2·3%)	17 (2·3%)	3 (2·9%)	0
HIV transmission route					
PWID	1876 (14·3%)	1817 (14·7%)	59 (7·9%)	19 (18·5%)	2 (15·4%)
MSM	6870 (52·3%)	6425 (51·8%)	445 (59·4%)	48 (46·6%)	4 (30·8%)
Male heterosexual	1768 (13·5%)	1680 (13·6%)	88 (11·8%)	14 (13·6%)	4 (30·8%)
Female heterosexual, homosexual, or bisexual	1714 (13·0%)	1609 (13·0%)	105 (14·0%)	15 (14·6%)	2 (15·4%)
Other	787 (6·0%)	741 (6·0%)	46 (6·1%)	7 (6·8%)	1 (7·7%)
Missing	127 (1·0%)	121 (1·0%)	6 (0·8%)	0	0
Years since HIV diagnosis	12·0 (7·0–18·7)	12·1 (7·1–18·9)	10·3 (6·1–15·7)	14·4 (9·4–20·7)	17·4 (12·7–21·7)
CD4 count (cells per μL)					
<200	413 (3·1%)	388 (3·1%)	25 (3·3%)	8 (7·8%)	2 (15·4%)
200–499	2716 (20·7%)	2552 (20·6%)	164 (21·9%)	30 (29·1%)	6 (46·2%)
≥500	9451 (71·9%)	8922 (72·0%)	529 (70·6%)	60 (58·3%)	5 (38·5%)
Missing	562 (4·3%)	531 (4·3%)	31 (4·1%)	5 (4·9%)	0
Median (IQR)	692·5 (500·0–917·0)	692·0 (500·0–917·0)	695·5 (483·5–912·3)	611·0 (387·5–865·8)	469·0 (250·0–587·0)
CD4/CD8 ratio	0·9 (0·6–1·2)	0·9 (0·6–1·2)	0·9 (0·6–1·2)	0·8 (0·6–1·1)	0·7 (0·5–1·0)
Plasma HIV RNA viral load					
Detectable	1068 (8·1%)	1017 (8·2%)	51 (6·8%)	14 (13·6%)	1 (7·7%)
Undetectable	10758 (81·9%)	10136 (81·8%)	622 (83·0%)	76 (73·8%)	10 (76·9%)
Missing	1316 (10·0%)	1240 (10·0%)	76 (10·2%)	13 (12·6%)	2 (15·4%)
Number of chronic comorbidities					
0	4489 (34·2%)	4231 (34·1%)	258 (34·5%)	5 (4·9%)	0
1	3434 (26·2%)	3247 (26·2%)	187 (25·0%)	21 (20·4%)	2 (15·4%)
2	2244 (17·1%)	2106 (17·0%)	138 (18·4%)	19 (18·5%)	1 (7·7%)
3	1325 (10·1%)	1253 (10·1%)	72 (9·6%)	22 (21·4%)	3 (23·1%)
≥4	1650 (12·6%)	1556 (12·6%)	94 (12·6%)	36 (35·0%)	7 (53·9%)

(Table 1 continues on next page)

to group the most prevalent chronic comorbidities in our population (appendix 4 p 2).

Socioeconomic status was classified according to the socioeconomic deprivation level index created by the Catalan Government according to the basic health area of residence.[18] This index is based on five indicators: proportion of manual workers, proportion of residents with low education level, proportion with low income, rate of premature mortality, and rate of avoidable hospitalisation.[18] The index produces a continuous variable of 0 to 100, with zero being the lowest level and 100 being the highest.[18] We divided our study

	People living with HIV (n=13 142)	SARS-CoV-2 negative (n=12 393)	SARS-CoV-2 positive (n=749)	Hospital admission (n=103)	Death (n=13)
(Continued from previous page)					
Type of chronic comorbidities					
Respiratory disease	1665 (12·7%)	1553 (12·5%)	112 (15·0%)	33 (32·0%)	6 (46·2%)
Cardiovascular disease	1912 (14·6%)	1800 (14·5%)	112 (15·0%)	31 (30·1%)	4 (30·8%)
Autoimmune disease	1376 (10·5%)	1282 (10·3%)	94 (12·6%)	22 (21·4%)	2 (15·4%)
Chronic kidney disease	569 (4·3%)	535 (4·3%)	34 (4·6%)	9 (8·7%)	2 (15·4%)
Chronic liver disease	2144 (16·3%)	2038 (16·4%)	106 (14·2%)	33 (32·0%)	4 (30·7%)
Neuropsychiatric	3458 (26·3%)	3272 (26·4%)	186 (24·8%)	48 (46·6%)	10 (76·9%)
Diabetes (any type)	741 (5·6%)	706 (5·7%)	35 (4·7%)	11 (10·7%)	0
Metabolic disease	2945 (22·4%)	2781 (22·4%)	164 (22·0%)	53 (51·5%)	5 (38·5%)
Cancer	1198 (9·1%)	1133 (9·1%)	65 (8·7%)	15 (14·6%)	5 (38·5%)
Hypertension	2752 (20·9%)	2585 (20·9%)	167 (22·3%)	42 (40·8%)	6 (46·2%)
Obesity	1114 (8·5%)	1042 (8·4%)	72 (9·6%)	19 (18·5%)	0
Years on ART§	9·4 (5·1–15·0)	9·5 (5·1–15·2)	7·8 (4·6–12·9)	11·7 (6·9–17·7)	15·4 (11·2–17·1)
Backbone ART					
Tenofovir alafenamide	6606 (50·3%)	6215 (50·2%)	391 (52·2%)	57 (55·3%)	7 (53·9%)
Tenofovir disoproxil fumarate	939 (7·2%)	891 (7·2%)	48 (6·4%)	7 (6·8%)	0
Abacavir plus lamivudine	3820 (29·1%)	3594 (29·0%)	226 (30·2%)	26 (25·2%)	3 (23·1%)
Other	670 (5·1%)	630 (5·1%)	40 (5·3%)	6 (5·8%)	1 (7·7%)
Missing	1107 (8·4%)	1063 (8·6%)	44 (5·9%)	7 (6·8%)	2 (15·4%)
Third ART					
Integrase inhibitors	8048 (61·2%)	7565 (61·0%)	483 (64·5%)	57 (55·3%)	7 (53·9%)
Protease inhibitors	2699 (20·5%)	2574 (20·8%)	125 (16·7%)	29 (28·2%)	3 (23·1%)
NNRTIs	3167 (24·1%)	2993 (24·4%)	174 (23·2%)	28 (27·2%)	4 (30·8%)
Other	68 (0·5%)	66 (0·5%)	2 (0·3%)	1 (1·0%)	0
Missing	255 (1·9%)	244 (2·0%)	11 (1·5%)	1 (1·0%)	0

Data are n (%) or median (IQR). ART=antiretroviral therapy. MSM=men who have sex with men. NNRTI=non-nucleoside reverse transcriptase inhibitor. PWID=people who inject drugs. *Sex at birth as registered in the health registries of the participating hospitals was used. One participant in the overall cohort had unknown sex. †Age for all patients was as at Feb 1, 2020. ‡Country of origin was as indicated by the Public Data Analysis for Health Research and Innovation Program of Catalonia, recorded as Spanish or non-Spanish. §Years on ART was defined as the difference in time between the first treatment administration date to the latest treatment date or the latest hospital visit if the latest treatment date was missing.

Table 1: **Characteristics of people with HIV with and without SARS-CoV-2 diagnosis, hospitalisation, and death**

population into a tertile, with the highest socioeconomic group being in the first tertile (least deprived) and the third tertile being the lowest (most deprived).

Statistical analysis

Categorical variables were expressed as counts and percentages and continuous variables were expressed as medians and IQRs. Proportions for categorical variables were compared using the χ^2 or Fisher's exact test when appropriate. Continuous variables were compared with the Mann-Whitney *U* test. Univariable and multivariable Cox proportional hazards regression models were estimated to identify risk factors associated with SARS-CoV-2 diagnosis and severe COVID-19, providing hazard ratios (HRs) and unadjusted HRs with 95% CIs.

We assessed the effect of immunosuppression on severe outcomes stratifying by unsuppressed and suppressed plasma HIV viral load, using survival analysis techniques. We reported the survival probability during the study period using the Kaplan-Meier estimator. We censored patients who did not have a severe outcome by the end of the follow-up period. The differences between the curves were assessed with the log-rank test. Statistical significance was set at a p value of less than 0·05 (two-sided). All analyses were done with R (version 4.0.0).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We linked 20 847 (72·8%) of 28 666 participants in the PISCIS cohort with PADRIS data. 749 (5·7%) of the 13 142 people with HIV who were followed up were diagnosed with SARS-CoV-2. 103 (13·8%) were hospitalised, seven (0·9%) were admitted to the ICU, and 13 (1·7%) died (figure 1).

The median age was 43·5 years (IQR 37·0–52·7) for co-infected patients and 47·6 years (39·6–54·9) for the overall cohort. Among co-infected patients, 618 (82·5%) were male, 131 (17·5%) were female, 347 (46·3%) had

non-Spanish origin, and 373 (49·8%) were in the least deprived socioeconomic stratum.

The median time since HIV diagnosis in the co-infected population was 10·3 years (IQR 6·1–15·7), 14·4 years (9·4–20·7) among hospitalised patients, and 17·4 years (12·7–21·7) among patients who died (table 1). The most frequently reported HIV transmission group among co-infected patients was MSM (table 1). 529 (70·9%) co-infected patients had a CD4 count of 500 cells per µL or greater and 622 (83·0%) had HIV viral suppression (table 1).

	SARS-CoV-2 diagnosis				Severe COVID-19 outcomes			
	HR (95% CI); n=13 142	p value	Adjusted HR (95% CI); n=10 227*	p value	HR (95% CI); n=13 142	p value	Adjusted HR (95% CI); n=10 227*	p value
Sex								
Female	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Male	1·06 (0·87–1·27)	0·58	1·15 (0·68–1·95)	0·61	0·82 (0·51–1·32)	0·42	0·70 (0·26–1·87)	0·47
Age, years								
16–39	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
40–64	0·65 (0·56–0·76)	<0·0001	0·70 (0·58–0·85)	<0·0001	1·73 (1·00–2·97)	0·05	1·03 (0·54–1·95)	0·94
65–74	0·68 (0·47–0·98)	0·036	0·65 (0·42–1·02)	0·059	3·38 (1·54–7·46)	<0·0001	1·53 (0·58–4·00)	0·39
≥75	0·79 (0·43–1·45)	0·45	1·00 (0·53–1·90)	>0·99	7·10 (2·78–18·14)	<0·0001	3·57 (1·21–10·51)	0·021
Place of birth								
Spain	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Outside Spain	1·64 (1·42–1·89)	<0·0001	1·55 (1·31–1·83)	<0·0001	1·40 (0·95–2·06)	0·09	2·34 (1·46–3·75)	<0·0001
Socioeconomic status								
Least deprived	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Mildly deprived	0·76 (0·62–0·94)	0·012	0·87 (0·69–1·10)	0·26	0·56 (0·30–1·05)	0·07	0·58 (0·29–1·16)	0·13
Most deprived	1·06 (0·91–1·25)	0·45	1·20 (0·99–1·45)	0·057	1·02 (0·66–1·57)	0·92	1·13 (0·69–1·84)	0·63
HIV transmission group								
Male heterosexual	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
PWID	0·63 (0·45–0·88)	0·0001	0·66 (0·44–0·98)	0·040	1·28 (0·64–2·55)	0·48	0·90 (0·36–2·21)	0·81
MSM	1·31 (1·04–1·65)	0·021	1·42 (1·09–1·86)	0·0098	0·88 (0·48–1·59)	0·67	1·49 (0·75–3·00)	0·26
Female heterosexual, homosexual, or bisexual	1·24 (0·93–1·64)	0·14	1·47 (0·79–2·71)	0·22	1·10 (0·53–2·28)	0·79	0·75 (0·21–2·70)	0·66
Other	1·18 (0·82–1·68)	0·37	1·12 (0·73–1·73)	0·59	1·12 (0·45–2·77)	0·81	1·00 (0·33–3·00)	0·99
CD4 count, cells per µL								
≥500	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
200–499	1·09 (0·91–1·29)	0·36	1·14 (0·94–1·39)	0·19	1·75 (1·13–2·71)	0·01	1·41 (0·86–2·31)	0·17
<200	1·11 (0·74–1·66)	0·60	1·34 (0·84–2·13)	0·21	3·11 (1·49–6·50)	<0·0001	1·87 (0·76–4·62)	0·17
Plasma HIV RNA viral load								
Undetectable	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Detectable	0·83 (0·62–1·10)	0·20	0·80 (0·59–1·08)	0·15	1·87 (1·06–3·30)	0·03	1·73 (0·93–3·23)	0·083
Backbone ART								
Other	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Tenofovir alafenamide	0·99 (0·72–1·37)	0·96	0·97 (0·68–1·38)	0·86	0·96 (0·42–2·24)	0·93	1·42 (0·51–3·99)	0·50
Tenofovir disoproxil fumarate	0·85 (0·56–1·30)	0·45	0·83 (0·52–1·33)	0·45	0·83 (0·28–2·48)	0·74	1·47 (0·41–5·26)	0·56
Abacavir plus lamivudine	0·99 (0·71–1·39)	0·96	1·04 (0·72–1·50)	0·82	0·76 (0·31–1·85)	0·55	0·99 (0·34–2·87)	0·98
Number of comorbidities								
0	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
1	0·95 (0·79–1·15)	0·60	1·04 (0·84–1·28)	0·74	5·51 (2·08–14·61)	<0·0001	5·90 (1·97–17·65)	<0·0001
2	1·08 (0·88–1·33)	0·47	1·25 (0·98–1·59)	0·07	7·64 (2·85–20·47)	<0·0001	8·48 (2·76–26·01)	<0·0001
3	0·96 (0·74–1·24)	0·74	1·23 (0·90–1·68)	0·19	15·09 (5·71–39·84)	<0·0001	18·77 (6·15–57·33)	<0·0001
≥4	1·02 (0·80–1·29)	0·89	1·46 (1·09–1·97)	0·01	20·01 (7·85–50·99)	<0·0001	22·63 (7·42–68·97)	<0·0001

HRs were calculated using Cox proportional hazards models. ART=antiretroviral therapy. HR=hazard ratio. MSM=men who have sex with men. PWID=people who inject drugs. *Model adjusted for sex, age, country of origin, socioeconomic status, HIV transmission group, backbone ART, plasma HIV RNA viral load (detectable or undetectable), CD4 cell count (<200 cells per µL, 200–499 cells per µL, and ≥500 cells per µL), and number of comorbidities.

Table 2: **Factors associated with SARS-CoV-2 diagnosis and severe COVID-19 outcomes among people living with HIV**

Among co-infected patients, 491 (65·5%) had chronic comorbidities, which was similar to the proportion in the overall cohort (table 1). The most prevalent comorbidities among co-infected patients were neuropsychiatric conditions, hypertension, and metabolic disease (table 1). All patients who died had at least one chronic comorbidity.

705 (94·1%) co-infected patients were on ART before a SARS-CoV-2 diagnosis (table 1). The median time on ART was 7·8 years (IQR 4·6–12·9; table 1). Most co-infected patients and those without SARS-CoV-2 diagnosis (57·3%) were receiving tenofovir-based ART (table 1).

Patient characteristics in terms of age, country of birth, HIV transmission group, years since HIV diagnosis, and years on ART varied significantly between people living with HIV with and without SARS-CoV-2 diagnosis (appendix 4 p 29).

In a multivariable Cox regression model, non-Spanish origin, being MSM, and having four or more chronic comorbidities were associated with an increased risk of SARS-CoV-2 diagnosis (table 2). Being a PWID and aged 40–64 years were negatively associated with SARS-CoV-2 diagnosis in adjusted analysis (table 2).

In a multivariable Cox regression analysis, we found that age 75 years or older, non-Spanish origin, and having one or more chronic comorbidities were associated with severe COVID-19 outcomes (table 2). Our adjusted analysis also showed an increased risk of severe COVID-19 outcomes for people living with HIV with neuropsychiatric conditions, autoimmune disease, respiratory disease, and metabolic disease (figure 2).

Kaplan-Meier survival analysis revealed that, compared with higher CD4 cell counts, a CD4 count of less than 200 cells per µL was significantly associated with severe COVID-19 outcomes during the study period (p=0·0010). A detectable HIV RNA viral load was also associated with severe COVID-19 outcomes (p=0·029; figure 3). We then did a Kaplan-Meier survival analysis, stratifying patients into detectable and undetectable HIV RNA. We found differences in the risk of severe outcomes according to CD4 counts in patients with detectable HIV RNA (p=0·039) but no differences were observed in patients with undetectable HIV RNA (p=0·15; figure 3).

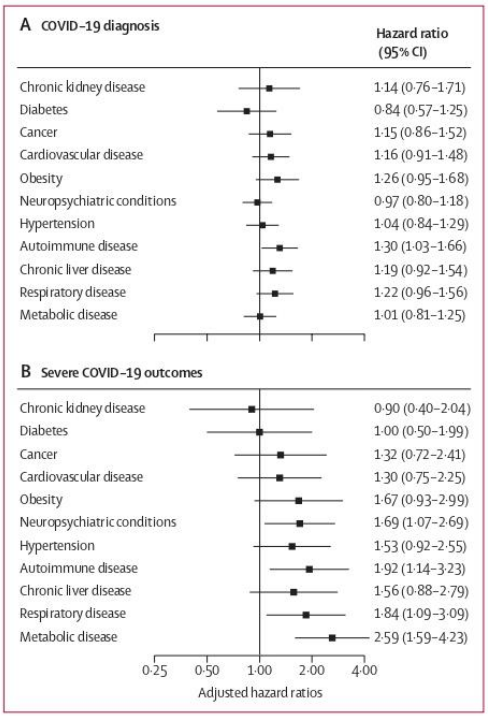

Figure 2: **Estimated hazard ratios for each chronic comorbidity for SARS-CoV-2 diagnosis and severe COVID-19 outcomes, from a multivariable Cox model**

Discussion

In a multicentre population-based cohort of people with HIV, SARS-CoV-2 diagnosis was more common among migrants, MSM, and those with four or more comorbidities; whereas, severe COVID-19 was associated with older age and increased numbers of chronic comorbidities. Notably, we observed differences in the risk of severe outcomes according to CD4 cell counts in patients with detectable HIV RNA viral loads. Our results show that people with HIV with chronic comorbidities and unsuppressed HIV RNA viral load could be at increased risk of severe outcomes and should be prioritised in terms of testing strategies, clinical management, and SARS-CoV-2 vaccination programmes.

The proportion of patients who tested positive for SARS-CoV-2 was higher in our study than in the general population in Catalonia during the same period. Existing data on the incidence of COVID-19 do not suggest that the incidence is higher among people living with HIV compared with the worldwide general population.[4] In a large study from New York (NY, USA), the rate of SARS-CoV-2 diagnosis was higher among people living with HIV compared with that of the general population (2·8% *vs* 1·9%) but, when the analysis was adjusted for sex, age, and region, the relative risk (RR) between HIV-positive and HIV-negative individuals was almost the same (RR 0·94, 95% CI 0·91–0·97).[12] The testing protocols in Spain might, however, mask the true diagnosis rate, because people living with HIV are not prioritised for SARS-CoV-2 testing.[19] With emerging data suggesting an increased risk of severe COVID-19 outcomes for people living with HIV, testing strategies should be revised to target this population.

The mortality rate from our study was lower than the reported mortality rates from other studies of patients co-infected with HIV and SARS-Cov-2.[4] The mortality

For **data on COVID-19 in Catalonia** see https://dadescovid.cat

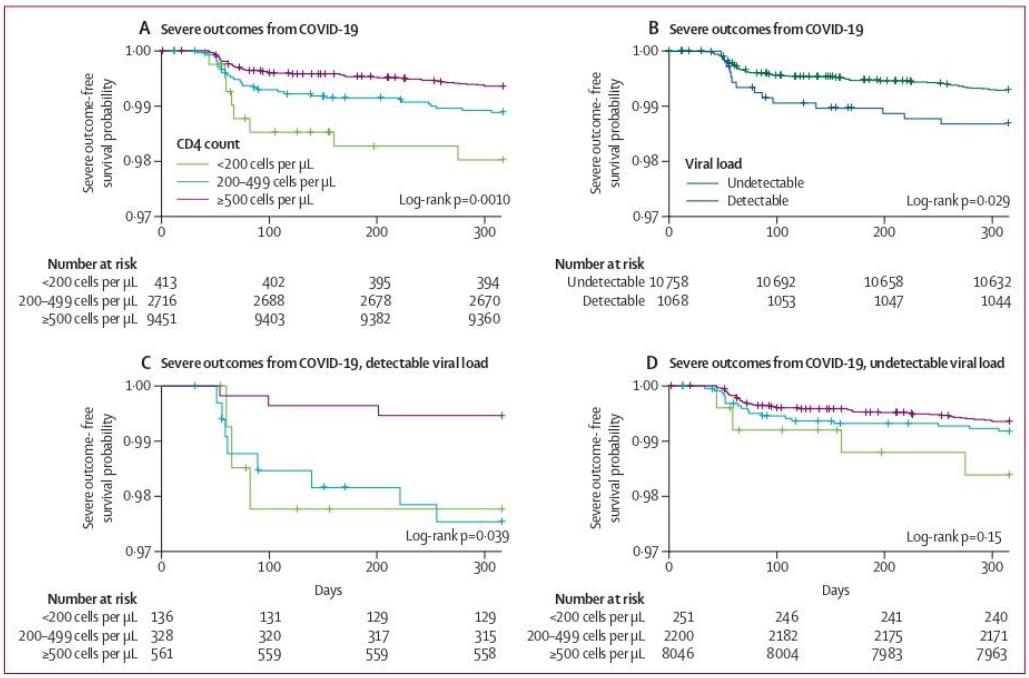

Figure 3: Kaplan-Meier survival curves for people living with HIV in Catalonia, Spain, from March 1 to Dec 15, 2020

rate in the general Catalan population was approximately double what we found in our population during the same period. Also, the rate of hospitalisation in our study was similar to the reported hospitalisation rates in the general Catalan population during the same period. In our cohort, patients were younger than in the general Catalan population and 34·5% of co-infected patients were without chronic comorbidities. Both older age and chronic comorbidities have been identified as major risk factors for severe COVID-19, which partially explains the lower incidence of poorer outcomes in our population.[4,20]

The COVID-19 pandemic has highlighted the existing health inequities affecting specific subpopulations because of their social background. After adjusting for potential confounders, SARS-CoV-2 diagnosis was more common among individuals born outside of Spain. A study from Catalonia has shown that precarious employment is more prevalent among migrants than among non-migrants and the positive association between precarious employment and poor health is well known.[21] During the COVID-19 pandemic, people in precarious employment might find it difficult to work from home or follow physical-distancing guidelines. This situation might partly explain why SARS-CoV-2 diagnosis is more prevalent in people of non-Spanish origin. Similar results were observed in the ENE-COVID study assessing the seroprevalence of SARS-CoV-2 in the overall Spanish population.[22] Intuitively, we would expect socioeconomic deprivation to have similar effects on SARS-CoV-2 diagnosis and severe outcomes as country of origin, but we did not find this association in our analysis. This finding could partly be explained by the fact that socioeconomic deprivation in our analysis was an ecological variable based on place of residence. Place of residence might not, however, always reflect the socioeconomic level of an individual.

Our results suggest the possibility of an increased SARS-CoV-2 diagnosis rate among MSM. Studies from London, UK,[23] Brazil,[24] and Portugal[24] showed that, despite implemented isolation measures to control COVID-19 transmission, a large proportion of MSM continued to engage in sex outside their homes that could potentially increase their risk of SARS-CoV-2 diagnosis. We, however, do not have data to support this finding among MSM in Catalonia. Surprisingly, the decreased risk of SARS-CoV-2 diagnosis among PWID was unanticipated. PWID face additional risk for COVID-19 infection due to potential difficulties in adhering to physical distancing and isolation measures, poor hygiene, stigmatisation, and reduced access to key services during the pandemic. These social health disparities could also hamper SARS-CoV-2 testing opportunities in this population and could contribute, albeit marginally, to explaining the decreased risk in our analysis. Our findings call for further studies to understand the increased risk of SARS-CoV-2 diagnosis among MSM and the reduced risk among PWID.

People living with HIV with four or more co-morbidities were also identified to have an increased risk of SARS-CoV-2 diagnosis. We conceive that people with more comorbidities are more likely to become ill and visit health-care centres more frequently. This explanation means that such patients are more likely to be tested for SARS-CoV-2 and hence their increased risk of SARS-CoV-2 diagnosis in our analysis.

As expected, older age (≥75 years) was associated with a higher risk of severe COVID-19 outcomes. This finding is similar to that of a large study on the risk factors of severe COVID-19 showing that people older than 80 years have at least a 20-times risk of severe COVID-19 compared with the 50–59 years age group.[25] We also observed an increased risk of severe outcomes for migrants. This finding is similar to findings from other studies in the general population that have reported an increased risk of severe outcomes for migrants and minority ethnic groups.[25,26] This finding also reflects the existing vulnerabilities among migrants including reduced patronage of health-care services, unequal socioeconomic factors, and an increased prevalence of comorbidities.[27]

The effect of comorbidities on severe COVID-19 has been established in different studies.[20] Our study shows an increasing risk of severe COVID-19 with increasing number of comorbidities. Neuropsychiatric conditions, autoimmune, respiratory, and metabolic disease were associated with an increased risk of severe COVID-19 outcomes compared with the group without chronic diseases. Similar findings have been reported in other studies.[25,28] Clinical outcomes for people with HIV with SARS-CoV-2 infection and comorbidities could be detrimental and therefore special consideration must be given in the clinical management of such individuals.

Early reports indicated that advanced HIV infection, immunosuppression, and high viraemia might restrict COVID-19-associated immune dysregulation and the development of cytokine storm and therefore might reduce disease severity.[5] However, our findings show that low CD4 count (<200 cells per µL) and detectable plasma HIV RNA viral load were associated with worse outcomes from HIV-COVID-19 co-infection. Notably, low CD4 cell count was not associated with severe outcomes among patients with HIV virological suppression. These findings are similar to those of a study by Hoffmann and colleagues who showed that low CD4 count (<350 cells per µL) or low nadir CD4 cell count were predictors of worse outcomes.[11] However, a multicentre study from the USA showed that CD4 count less than 200 cells per µL, regardless of virological suppression, was associated with worse outcomes of HIV-COVID-19 co-infection.[29] Immunosuppression was not associated with worse outcomes among patients with virological suppression in our study.

This study has some limitations. First, because our overall cohort has not been tested for SARS-CoV-2, we cannot precisely assess the incidence of the infection in our study population. The fact that we found a higher diagnosis rate than did reports from other cohorts of people with HIV suggests that, at least during the first year of the pandemic in Spain, HIV-positive patients were not specifically targeted for SARS-CoV-2 screening, but rather testing was done on the basis of presenting symptoms, existing comorbidities, or age.[19] Therefore, we might have overestimated the diagnosis rate in this population. Second, our data do not include information on smoking and body-mass index. Both factors are associated with worse COVID-19 outcomes. Third, we could not link patient-level information for some PISCIS cohort participants with the PADRIS data. We were able to link 20 847 out of the 28 666 (72·8%) participants of the PISCIS cohort with the PADRIS data. But the proportion of participants alive as of Feb 1, 2020, and followed up was still a good representable sample size to be analysed and make deductions.

In conclusion, our results show that among people living with HIV, migrants, MSM, and those with comorbidities were at an increased risk of SARS-CoV-2 diagnosis; however, the diagnosis rate of SARS-CoV-2 infection could be masked because of the absence of specific testing policies addressing this population, because testing in Spain has been based on presenting signs and symptoms and contact tracing. The fact that people with HIV were not prioritised for SARS-CoV-2 testing could disguise the real picture of the pandemic in this population. Finally, our findings also suggest that people with HIV with immunosuppression, detectable HIV viraemia, chronic comorbidities, and subpopulations (eg, older people and migrants) could be more susceptible to severe outcomes from COVID-19 and should be prioritised in testing strategies, clinical management, and considered a target group for SARS-CoV-2 vaccination programmes.

Contributors

DKN, JR-U, YD, and JMM conceived and designed the study. DKN, JR-U, and YD had full access to all of the study data, verified the data, and take responsibility for the integrity of the data and the accuracy of the data analysis. DKN, JR-U, YD, SM, and JA did the analyses. DKN and JRU wrote the first draft of the paper and incorporated revisions. All authors contributed in the interpretation of results. All authors critically revised and approved the final manuscript.

Declaration of interests

JMM reports receiving a personal 80:20 research grant from Institut d'Investigacions Biomèdiques August Pi I Sunyer, Barcelona, Spain, during 2017–21. EL reports receiving honoraria for lectures and presentations from ViiV Healthcare, Gilead Sciences, and Jansen Therapeutics; travel support for attending meetings from ViiV Healthcare and Jansen Therapeutics; payments for participating in the data safety monitoring and advisory board of ViiV Healthcare; being a full time employee of ViiV Healthcare since May 3, 2020; and payments made from Juan Rodés to the Spanish Government on his behalf. PD reports that his institution received grants from Gilead Sciences, Janssen-Cilag, and ViiV Healthcare; and he personally received honoraria from Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme, ViiV Healthcare, Roche, and Thera Technologies. AI reports that his institution received grants from Gilead Sciences and Merck Sharp & Dohme; and he personally received consultation fees from Gilead Sciences, ViiV Healthcare, and Thera Technologies; honoraria for lectures and presentations from Gilead Sciences, Merck Sharp &

Dohme, Jansen Therapeutics, and ViiV Healthcare; and travel support for attending meetings from Gilead Sciences, Jansen, and ViiV Healthcare. VF reports that his institution received grants from Gilead Sciences, ViiV Healthcare, and Merck Sharp & Dohme; and he personally received consultation fees from ViiV Healthcare; honoraria for lectures and presentations from ViiV Healthcare, Gilead Sciences, Jansen Therapeutics, and Merck Sharp & Dohme; and travel support for attending meetings from Gilead Sciences. All other authors declare no competing interests.

Data sharing

The study protocol is available from JR-U (jmreyes@iconcologia.net). Statistical code for the analysis can be requested from YD, SM, or JA (ydiaz@igtp.cat, smorenof@iconcologia.net, oe jaceiton@igtp.cat). The data for this study are available from the Centre for Epidemiological Studies of Sexually Transmitted Diseases and HIV/AIDS in Catalonia (CEEISCAT), the coordinating centre of the PISCIS cohort study and from each of the collaborating hospitals upon request. Requests can be made via https://pisciscohort.org/contacte/.

Acknowledgments

This study was funded by the COVIHCAT grant from Fundació "la Caixa". We also want to thank PADRIS and the Programme for the Prevention, Control and Care for HIV, Sexually Transmitted Diseases and Viral Hepatitis of the Ministry of Health of the Government of Catalonia for their support.

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Article 3

Impact of tenofovir on SARS-CoV-2 infection and severe outcomes among people living with HIV: a propensity score matched study

Article III

Impact of tenofovir on SARS-CoV-2 infection and severe outcomes among people living with HIV: a propensity score-matched study

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Journal of Antimicrobial Chemotherapy. Volume 77, Issue 8, August 2022, Pages 2265–2273,

Summary

Public health professionals, researchers, clinicians, and governments across the globe have been challenged to find short- and long-term solutions to curb the current COVID-19 pandemic. Different drugs have been proposed as potential treatments for COVID-19. Some researchers suggested that certain antiretroviral regimens could be protective against COVID-19 among PLWH. Prominent among the proposed regimens was tenofovir. The nucleotide analogue has become very prominent in antiretroviral treatment and is available as the prodrugs TAF and TDF. The two medicines have also proven to be efficacious as PrEP in high-risk populations without HIV infection. In pre-clinical studies, tenofovir showed some activity against SARS-CoV-2 inhibiting its RNA-dependent RNA polymerase (RdRp). Furthermore, triphosphate forms of tenofovir were believed to be incorporated by SARS-CoV-2 RdRp and recess polymerase extension which could explain why the nucleotide analogue could inhibit SARS-CoV-2.

Prior to this study, we identified seven observational studies that evaluated the influence of tenofovir on SARS-CoV-2 incidence and disease severity among PLWH, two among HIV-negative PrEP users, and one clinical trial. The study from Boulle et al from Western Cape, South Africa, demonstrated lower mortality among HIV-infected individuals receiving TDF/FTC compared to abacavir or zidovudine, and the results from Del Amo et al (2020) suggested a lower risk of SARS-CoV-2 diagnosis and associated hospitalisation among patients receiving TDF/FTC comparing with other antiretroviral therapies (ART). The clinical trial involving 60 patients from Parienti et al concluded that TDF/FTC accelerates the natural clearance of nasopharyngeal SARS-CoV-2. However, in a study including HIV-negative individuals receiving tenofovir as PrEP, SARS-CoV-2 seroprevalence was higher among tenofovir users and clinical manifestation of the infection was not different between individuals receiving tenofovir and those not. Similarly, two studies from France showed no reduction SARS-CoV-2 prevalence or clinical severity among TDF/FTC. a recent comprehensive set of in vitro data performed by the drug manufacturer indicates that tenofovir, TAF, TDF, and FTC are inactive against SARS-CoV-2. These results are corroborated by the lack of interaction between the respective NRTI-TPs and SARS-CoV-2 RdRp observed both in biochemical assays and in structural modeling analyses.

It is uncertain if tenofovir prevents the incidence of SARS-CoV-2 or reduces disease severity among PLWH. Understanding the preventive effect of tenofovir is very relevant given the rapidly changing COVID-19 situation and the surge of new variants with the potential to escape vaccine-induced-immune protection.

We mitigated the limitations existing in previous studies by employing a propensity score matching technique to evaluate the protective effect of tenofovir-based ART against SARS-CoV-2 infection and severe clinical outcomes. We did three separate propensity score matching in a ratio 1:1 for TAF/FTC versus ABC/3TC, and 1:3 for TDF/FTC versus ABC/3TC, and TDF/FTC versus TAF/FTC. We

matched patients by sex, age, plasma HIV RNA (detectable and undetectable), and number of comorbidities. We used Cox regression models to provide double adjustment and remove possible residual confounding.

After propensity score-matching, SARS-CoV-2 diagnosis rates were similar in TAF/FTC versus ABC/3TC recipients (11.6% versus 12.5%, P = 0.256); lower among TDF/FTC versus ABC/3TC recipients (9.6% versus 12.8%, P = 0.021); and lower among TDF/FTC versus TAF/FTC recipients (9.6% versus 12.1%, P = 0.012). In well-adjusted logistic regression models, TAF/FTC was no longer associated with reduced SARS-CoV-2 diagnosis [adjusted odds ratio (aHR) 0.90; 95% confidence interval (CI), 0.78-1.04] or hospitalization (aHR 0.93; 95% CI, 0.60-1.43). When compared with ABC/3TC, TDF/FTC was not associated with reduced SARS-CoV-2 diagnosis (aHR 0.79; 95% CI, 0.60-1.04) or hospitalization (aHR 0.51; 95% CI, 0.15-1.70). TDF/FTC was not associated with reduced SARS-CoV-2 diagnosis (aHR 0.79; 95% CI, 0.60-1.04) or associated hospitalization (aHR 0.33; 95% CI, 0.10-1.07) compared with TAF/FTC.

Our findings do not support a protective effect of either TDF or TAF against SARS-CoV-2 infection or severe outcomes, and actually suggest that subjects treated with TDF have intrinsic characteristics that lend them a lower risk for SARS-CoV-2 infection or poorer COVID-19 outcomes. This underlying bias could explain the protective effect found in some incompletely adjusted analyses reported so far. Tenofovir exposure should not modify any preventive or therapeutic SARS-CoV-2 infection management.

J Antimicrob Chemother 2022; **77**: 2265–2273
https://doi.org/10.1093/jac/dkac177 Advance Access publication 9 June 2022

Journal of Antimicrobial Chemotherapy

Impact of tenofovir on SARS-CoV-2 infection and severe outcomes among people living with HIV: a propensity score-matched study

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Received 22 February 2022; accepted 13 May 2022

Background: Reports on the impact of some antiretrovirals against SARS-CoV-2 infection and disease severity are conflicting.

Objectives: We evaluated the effect of tenofovir as either tenofovir alafenamide/emtricitabine (TAF/FTC) or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) against SARS-CoV-2 infection and associated clinical outcomes among people living with HIV (PLWH).

Methods: We conducted a propensity score-matched analysis in the prospective PISCIS cohort of PLWH ($n=14$ 978) in Catalonia, Spain. We used adjusted Cox regression models to assess the association between tenofovir and SARS-CoV-2 outcomes.

Results: After propensity score-matching, SARS-CoV-2 diagnosis rates were similar in TAF/FTC versus ABC/3TC recipients (11.6% versus 12.5%, $P=0.256$); lower among TDF/FTC versus ABC/3TC recipients (9.6% versus 12.8%, $P=0.021$); and lower among TDF/FTC versus TAF/FTC recipients (9.6% versus 12.1%, $P=0.012$). In well-adjusted logistic regression models, TAF/FTC was no longer associated with reduced SARS-CoV-2 diagnosis [adjusted odds ratio (aOR) 0.90; 95% confidence interval (CI), 0.78–1.04] or hospitalization (aOR 0.93; 95% CI, 0.60–1.43). When compared with ABC/3TC, TDF/FTC was not associated with reduced SARS-CoV-2 diagnosis (aOR 0.79; 95% CI, 0.60–1.04) or hospitalization (aOR 0.51; 95% CI, 0.15–1.70). TDF/FTC was not associated with reduced SARS-CoV-2 diagnosis (aOR 0.79; 95% CI, 0.60–1.04) or associated hospitalization (aOR 0.33; 95% CI, 0.10–1.07) compared with TAF/FTC.

Conclusions: TAF/FTC or TDF/FTC were not associated with reduced SARS-CoV-2 diagnosis rates or associated hospitalizations among PLWH. TDF/FTC users had baseline characteristics intrinsically associated with more benign SARS-CoV-2 infection outcomes. Tenofovir exposure should not modify any preventive or therapeutic SARS-CoV-2 infection management.

Introduction

Tenofovir has been postulated as a treatment candidate for COVID-19.[1] This nucleotide analogue is very prominent in antiretroviral treatment (ART) and is available as the prodrugs tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF). The two medicines are also efficacious as HIV pre-exposure prophylaxis (PrEP) in high-risk populations without HIV infection.[2] The repurposing of TAF and TDF is due to their well-established safety profile, the wide availability of the generic forms, and the low cost of TDF.[3] In pre-clinical studies, tenofovir showed some *in vitro* activity against SARS-CoV-2, inhibiting its RNA-dependent RNA polymerase (RdRp).[4] Furthermore, triphosphate forms of tenofovir are believed to be incorporated by SARS-CoV-2 RdRp and retard polymerase extension, which could explain why the nucleotide analogue could inhibit SARS-CoV-2.[5] However, a recent comprehensive set of *in vitro* analyses performed by the drug manufacturer has finally indicated that neither TAF, TDF, nor emtricitabine (FTC) are inactive against SARS-CoV-2.[6] These results are corroborated by the lack of interaction between tenofovir triphosphates and SARS-CoV-2 RdRp observed both in biochemical assays and in structural modelling analyses.[6]

A study of people living with HIV (PLWH) receiving ART in Spain suggested that individuals receiving TDF/FTC were at a lower risk of COVID-19 and related hospitalization than those receiving other antiretroviral regimens.[7] However, the analysis was not adjusted for baseline co-morbidities and important sociodemographic characteristics, and could be overestimating the protective effect of TDF/FTC because recipients of TDF/FTC are likely to be younger and without comorbidities such as renal and cardiovascular diseases, which have been established as risk factors for COVID-19 and severe outcomes.[8–10] In another study, from South Africa, TDF/FTC (versus abacavir or zidovudine) was again associated with lower mortality among PLWH after adjusting for kidney disease, viral suppression, and antiretroviral treatment duration.[11] Zidovudine, a second-line regimen, is however associated with prior virological failure or presence of tuberculosis, both of which were not adjusted for in that study. Similarly, among HIV-negative individuals with chronic hepatitis B infection, lower rates of severe COVID-19, ICU admission, need for respiratory support, and shorter hospitalization duration were found among patients receiving TDF/FTC compared with entecavir.[12] However, again, the prevalence of chronic comorbidities was significantly lower among those receiving TDF/FTC, establishing again a channelling prescription bias.[12]

A study that assessed the protective effects of tenofovir against SARS-CoV-2 infection among HIV-negative individuals found just the opposite: a higher SARS-CoV-2 seroprevalence among PrEP (tenofovir) users compared with persons not receiving tenofovir (15.5% versus 9.2%, $P = 0.026$).[13] The study found no statistically significant differences in COVID-19 clinical manifestations between users of PrEP, TDF/FTC or TAF/FTC and the control group.[13] Similarly, the PREVENIR-ANRS and SAPRIS-Sero study from France also showed no reduction in SARS-CoV-2 seroprevalence among TDF/FTC PrEP users.[14] That study is particularly relevant as there were no baseline patient characteristics biasing the analysis through a channelling prescription.

There are several on-going clinical trials assessing the potential of tenofovir as prophylaxis against SARS-CoV-2 infection and treatment for COVID-19.[3] Understanding the preventive effect of tenofovir is very relevant given the rapidly changing COVID-19 situation and the surge of new variants with potential to escape vaccine- or infection-induced immune protection.

We evaluated the association between TAF/FTC and TDF/FTC exposure against SARS-CoV-2 infection and severe COVID-19 among PLWH, mitigating the limitations in existing studies by adjusting adequately for potential baseline confounders.

Patients and methods

Study population and design

We performed a retrospective study using data from the Populational HIV Cohort from Catalonia and Balearic Islands (PISCIS). PISCIS is a prospective, multicentre, population-based cohort which follows PLWH aged ≥16 years accessing care at 15 hospitals in Catalonia, Spain.[15] We linked PISCIS data with data from several administrative official public health databases to obtain information about chronic comorbidities, SARS-CoV-2 diagnosis, and related clinical outcomes. Data were managed through the Analytical Data for Research and Innovation in Health Project of Catalonia (PADRIS) so as to ensure anonymization in accordance with current data protection legislation.[16] The study period was from 1 March 2020 to 18 July 2021. We excluded patients who were reported dead before 1 March 2020, those without information on ART, and those who had at any point switched their ART regimen since cohort entry.

Study definitions and outcomes

We divided the study population into three groups according to nucleos(t)ide reverse transcriptase inhibitor (NRTI) exposure: (i) TAF/FTC; (ii) TDF/FTC; and (iii) abacavir/lamivudine (ABC/3TC). The primary outcome variables of interest were SARS-CoV-2 diagnosis confirmed by a positive reverse transcription polymerase chain reaction (RT-PCR) and/or antigen detection; and COVID-19 outcomes graded as asymptomatic, symptomatic requiring community management (mild symptoms managed as outpatients or at the emergency department for <24 h), and hospital admissions (>24 h with any of the following signs: dyspnoea, tachypnoea, hypoxaemia, asphyxia or hyperventilation). Among hospitalized patients, we also assessed admission to the ICU (suffered a respiratory failure or sepsis) and death.

Independent variables in the study included patient sociodemographic characteristics: age; sex; socioeconomic deprivation based on the Catalonian Government socioeconomic deprivation index classified as least deprived, mildly deprived, and moderately/severely deprived;[17] and country of origin (Spanish and non-Spanish origin). The HIV-associated variables we included in the study were HIV acquisition risk groups as stated in Table 1; duration since HIV diagnosis in years; CD4 cell count (categorized <350 cells/mm^3, 350–499 cells/mm^3, and ≥500 cells/mm^3) and CD4/CD8 cell ratio; plasma HIV-RNA [detectable and undetectable (≤50 copies/mL)]; and duration on ART in years. We included chronic comorbidities extracted using the International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) and tenth revision (ICD-10-CM) and grouped them into 11 groups (Table S1, available as Supplementary data at *JAC* Online).

Statistical analysis

Continuous variables are presented as median with interquartile ranges (IQR) and frequencies with percentages for categorical variables. Proportions for categorical variables were compared using the χ^2 or Fisher's exact test where appropriate. Continuous variables were

Table 1. Propensity score-matched[a] baseline characteristics of people living with HIV receiving (i) TAF/FTC versus ABC/3TC, (ii) TDF/FTC versus ABC/3TC, or (iii) TAF/FTC versus TDF/FTC

	TAF/FTC versus ABC/3TC				TDF/FTC versus ABC/3TC				TAF/FTC versus TDF/FTC			
Characteristic	Total ($n=7024$)	TAF/FTC ($n=3512$)	ABC/3TC ($n=3512$)	*P* value	Total ($n=3052$)	TDF/FTC (=763)	ABC/3TC ($n=2289$)	*P* value	Total ($n=3080$)	TAF/FTC ($n=2310$)	TDF/FTC ($n=770$)	*P* value
Sex, *n* (%)				0.926				1.000				0.557
Male	5678 (80.8)	2841 (80.9)	2837 (80.8)		2476 (81.1)	619 (81.1)	1857 (81.1)		2504 (81.3)	1884 (81.6)	620 (80.5)	
Female	1346 (19.2)	671 (19.1)	675 (19.2)		576 (18.9)	144 (18.9)	432 (18.9)		576 (18.7)	426 (18.4)	150 (19.5)	
Age, years, median (IQR)	48.2 (39.6–55.4)	48.0 (39.4–55.2)	48.4 (39.8–55.6)	0.117	45.2 (38.0–53.1)	45.0 (38.3–52.4)	45.3 (37.9–53.2)	0.803	45.0 (38.3–52.5)	45.1 (38.3–52.6)	44.9 (37.9–52.3)	0.542
Age category, years				0.642				0.893				0.587
16–39	1832 (26.08)	932 (26.54)	900 (25.63)		1014 (33.2)	250 (32.8)	764 (33.4)		988 (32.1)	730 (31.6)	258 (33.5)	
40–64	4706 (67)	2346 (66.8)	2360 (67.2)		1907 (62.5)	480 (62.9)	1427 (62.3)		1957 (63.5)	1477 (63.9)	480 (62.3)	
65–74	393 (5.6)	192 (5.47)	201 (5.72)		97 (3.2)	26 (3.4)	71 (3.1)		113 (3.7)	88 (3.8)	25 (3.3)	
≥75	93 (1.32)	42 (1.2)	51 (1.45)		34 (1.1)	7 (0.9)	27 (1.2)		22 (0.7)	15 (0.7)	7 (0.9)	
Country of origin, *n* (%)				0.007				0.608				0.621
Spain	4354 (62.0)	2121 (60.4)	2233 (63.6)		1838 (60.2)	453 (59.4)	1385 (60.5)		1794 (58.3)	1339 (58.0)	455 (59.1)	
Outside Spain	2669 (38.0)	1390 (39.6)	1279 (36.4)		1214 (39.8)	310 (40.6)	904 (39.5)		1285 (41.7)	970 (42.0)	315 (40.9)	
Socioeconomic deprivation, *n* (%)				0.001				0.978				0.032
Least deprived	3361 (47.9)	1754 (49.9)	1607 (45.8)		1443 (47.3)	361 (47.3)	1082 (47.3)		1559 (50.6)	1196 (51.8)	363 (47.1)	
Mildly deprived	1372 (19.5)	659 (18.8)	713 (20.3)		597 (19.6)	137 (18.0)	460 (20.1)		559 (18.2)	421 (18.2)	138 (17.9)	
Moderately/severely deprived	2123 (30.2)	1021 (29.1)	1102 (31.4)		933 (30.6)	237 (31.1)	696 (30.4)		884 (28.7)	643 (27.8)	241 (31.3)	
Missing	168 (2.4)	78 (2.2)	90 (2.6)		79 (2.6)	28 (3.7)	51 (2.2)		78 (2.5)	50 (2.2)	28 (3.6)	
HIV acquisition risk group, *n* (%)				0.058				0.938				0.266
PWID	853 (12.1)	442 (12.6)	411 (11.7)		291 (9.5)	71 (9.3)	220 (9.6)		335 (10.9)	264 (11.4)	71 (9.2)	
MSM	3631 (51.7)	1835 (52.3)	1796 (51.1)		1663 (54.5)	408 (53.5)	1255 (54.8)		1663 (54.0)	1255 (54.3)	408 (53.0)	
Male heterosexual	978 (13.9)	469 (13.4)	509 (14.5)		427 (14.0)	111 (14.6)	316 (13.8)		401 (13.0)	290 (12.6)	111 (14.4)	
Female hetero/homo/bisexual	1032 (14.7)	526 (15.0)	506 (14.4)		448 (14.7)	111 (14.6)	337 (14.7)		451 (14.6)	336 (14.6)	115 (14.9)	
Other	397 (5.7)	175 (5.0)	222 (6.3)		171 (5.6)	46 (6.0)	125 (5.5)		175 (5.7)	126 (5.5)	49 (6.4)	
Missing	133 (1.9)	65 (1.9)	68 (1.9)		52 (1.7)	16 (2.1)	36 (1.6)		55 (1.8)	39 (1.7)	16 (2.1)	
Years since HIV diagnosis, median (IQR)	11.7 (6.3–18.1)	11.6 (6.6–18.1)	11.8 (6.0–18.1)	0.877	11.1 (5.8–16.9)	11.7 (7.4–17.2)	10.8 (5.0–16.8)	<0.001	11.0 (6.3–17.0)	10.7 (6.0–16.8)	11.7 (7.3–17.1)	0.001
CD4 count (cells/mm^3) category				0.057				0.869				0.983
<350	781 (11.1)	424 (12.1)	357 (10.2)		303 (9.9)	79 (10.4)	224 (9.8)		335 (10.9)	254 (11.0)	81 (10.5)	
350–499	981 (14.0)	482 (13.7)	499 (14.2)		431 (14.1)	105 (13.8)	326 (14.2)		428 (13.9)	320 (13.9)	108 (14.0)	
≥500	5262 (74.9)	2606 (74.2)	2656 (75.6)		2318 (76.0)	579 (75.9)	1739 (76.0)		2317 (75.2)	1736 (75.2)	581 (75.5)	
CD4 count (cells/mm^3), median (IQR)	695.5 (499.0–926.0)	680.0 (490.0–904.0)	711.0 (506.0–950.0)	<0.001	707.0 (509.8–937.0)	690.0 (508.0–918.5)	712.0 (510.0–944.0)	0.103	686.0 (500.0–910.0)	684.5 (500.0–906.0)	688.5 (505.3–917.5)	0.681
CD4/CD8 ratio, median (IQR)	0.9 (0.6–1.2)	0.9 (0.6–1.2)	0.9 (0.6–1.2)	0.323	0.9 (0.6–1.3)	0.9 (0.7–1.3)	0.9 (0.6–1.2)	0.030	0.9 (0.6–1.3)	0.9 (0.6–1.2)	0.9 (0.7–1.3)	0.011
Plasma HIV-RNA, *n* (%)				0.581				0.840				1.000

Continued

Table 1. *Continued*

Characteristic	TAF/FTC versus ABC/3TC				TDF/FTC versus ABC/3TC				TAF/FTC versus TDF/FTC			
	Total ($n=7024$)	TAF/FTC ($n=3512$)	ABC/3TC ($n=3512$)	*P* value	Total ($n=3052$)	TDF/FTC (=763)	ABC/3TC ($n=2289$)	*P* value	Total ($n=3080$)	TAF/FTC ($n=2310$)	TDF/FTC ($n=770$)	*P* value
Detectable[b]	511 (7.3)	262 (7.5)	249 (7.1)		219 (7.2)	53 (7.0)	166 (7.3)		220 (7.1)	165 (7.1)	55 (7.1)	
Undetectable[b]	6513 (92.7)	3250 (92.5)	3263 (92.9)		2833 (92.8)	710 (93.1)	2123 (92.8)		2860 (92.9)	2145 (92.9)	715 (92.9)	
Number of comorbidities, *n* (%)				0.715								0.978
0	2041 (29.1)	1048 (29.8)	993 (28.3)					0.983	1218 (39.6)	920 (39.8)	298 (38.7)	
1	1651 (23.5)	818 (23.3)	833 (23.7)		1150 (37.7)	291 (38.1)	859 (37.5)		754 (24.5)	561 (24.3)	193 (25.1)	
2	1244 (17.7)	613 (17.5)	631 (18.0)		792 (26.0)	193 (25.3)	599 (26.2)		507 (16.5)	381 (16.5)	126 (16.4)	
3	773 (11.0)	383 (10.9)	390 (11.1)		507 (16.6)	126 (16.5)	381 (16.6)		264 (8.6)	198 (8.6)	66 (8.6)	
≥4	1315 (18.7)	650 (18.5)	665 (18.9)		253 (8.3)	66 (8.7)	187 (8.2)		337 (10.9)	250 (10.8)	87 (11.3)	
Type of comorbidities, *n* (%)					350 (11.5)	87 (11.4)	263 (11.5)					
Respiratory disease	1596 (22.7)	811 (23.1)	785 (22.4)	0.477					539 (17.5)	390 (16.9)	149 (19.4)	0.132
Cardiovascular disease	1220 (17.4)	612 (17.4)	608 (17.3)	0.925	554 (18.2)	149 (19.5)	405 (17.7)	0.278	360 (11.7)	267 (11.6)	93 (12.1)	0.746
Autoimmune disease	840 (12.0)	393 (11.2)	447 (12.7)	0.051	378 (12.4)	93 (12.2)	285 (12.5)	0.899	311 (10.1)	239 (10.4)	72 (9.4)	0.468
Chronic kidney disease	374 (5.3)	136 (3.9)	238 (6.8)	<0.001	295 (9.7)	72 (9.4)	223 (9.7)	0.860	70 (2.3)	61 (2.6)	9 (1.2)	0.026
Chronic liver disease	1393 (19.8)	722 (20.6)	671 (19.1)	0.135	116 (3.8)	9 (1.2)	107 (4.7)	<0.001	506 (16.4)	379 (16.4)	127 (16.5)	1.000
Neuropsychiatric	2128 (30.3)	1077 (30.7)	1051 (29.9)	0.516	467 (15.3)	127 (16.6)	340 (14.9)	0.258	771 (25.0)	564 (24.4)	207 (26.9)	0.187
Diabetes	464 (6.6)	210 (6.0)	254 (7.2)	0.039	746 (24.4)	207 (27.1)	539 (23.6)	0.052	126 (4.1)	89 (3.9)	37 (4.8)	0.294
Metabolic disease	1839 (26.2)	878 (25.0)	961 (27.4)	0.026	140 (4.6)	37 (4.9)	103 (4.5)	0.764	558 (18.1)	424 (18.4)	134 (17.4)	0.589
Cancer	789 (11.2)	381 (10.9)	408 (11.6)	0.326	598 (19.6)	134 (17.6)	464 (20.3)	0.114	228 (7.4)	161 (7.0)	67 (8.7)	0.131
Hypertension	1630 (23.2)	790 (22.5)	840 (23.9)	0.166	262 (8.6)	67 (8.8)	195 (8.5)	0.881	504 (16.4)	384 (16.6)	120 (15.6)	0.536
Obesity	699 (10.0)	342 (9.7)	357 (10.2)	0.577	526 (17.2)	120 (15.7)	406 (17.7)	0.223	230 (7.5)	170 (7.4)	60 (7.8)	0.752
Years on ART, median (IQR)	9.9 (5.4–15.3)	9.8 (5.7–14.9)	10.1 (5.3–15.5)	0.213	234 (7.7)	60 (7.9)	174 (7.6)	0.875	9.5 (5.6–13.7)	9.3 (5.4–13.6)	10.4 (6.1–14.1)	0.003

Abbreviations: IQR, interquartile range; PWID, people who inject drugs; MSM, men who have sex with men; ART, antiretroviral therapy; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ABC/3TC, abacavir/lamivudine.

[a]Propensity score-matching ratio is 1:1 for TAF/FTC versus ABC/3TC, 1:3 for TDF/FTC versus ABC/3TC, and 1:3 for TDF/FTC versus TAF/FTC.

[b]HIV-RNA viral load (detectable: ≥50 copies per mL, undetectable: <50 copies per mL).

Table 2. SARS-Cov-2 diagnosis and clinical severity in propensity score-matched groups of PLWH based on antiretroviral therapy (ART) and results from Cox regression models that evaluated the effect of ART regimens on SARS-CoV-2 diagnosis and associated hospitalization

	TAF/FTC versus ABC/3TC					
	Total[a]	TAF/FTC[a]	ABC/3TC[a,b]	*P* value[c]	uOR (95% CI)	aOR (95% CI)
SARS-CoV-2 diagnosis				0.256	0.92 (0.80–1.05)	0.90 (0.78–1.04)
Positive	848 (12.1)	408 (11.6)	440 (12.5)			
Negative	6176 (87.9)	3104 (88.4)	3072 (87.5)			
Clinical severity				0.838		
Asymptomatic	380 (44.8)	186 (45.6)	194 (44.1)			
Symptomatic mild community management	370 (43.6)	172 (42.3)	198 (45.0)			
Hospitalization[d]	98 (11.6)	50 (12.3)	48 (10.9)		1.04 (0.70–1.55)	0.93 (0.60 -1.43)
ICU admission	4 (0.5)	2 (0.5)	2 (0.5)			
Death[e]	17 (2.0)	9 (2.2)	8 (1.8)			
	TDF/FTC versus ABC/3TC					
	Total	TDF/FTC	ABC/3TC[b]	*P* value[c]	uOR (95% CI)	aOR (95% CI)
SARS-CoV-2 diagnosis				0.021	**0.74 (0.57–0.95)**	0.79 (0.60–1.04)
Positive	369 (12.0)	74 (9.6)	295 (12.8)			
Negative	2704 (88.0)	697 (90.4)	2007 (87.2)			
Clinical severity				0.352		
Asymptomatic	172 (46.6)	40 (54.1)	132 (44.8)			
Symptomatic mild community management	170 (46.1)	31 (41.9)	139 (47.1)			
Hospitalization[d]	27 (7.3)	3 (4.1)	24 (8.1)		0.37 (0.11–1.24)	0.51 (0.15–1.70)
ICU admission	2 (0.5)	0 (0)	2 (0.7)			
Death[e]	3 (0.8)	0 (0)	3 (1.0)			
	TAF/FTC versus TDF/FTC					
	Total	TAF/FTC[b]	TDF/FTC	*P* value[c]	uOR (95% CI)	aOR (95% CI)
SARS-CoV-2 diagnosis				0.012	**0.72 (0.56–0.93)**	0.79 (0.60–1.04)
Positive	377 (12.2)	303 (13.1)	74 (9.6)			
Negative	2703 (87.8)	2007 (86.9)	696 (90.4)			
Clinical severity				0.274		
Asymptomatic	190 (50.4)	150 (49.5)	40 (54.1)			
Symptomatic mild community management	150 (39.8)	119 (39.3)	31 (41.9)			
Hospitalization[d]	37 (9.8)	34 (11.2)	3 (4.1)		**0.26 (0.08–0.86)**	0.33 (0.10–1.07)
ICU admission	3 (0.8)	3 (1.0)	0 (0)			
Death[e]	6 (1.6)	6 (2.0)	0 (0)			

Adjusted model: Adjusted for country of origin, socioeconomic status, CD4 count (continuous variable), time in years on ART, CD4/CD8 ratio, diabetes, chronic kidney disease, chronic liver disease, and metabolic disease.

Abbreviations: TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ABC/3TC, abacavir/lamivudine; ICU, intensive care unit, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; OR, odds ratio; uOR, unadjusted odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

[a]Data in this category is presented as *n* (%).

[b]Reference group for odds ratios.

[c]Numbers in bold indicate significant differences ($P < 0.05$).

[d]Including ICU admissions.

[e]Also included in hospitalized patients.

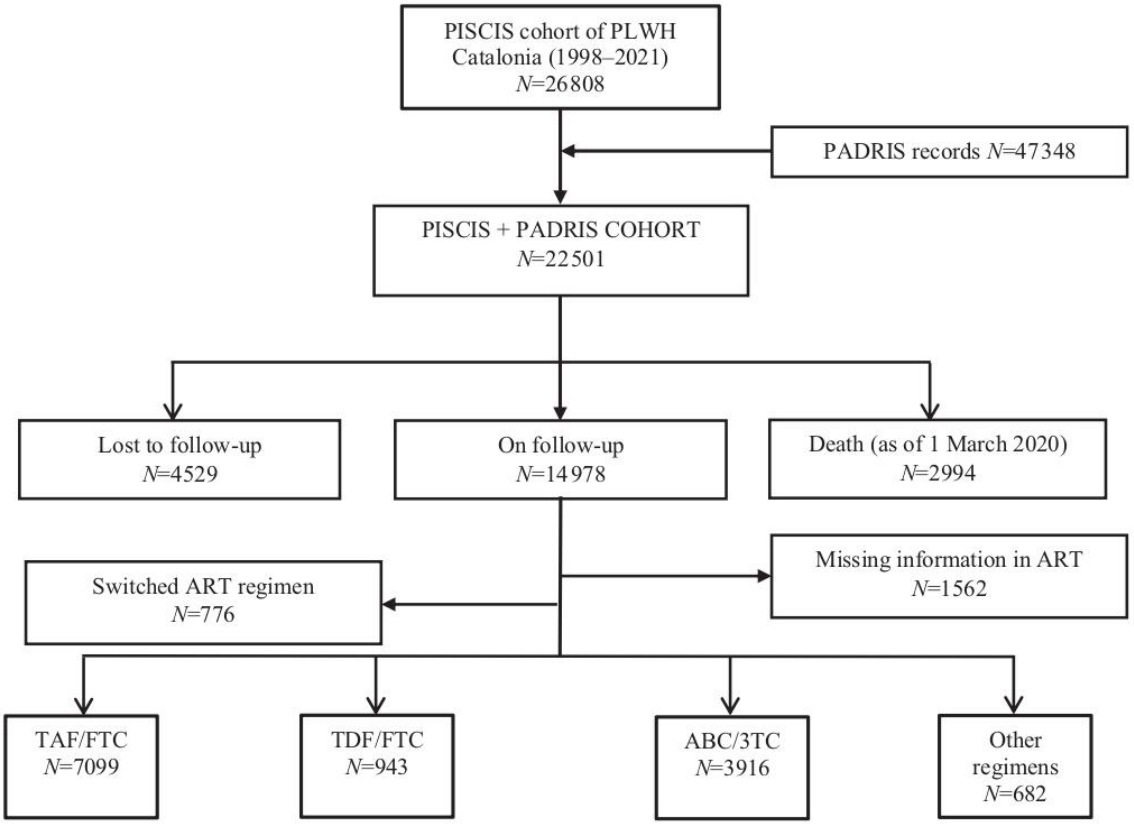

Figure 1. Flow diagram of people living with HIV in the PISCIS cohort in Catalonia showing the reception ART regimens and inclusion into the analysis. Abbreviations: PADRIS, Analytical Data for Research and Innovation in Health Project of Catalonia; ART, antiretroviral therapy; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ABC/3TC, abacavir/lamivudine.

compared using the Kruskal Wallis test. We performed four rounds of propensity-score matching for TAF/FTC versus ABC/3TC and a single round for TDF/FTC versus ABC/3TC and TAF/FTC versus TDF/FTC using nearest-neighbour algorithms with a calliper width of 0.1 of the pooled standard deviations to ensure that key baseline characteristics of the groups were adequately balanced. We matched patients by sex, age, plasma HIV-RNA [detectable and undetectable (HIV RNA <50 copies/mL)], and number of comorbidities (none, one, two, three, four or more). We did three separate propensity score matches in a ratio 1:1 for TAF/FTC versus ABC/3TC, and 1:3 for TDF/FTC versus ABC/3TC, and TDF/FTC versus TAF/FTC. To evaluate the effect of ART regimens on SARS-CoV-2 diagnosis and severe outcomes, we used Cox regression models and provided adjusted odds ratios (aOR) and unadjusted odds ratios (uOR) along with their 95% confidence intervals (95% CI) to remove residual confounding.[18] We adjusted for the factors that were significantly different after propensity score matching. We adjusted for country of origin, socioeconomic status, CD4 count (continuous variable), time in years on ART, CD4/CD8 ratio, diabetes, chronic kidney disease, and metabolic disease. In multivariable analysis, we removed the time since HIV diagnosis due to collinearity with the time in years on ART (Table S2). Records of missing values for adjustment covariates were excluded in adjusted analyses, as they were few and not expected to affect estimates significantly. A two-sided *P* value <0.05 was considered statistically significant. We performed all statistical analyses using R Statistical Software version 4.0.2.

Ethics

The PISCIS cohort study was approved by the Ethics Committee of the Germans Trias i Pujol University Hospital, Badalona, Spain (EO-11–108). Data collection was also approved by the ethics committees of participating hospitals. Patient-level information obtained from PADRIS was anonymized and de-identified before the analysis. This study follows the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.[19] The planning, conduct, and reporting of the study was in line with the Declaration of Helsinki, as revised in 2013.

Access to data

The study protocol is available from Dr Juliana Reyes-Urueña (e-mail: jmreyes@iconcologia.net). Statistical code for the analysis can be requested from Yesika Diáz, Sergio Moreno, and Jordi Aceiton (ydiazr@iconcologia.net, smorenof@iconcologia.net, jaceiton@igtp.cat). The data for this study is available at the Centre for Epidemiological Studies of Sexually Transmitted Diseases and HIV/AIDS in Catalonia (CEEISCAT),

the coordinating centre of the PISCIS cohort and from each of the collaborating hospitals upon request via https://pisciscohort.org/contacte/.

Results

Out of 14 978 PLWH (median age: 46.4 years, male sex: 82.1%) on follow-up in our cohort, 1562 had missing information on ART, 776 had switched their ART regimen at least once during the study period, and 11 958 were included in the present analysis. Of them, 7099 were treated with TAF/FTC, 943 with TDF/FTC, 3916 with ABC/3TC, and 682 were receiving other regimens (Figure 1). PLWH receiving TDF/FTC were younger (median age 44.6 years) compared with those receiving TAF/FTC (45.6 years) or ABC/3TC (48.2 years) ($P<0.001$). Individuals receiving TDF/FTC had a lower number of comorbidities than those receiving TAF/FTC or ABC/3TC ($P<0.001$) and significantly different socioeconomic deprivation (Table S3).

Of the patients included in the analysis, 1445 (12.1%) individuals had tested positive for SARS-CoV-2 as of 18 July 2021, of whom 670 (46.4%) were asymptomatic, 630 (43.6%) were symptomatic with mild disease requiring community management, and 145 (10.0%) were hospitalized. In the latter, 7 (0.5%) were admitted to the ICU, and 20 (1.4%) died.

Out of 7099 PLWH receiving TAF/FTC, 3512 were matched 1:1 to an equal number of ABC/3TC recipients ($n=3512$). Out of 943 TDF/FTC recipients, 763 were matched 1:3 to 2289 ABC/3TC recipients; and 770 TDF/FTC recipients were matched 1:3 to 2310 TAF/FTC recipients. No key covariates exhibited major imbalances (standard mean difference <0.1) (Figure S1). The baseline characteristics of the propensity score-matched groups are presented in Table 1.

TAF/FTC was not associated with a reduction in SARS-CoV-2 diagnosis (aOR 0.90; 95% CI, 0.78–1.04) or associated hospitalization (aOR 0.93; 95% CI, 0.60–1.43) compared with ABC/3TC in adjusted analysis. TDF/FTC compared with ABC/3TC was not associated with a reduction in SARS-CoV-2 diagnosis (aOR 0.79; 95% CI, 0.60–1.04) or hospitalization (aOR 0.51; 95% CI, 0.15–1.70). We finally compared the association between TDF/FTC and TAF/FTC in adjusted analysis. TDF/FTC was not associated with a reduction in SARS-CoV-2 diagnosis (aOR 0.79; 95% CI, 0.60–1.04) or associated hospital admissions (aOR 0.33; 95% CI, 0.10–1.07) compared with TAF/FTC (Table 2).

Discussion

We assessed the association between current TAF/FTC and TDF/FTC treatment and SARS-CoV-2 diagnosis and COVID-19 outcomes in a prospective multicentre cohort of PLWH using a propensity score-matched approach. TAF/FTC and TDF/FTC were not significantly associated with a reduction in SARS-CoV-2 diagnosis and poorer COVID-19-related outcomes including hospitalizations, ICU admissions, and death among PLWH. We found no significant association either when TAF/FTC or TDF/FTC were compared with ABC/3TC or against each other.

Importantly, we found significantly lower rates of SARS-CoV-2 infection and associated hospitalizations in unadjusted analyses among those receiving TDF/FTC. Compared with patients receiving TAF/FTC and ABC/3TC, those receiving TDF/FTC were significantly younger, and had a lower number and prevalence of comorbidities. When the analysis was adjusted for these variables, the potential protective effect disappeared. This finding supports that the differences in baseline factors intrinsically associated with lower SARS-CoV-2 infection rates and more benign SARS-CoV-2 infection outcomes constitute a channelling bias that could have influenced many previous analyses that indicated that TDF could have a protective role against SARS-CoV-2 infection, but lacked an adequate adjustment of these variables that are directly correlated with the primary outcome.[7,11]

Analyses performed in PrEP studies with TDF/FTC, such as PREVENIR-ANRS and SAPRIS-Sero[14] sub-study from France, where these biases do not exist, found no reduced risk in SARS-CoV-2 infection among TDF/FTC PrEP users.

Similarly, TDF/FTC in our study reduced COVID-19-associated hospitalizations in unadjusted analysis but not in adjusted analysis, which is contrary to previous large studies.[7,11] As previously discussed, the lack of adjustment for baseline patient characteristics probably influenced the results of the study from del Amo *et al.*[7] by confounding and channelling bias. In the subsequent large study from the Western Cape, South Africa,[11] there was an adjustment for kidney disease, viral suppression, and antiretroviral treatment. Zidovudine use (the alternative to TDF), however, was preferentially prescribed to individuals with prior virologic failure as per the WHO guidelines[20] and can be associated with higher rates of tuberculosis, both of which were not adjusted for in that study.

The rationale behind the possible protective benefits of tenofovir was a result of the potential activity that the nucleotide analogue showed against SARS-CoV-2 in pre-clinical studies and animal models (ferrets)[4,21] and the more potent immunomodulatory effects of TDF[22] including the decreased production of interleukin-8 and -10,[23] and the higher penetration into mucosal tissues.[24] However, in a recent analysis, none of these drugs (TAF, TDF or FTC) showed any significant *in vitro* anti-SARS-CoV-2 effect at concentrations up to 100-fold higher than the clinically relevant levels.[6] These results are corroborated by the lack of interaction between the respective NRTI-triphosphates and SARS-CoV-2 RdRp observed both in biochemical assays and in structural modelling analyses.[6]

Our finding that TAF does not prevent SARS-CoV-2 diagnosis or severe disease is in-line with a report from Ayerdi *et al.*[13] who actually found a higher SARS-CoV-2 seroprevalence among HIV-negative PrEP users receiving TAF or TDF versus those without PrEP. That study also demonstrated no differences in terms of clinical manifestations between people receiving tenofovir (TAF or TDF) and those not on tenofovir.[13]

The study by del Amo *et al.*[7] found a lower risk for SARS-CoV-2 diagnosis among persons receiving TDF/FTC compared with those on other regimens. SARS-CoV-2 diagnosis in Spain has also been disproportionately affected by sociodemographic factors including country of origin and socioeconomic status in both the general population[25] and among PLWH.[15] The del Amo *et al.*[7] study did not adjust for these sociodemographic factors.

In recent findings from a clinical trial involving 30 participants on TDF/FTC and a control group of 30 participants on standard of care therapy, TDF/FTC did not expedite the natural clearance of nasopharyngeal SARS-CoV-2 viral load at day 4 (primary endpoint), there were no differences in the time to symptom recovery nor in the hospitalization rates.[26] However, there was a

significantly greater increase in the Ct RT-PCR on the seventh day, with an effect corresponding to approximately 0.8 $\log_{10}$ decrease of SARS-CoV-2 RNA, a reduction of unknown microbiological or clinical relevance.

Our study is limited by its epidemiological nature, depriving us of having information on treatment adherence and exposure to SARS-CoV-2, which are both relevant given the objectives of our study. Secondly, assessing the association between ART and SARS-CoV-2 infection is challenging in a scenario where not everyone is tested equally for SARS-CoV-2. For example, testing could be more frequent among patients with higher risks of poor COVID-19 outcomes. The identification of a higher incidence of SARS-CoV-2 infection and associated hospitalizations in unadjusted analyses that disappears in the propensity score matching and adjusted Cox regression models suggests that indeed subjects treated with TDF have intrinsic characteristics that lend them a lower risk for SARS-CoV-2 infection or poorer COVID-19 outcomes. Our analyses demonstrate that failure to evaluate potential sociodemographic and clinical confounding factors can bias observational study results and lead to erroneous inferences.

In conclusion, the use of TAF/FTC or TDF/FTC among PLWH was not associated with a reduction in SARS-CoV-2 diagnosis or poorer COVID-19 outcomes including hospital and ICU admissions or death. Until well-designed randomized clinical trials reveal new robust evidence, existing preventive measures and treatment approaches for PLWH against SARS-CoV-2 infection should be maintained, independent of tenofovir exposure.

Acknowledgements

We thank the Public Data Analysis for Health Research and Innovation Program of Catalonia (PADRIS) and the Programme for the Prevention, Control and Care for HIV, Sexually Transmitted Diseases and Viral Hepatitis (PCAVIHV) of the Ministry of Health, Government of Catalonia for their support.

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Funding

This work was supported by Fundació 'La Caixa' (grant number: COVIHCAT). The funder of the study had no role in study design, data collection, data analysis, data interpretation, or report writing.

Transparency declarations

J.M.M. reported receiving a personal 80:20 research grant from Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, during 2017–22 and consulting honoraria and/or research grants from Angelini, Contrafect, Genentech, Gilead Sciences, Jansen, Lysovant, Medtronic, MSD, Novartis, Pfizer, and ViiV Healthcare, outside the submitted work. P.D. reported that his institution received grants from Gilead Sciences, Janssen & Cilag, and ViiV Healthcare; and he personally received honoraria from Gilead Sciences, Janssen & Cilag, MSD, ViiV Healthcare, Roche, and Thera Technologies. A.I. reported that his institution received grants from Gilead Sciences and MSD; and he personally received consultation fees from Gilead Sciences, ViiV Healthcare, and Thera Technologies; honoraria for lectures and presentations from Gilead Sciences, MSD, Jansen, and ViiV Healthcare; travel support for attending meetings from Gilead Sciences, Jansen, and ViiV Healthcare. J.M.L. has received honoraria from Gilead Sciences, Janssen-Cilag, and ViiV Healthcare outside of the present work. J.N. has received honoraria and/or speakers' fees from Abbvie, Gilead, Janssen-Cilag, Merck Sharp & Dohme and ViiV Healthcare outside of the submitted work. All other authors: none to declare.

Author contributions

D.K.N., J.R.U., Y.D., and J.M.M. conceived and designed the study. D.K.N., J.R.U., Y.D. had full access to all of the study data, verified the data, and take responsibility for the integrity of the data and the accuracy of the data analysis. D.K.N., J.R.U., Y.D., S.M. and J.A. performed the analyses. D.K.N. and J.R.U. wrote the first draft of the paper and incorporated revisions. All authors contributed to the interpretation of results. All authors critically revised and approved the final manuscript.

Supplementary data

Figure S1 and Tables S1 to S4 are available as Supplementary data at *JAC* Online.

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Article 4

SARS-CoV-2 vaccination coverage and factors associated with low uptake in a cohort of people living with HIV

Article IV

SARS-CoV-2 vaccination coverage and factors associated with low uptake in a cohort of people living with HIV

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Microorganisms. 2022 Aug 18;10(8):1666.

Summary

In Spain, Catalonia is one of the most affected autonomous communities with the current COVID-19 pandemic. The region also has one of the highest HIV new diagnoses rates in the country. In recent studies from Catalonia PLWH tested less frequently for SARS-CoV-2 compared to the general HIV-negative population and sub-populations of PLWH like immigrants, the elderly, those with comorbidities, detectable HIV viremia, and low CD4 cell count were more vulnerable to poor COVID-19 prognosis. A report from the WHO found that PLWH had a 30% higher risk of dying from COVID-19 after hospital admission than people without HIV. The SARS-CoV-2 vaccines provide protection against COVID-19 being effective against symptomatic infection and severe outcomes. PLWH especially those with cellular immunodeficiency were prioritized for vaccine eligibility in many countries because of their probable high risk to severe COVID-19 outcomes. Therefore, epidemiological surveillance of vaccination coverage and timely identification of suboptimally vaccinated PLWH is vital.

Prior to this analysis, we found 28 articles about SARS-CoV-2 vaccines in HIV-infected individuals. Four of these studies assessed vaccine hesitancy and acceptance among people living with HIV (PLWH), one study investigated the immunological changes in an HIV-infected patient post SARS-CoV-2 vaccination, one study developed a national strategy to effectively disseminate vaccines among PLWH, and the other studies mainly evaluated immune responses to SARS-CoV-2 vaccines. However, none of the existing studies reported vaccine coverage, evolution, and barriers to access PLWH or described COVID-19 outcomes among vaccinated PLWH compared to unvaccinated.

To our knowledge, our study is the first reporting SARS-CoV-2 vaccination coverage and factors associated with low vaccine uptake in a prospective cohort of PLWH. The study also describes COVID-19 outcomes (SARS-CoV-2 diagnosis, associated hospital admissions, intensive care unit admission, and death) among vaccinated PLWH compared to the unvaccinated. Between December 27, 2020 and July 11, 2021, 9945 (66.6%) of PLWH in our cohort had received at least one dose of a SARS-CoV-2 vaccine. Non-Spanish origin (adjusted odds ratio [aOR] 0.64, 95% CI 0.59-0.70); CD4 count of 200-349 cells/μL (aOR 0.74, 95% CI 0.64-0.86) or 350-499 cells/μL (aOR 0.79, 95% CI 0.70 - 0.88); detectable plasma HIV-RNA (aOR 0.61 95% CI 0.53-0.70); and previous SARS-CoV-2 diagnosis (aOR 0.58 95% CI 0.51-0.65) were associated with under-vaccination. SARS-CoV-2 diagnosis (437 [9.5%] vs. 323 [3.5%], P<0.001), associated hospitalisations (10[2.3%] vs. 0[0%], P <0.001), intensive care unit ad-missions (6[1.4%] vs. 0[0%], P<0.001), and deaths (10[2.3%] vs. 0[0%], P<0.001) were higher among unvaccinated PLWH. Vaccination coverage was lower among PLWH with CD4 count >200 cells/μL, detectable plasma HIV-RNA, previous SARS-CoV-2 diagnosis, and migrants. SARS-CoV-2 diagnosis, associated hospitalisations, and deaths among PLWH were lower among vaccinated compared to the unvaccinated.

In conclusion, our study reveals that a 66.6% of PLWH in our cohort had received at least one dose of a SARS-CoV-2 vaccine as of July 11, 2021 mirroring what happened in the general population.

Nevertheless, non-Spanish origin, CD4 cell count >200 cells per μL, detectable plasma HIV-RNA, and previous SARS-CoV-2 diagnosis were associated with lower vaccination coverage suggesting that vaccine strategies towards PLWH has been driven by general criteria and not taking into account specific vulnerability factors. Our data confirms the benefits of the SARS-CoV-2 vaccine also to PLWH and reinforce the need to proactively identify PLWH at-risk for under-vaccination and to design targeted public health strategies to improve vaccine uptake in these specific socio-demographic and clinical groups.

microorganisms

MDPI

Article

SARS-CoV-2 Vaccination Coverage and Factors Associated with Low Uptake in a Cohort of People Living with HIV

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† The PISCIS Study Group is provided in the Acknowledgments.

Citation: Nomah, D.K.; Llibre, J.M.; Díaz, Y.; Moreno, S.; Aceiton, J.; Bruguera, A.; Gutiérrez-Macià, M.; Imaz, A.; Suanzes, P.; Navarro, G.; et al. SARS-CoV-2 Vaccination Coverage and Factors Associated with Low Uptake in a Cohort of People Living with HIV. *Microorganisms* **2022**, *10*, 1666. https://doi.org/10.3390/microorganisms10081666

Academic Editor: Paweł Stefanoff

Received: 22 June 2022
Accepted: 16 August 2022
Published: 18 August 2022

Abstract: People living with HIV (PLWH) are prioritised for SARS-CoV-2 vaccination due to their vulnerability to severe COVID-19. Therefore, the epidemiological surveillance of vaccination coverage and the timely identification of suboptimally vaccinated PLWH is vital. We assessed SARS-CoV-2 vaccination coverage and factors associated with under-vaccination among PLWH in Catalonia, Spain. As of 11.12.2021, 9945/14942 PLWH (66.6%) had received ≥1 dose of a SARS-CoV-2 vaccine. Non-Spanish origin (adjusted odds ratio (aOR) 0.64, 95% CI 0.59–0.70), CD4 count of 200–349 cells/μL (aOR 0.74, 95% CI 0.64–0.86) or 350–499 cells/μL (aOR 0.79, 95% CI 0.70–0.88), detectable plasma HIV-RNA (aOR 0.61 95% CI 0.53–0.70), and previous SARS-CoV-2 diagnosis (aOR 0.58 95% CI 0.51–0.65) were associated with under-vaccination. SARS-CoV-2 diagnosis (437 [9.5%] vs. 323 [3.5%], $p < 0.001$), associated hospitalisations (10 [2.3%] vs. 0 [0%], $p < 0.001$), intensive care unit admissions (6 [1.4%] vs. 0 [0%], $p < 0.001$), and deaths (10 [2.3%] vs. 0 [0%], $p < 0.001$) were higher among unvaccinated PLWH. Vaccination coverage was lower among PLWH with a CD4 count >200 cells/μL, detectable plasma HIV-RNA, previous SARS-CoV-2 diagnosis, and migrants. SARS-CoV-2 diagnosis, associated hospitalisations, and deaths among PLWH were lower among the vaccinated compared with the unvaccinated. SARS-CoV-2 vaccination prioritisation has not completely reached vulnerable PLWH with poorer prognosis. This information can be used to inform public health strategies.

Keywords: HIV; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); coronavirus disease 2019 (COVID-19); vaccination; vaccine effectiveness

1. Introduction

The World Health Organization (WHO) [1] and the US Center for Disease Control and Prevention (CDC) [2] recommend that people living with HIV (PLWH) are prioritised for SARS-CoV-2 vaccination because of the evidence of their vulnerability to severe COVID-19. Older people infected with HIV, and those with comorbidities, detectable HIV viremia, or advanced immunodeficiency are especially susceptible to a poor COVID-19 prognosis [2,3]. SARS-CoV-2 vaccines provide an opportunity to minimise transmission and severe clinical outcomes from COVID-19, proving their efficacy in clinical trials [4,5] and in real-world settings [6,7]. In an earlier WHO report, out of 100 pooled countries, 40 had prioritised PLWH, especially those with a lower CD4 cell count, for vaccination against SARS-CoV-2 [8].

As of the time of writing, the European Medicines Agency has authorised the Pfizer-BioNTech, Moderna, AstraZeneca/Oxford, and Janssen SARS-CoV-2 vaccines for use in the European Union [9].

These authorised vaccines have no contraindications for use among PLWH, and studies among PLWH receiving mRNA- and adenovirus-based vaccines have shown no safety concerns [10,11]. There are conflicting data regarding the response elicited by SARS-CoV-2 vaccines in PLWH. Some studies have found no difference in anti-SARS-CoV-2 IgM, IgG, and IgA antibody kinetics, peak titres, or neutralisation activity in PLWH compared with individuals who are HIV-negative [12]. However, other studies found that humoral and cellular immune response in PLWH correlates with the CD4 cell count levels with response being significantly weaker in those with a CD4 < 200 cells per μL [13].

In Spain, a technical working group was set up to provide strategic recommendations on the mass vaccine rollout with the objective of reducing COVID-19 morbidity and mortality and protecting the most vulnerable groups [14]. The national vaccination program started on 27 December 2020, initially prioritising older adults, health and socio-sanitary professionals, residents and staff of senior and disability care homes, and highly dependent people not living in care homes, due to vaccine shortage [14]. The vaccines were originally administered in hospitals and primary care centres, and subsequently at established mass vaccination centres. Regardless of the place of administration, all vaccination information is recorded in the individuals' primary care records. By 31 August 2021, the Spanish government's target of fully vaccinating 70% of the total population had been achieved [15].

The vaccination campaign prioritised the population based on older age, chronic comorbidities, and the nature of jobs, not on HIV seropositivity [14]. On 21 March 2021, PLWH with a CD4 cell count fewer than 200 cells per μL and those less than 60 years old with chronic comorbidities were included in vaccination priority groups [14]. Nevertheless, there is little information on how vaccines reached specific vulnerable sub-groups.

Reports from previous studies show lower rates of vaccination for other infectious diseases among PLWH compared with the general HIV-negative population, despite their increased risk of infections [16]. Some of the concerns raised by PLWH about vaccinations include fear of clinical side effects, uncertainty about worsening the prognosis of HIV infection, and worry about poor immune response due to their compromised immune systems [17,18].

The epidemiological surveillance of vaccination coverage among PLWH and the timely identification of suboptimally-vaccinated sub-groups is important because social and cultural differences present in this population could make vaccines inaccessible to them, according to reports of vaccine hesitancy in this population [19]. To address this in Catalonia, we assessed the SARS-CoV-2 vaccination coverage in the PISCIS cohort of PLWH in Catalonia, Spain, to describe the distribution and identify sociodemographic, clinical, and epidemiological factors associated with low vaccination uptake. Additionally, we compared SARS-CoV-2 diagnosis and associated clinical outcomes among vaccinated and unvaccinated PLWH without a previous SARS-CoV-2 infection in our cohort.

2. Materials and Methods

2.1. Study Design and Participants

We conducted a retrospective study leveraging the unique dataset of the PISCIS cohort linked with several administrative health databases (primary care, SARS-CoV-2 vaccination, laboratory, emergency room use, infectious diseases surveillance registries, in-patient hospitalisation, pharmacy, and mortality) under the Public Data Analysis for Health Research and Innovation Program of Catalonia, Spain (PADRIS) [20]. Detailed information about the PISCIS cohort and PADRIS has been described in a previous study [3]. Briefly, the PISCIS cohort is an open, prospective, multicentre, population-based, observational cohort study that follows PLWH aged ≥16 years receiving care at 16 collaborating hospitals in Catalonia. The cohort, which was started in 1998, includes about 80% of all PLWH in Catalonia. The study period was between 27 December 2020, the day that the National Vaccination Program started in Spain, and 11 July 2021. For the purposes of this study, we only included patients who were on clinical follow-up (patients who had used the public healthcare system in the last 18 months).

2.2. Procedures

We extracted data on vaccination (type and dates of vaccination), comorbid conditions, SARS-CoV-2 diagnosis confirmed by nucleic acid amplification test (NAAT) and/or antigen detection, and associated clinical outcomes (hospital admissions (more than 24 h with suspicion of respiratory infection and any of the following signs: dyspnea, tachypnea, hypoxemia, asphyxia, or hyperventilation) and intensive care unit (ICU) admission (suffered respiratory failure or sepsis) and death) from the PADRIS. The primary outcome was the reception of a SARS-CoV-2 vaccine (as a binary: vaccinated or unvaccinated). In our analysis, participants were considered vaccinated if they had received a first dose of the Pfizer-BioNTech, Moderna, or Oxford-AstraZeneca SARS-CoV-2 vaccines or the single dose of the Janssen SARS-CoV-2 vaccine. Fully vaccinated individuals were those who had received at least two doses of the Pfizer-BioNTech, Moderna, or Oxford-AstraZeneca SARS-CoV-2 vaccines or a single dose of the Janssen SARS-CoV-2 vaccine. We included data of potential confounders to enable adjusted analyses. Data on sociodemographic characteristics (age, sex, country of origin, and socioeconomic deprivation), HIV-associated variables (median years since HIV diagnosis, HIV exposure risk groups (people who inject drugs (PWID), men who have sex with men (MSM), male heterosexual, female homo/hetero/bisexual), median years on antiretroviral therapy (ART), current ART, most recent CD4 cell count (categorised <200 cells per μL, 200–349 cells per μL, 350–499 cells per μL, and ≥500 cells per μL), plasma HIV-RNA (detectable and undetectable (HIV-RNA of ≤50 copies/mL)), chronic comorbidities, and previous laboratory-confirmed SARS-CoV-2 diagnosis were included. We used the international classification of diseases clinical modifications 9 (ICD-9-CM) and 10 (ICD-10-CM) to extract chronic comorbidities. The ICD classification system was modified to group the most prevalent chronic comorbidities in our population into 11 groups (Supplementary Table). We counted the number of comorbidities and categorised them into no comorbidities, one comorbidity, two comorbidities, three comorbidities, and four or more comorbidities. We classified socioeconomic deprivation in tertiles (least deprived, mildly deprived, and most deprived) according to the socioeconomic deprivation level index of the Catalan government based on health area of residence (ABS) [21].

2.3. Statistical Analysis

We described the baseline characteristics of the vaccinated and unvaccinated groups using proportions. We presented descriptive statistics as the median and interquartile ranges (IQR) for continuous variables and frequencies for categorical variables. Proportions for categorical variables were compared using the $\chi 2$ or Fisher's exact test where appropriate. Continuous variables were compared using the Mann–Whitney U test. We used univariable and multivariable logistic regression models to assess the factors

associated with vaccination coverage. In the multivariable model, we adjusted for sex, age, country of origin, socioeconomic deprivation, HIV-exposure group, CD4 levels, plasma HIV RNA, number of chronic comorbidities, and previous SARS-CoV-2 diagnosis. We calculated odds ratios (OR) with 95% confidence intervals (CI) to assess the strength of association. We compared SARS-CoV-2 diagnosis among vaccinated and unvaccinated PLWH without a previous SARS-CoV-2 diagnosis. Among those with confirmed SARS-CoV-2 diagnosis, we compared associated hospital admissions, ICU admissions, and death between the two groups. Records of missing values for adjustment covariates were excluded in the adjusted analyses, as there were few of them and they were not expected to affect estimates significantly. The level of significance of p was set at <0.05. We used the R studio software version 4.0.2 to perform all the analyses.

2.4. Ethics Statement

The Institutional Review Board of Germans Trias i Pujol Hospital, Badalona, Spain has approved the PISCIS cohort study (EO-11-108). Patient-level information obtained from PADRIS was anonymised and deidentified before the analysis. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [22].

3. Results

3.1. Characteristics of the Study Population

A total of 14,942 PLWH were on clinical follow-up in our cohort as of December 2020. These consisted of 12,257 (82.0%) males, with a median age of 46.4 years. The major transmission group was MSM (52.7%), followed by heterosexual males (13.8%), and 6132 (41.0%) were of non-Spanish origin. Almost half (48.1%) of our study population had a high socioeconomic class, with minimal socioeconomic deprivation. Those in our study population had lived with HIV for a median duration of 11.0 years (IQR 5.7–17.7 years). The median CD4 count was 680.0 cells/μL, with 3069 (20.5%) having CD4 levels of <200 cells/μL. Plasma HIV-RNA was undetectable in 11,891 (79.6%) patients. Regarding comorbidities, 4849 (32.5%) PLWH were without comorbidities (Table 1).

Table 1. Baseline characteristics of people living with HIV in Catalonia according to SARS-CoV-2 vaccine status (December 2020–July 2021).

	Overall Cohort (n = 14,942)	Vaccinated [x] (n = 9945)	Unvaccinated (n = 4997)	*p* Value
Characteristic	**n (%)**	**n (%)**	**n (%)**	
Sex [a]				<0.001
Male	12257 (82.0)	8271 (83.2)	3986 (79.8)	
Female	2684 (18.0)	1673 (16.8)	1011 (20.2)	
Missing	1 (0.01)	1 (0.01)	0 (0)	
Age, median (IQR), y [b]	46.4 (38.3–54.2)	49.0 (41.4–55.8)	40.8 (32.8–49.3)	<0.001
Age category, y [b]				<0.001
16–39	4479 (30.0)	2106 (21.2)	2373 (47.5)	
40–64	9593 (64.2)	7124 (71.6)	2469 (49.4)	
65–74	678 (4.5)	553 (5.6)	125 (2.5)	
≥75	192 (1.3)	162 (1.6)	30 (0.6)	
Country of origin [c]				<0.001
Spain	8808 (59.0)	6409 (64.4)	2399 (48.0)	
Outside Spain	6132 (41.0)	3535 (35.6)	2597 (52.0)	
Unknown	2 (0.01)	1 (0.01)	1 (0.02)	
Socioeconomic deprivation				
Least deprived	7188 (48.1)	4749 (47.8)	2439 (48.8)	0.52
Mildly deprived	2839 (19.0)	1997 (20.1)	842 (16.9)	
Most deprived	4574 (30.6)	2962 (29.8)	1612 (32.3)	

Missing	341 (2.3)	237 (2.4)	104 (2.1)	
HIV transmission route				<0.001
PWID	1727 (11.6)	1200 (12.1)	527 (10.6)	
MSM	7835 (52.4)	5281 (53.1)	2554 (51.1)	
Male heterosexual	2055 (13.8)	1391 (14.0)	664 (13.3)	
Female hetero/homo/bisexual	2008 (13.4)	1266 (12.7)	742 (14.9)	
Other	856 (5.7)	534 (5.4)	322 (6.4)	
Missing	461 (3.1)	273 (2.8)	188 (3.8)	
CD4 count (cells/μL) category				<0.001
<200	3069 (20.5)	2051 (20.6)	1018 (20.4)	
200–349	1266 (8.5)	802 (8.1)	464 (9.3)	
350–499	2066 (13.8)	1341 (13.5)	725 (14.5)	
≥500	7833 (52.4)	5425 (54.6)	2408 (48.2)	
Missing	708 (4.7)	326 (3.3)	382 (7.6)	
HIV-RNA				<0.001
Detectable	1476 (9.9)	783 (7.9)	693 (13.9)	
Undetectable	11891 (79.6)	8317 (83.6)	3574 (71.5)	
Missing	1575 (10.5)	845 (8.5)	730 (14.6)	
Number of comorbidities				<0.001
0	4849 (32.5)	2735 (27.5)	2114 (42.3)	
1	3661 (24.5)	2422 (24.4)	1239 (24.8)	
2	2596 (17.4)	1878 (18.9)	718 (14.4)	
3	1602 (10.7)	1201 (12.1)	401 (8.0)	
≥4	2234 (15.0)	1709 (17.2)	525 (10.5)	
Previous SARS-CoV-2 diagnosis				<0.001
Yes	1610 (10.8)	878 (8.8)	732 (14.7)	
No	13332 (89.2)	9067 (91.2)	4265 (85.4)	

Abbreviations: PLWH, people living with HIV; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IQR, interquartile range; PWID, people who inject drugs; MSM, men who have sex with men. [a] Sex at birth as registered in the health registries of the participating hospitals was used. One participant in the overall cohort had an unknown sex. [b] Age for all patients was as of December 1, 2020. [c] Country of origin was as indicated by the Public Data Analysis for Health Research and Innovation Program of Catalonia (PADRIS) recorded as Spanish or Non-Spanish. [x] ≥1 dose of SARS-CoV-2 vaccine.

3.2. SARS-CoV-2 Vaccination

Between 27 December 2020 and 11 July 2021, 9945 out of 14,942 PLWH (66.6%) in our cohort received at least one dose of a SARS-CoV-2 vaccine. The findings showed that 6949 (69.9%) were fully vaccinated and 2996 (30.1%) had received a first dose (Supplementary Table). Vaccination among PLWH in Catalonia peaked between 14 and 20 June 2021 (week 24) (Figure 1). A majority of our cohort received the Pfizer-BioNTech vaccine (56.7%), followed by Moderna (23.2%), AstraZeneca (12.9%), and Janssen (7.2%).

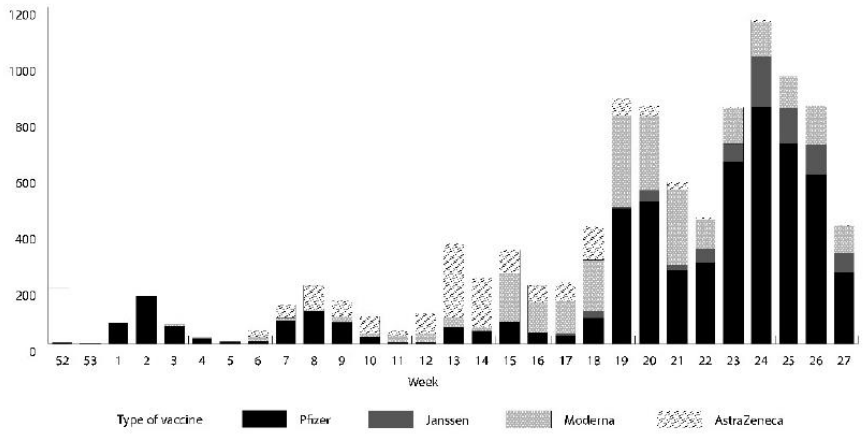

Figure 1. Number of vaccinated people living with HIV in Catalonia by manufacturer and calendar week (Week 52: 21–27 December 2020; Week 27: 5–11 July 2021).

Vaccination was less common among females (62.3%) than males (67.5%) ($p < 0.001$) (Figure 2).

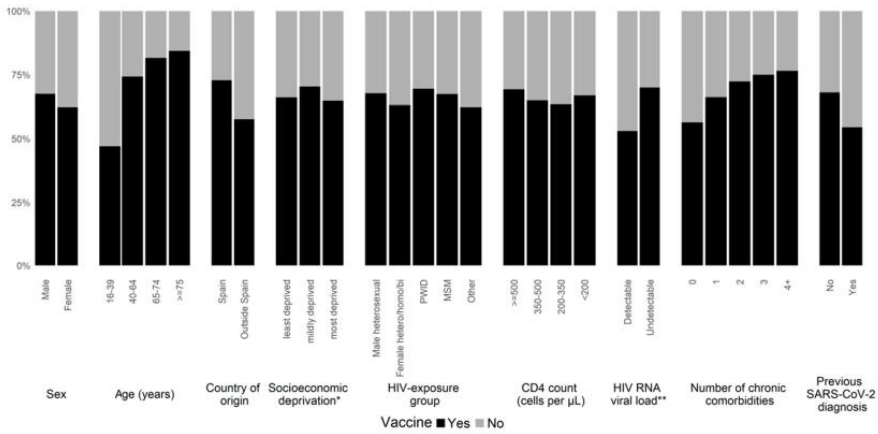

Figure 2. SARS-CoV-2 vaccination uptake according to various sociodemographic and clinical groups in the PISCIS cohort of people living with HIV (27 December 2020–11 July 2021). Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PWID, people who inject drugs; MSM, men who have sex with men; * According to the socioeconomic deprivation level index of the Catalan government based on the health area of residence. ** plasma HIV-RNA undetectable: ≤50 copies/mL.

The median age in the vaccinated population was higher (49.0 years, IQR 41.4–55.8) than in the unvaccinated population (40.8 years, IQR 32.8–49.3) $p < 0.001$). The proportion of migrants was higher in the unvaccinated group compared with the vaccinated group (52.0% vs. 35.6%, $p < 0.001$). Vaccination uptake was similar across all socioeconomic deprivation categories ($p = 0.52$). Regarding HIV exposure groups, we observed a slightly higher vaccination uptake among PWID (69.5%), followed by heterosexual males (67.7%), MSM (67.4%), and female hetero/homo/bisexuals (63.0%). CD4 cell levels were higher among the vaccinated than the unvaccinated (median 689.0 cells per µL vs. 662.0 cells per µL, $p < 0.001$). Vaccination coverage was higher among PLWH with undetectable plasma HIV-RNA compared with those with unsuppressed HIV viraemia (69.9% vs 53.3%, $p <$

0.001). We found a higher coverage among PLWH with comorbidities than those without (72.5% vs. 57.7%, $p < 0.001$). Vaccination coverage increased with an increasing number of comorbidities (no comorbidities: 56.4%; one comorbidity: 66.2%; two comorbidities: 72.3%; three comorbidities: 75.0%; four or more comorbidities: 76.5%) (Figure 2). Among vaccinated PLWH in our cohort, 1057 (10.6%) had previous SARS-CoV-2 infection, and this was higher among unvaccinated patients (732/4997, 14.7%, $p < 0.001$) (Table 1).

3.3. Factors Associated with Low Uptake of SARS-CoV-2 Vaccines

In order to identify sub-groups that could be undervaccinated, we used multivariable logistic regression analysis. After controlling for possible confounding factors, PLWH were found to be less likely to receive the SARS-CoV-2 vaccine if they were born outside of Spain (aOR 0.64, 95% CI 0.59–0.7), had a CD4 cell count of 200–349 cells per μL (aOR 0.74, 95% CI 0.64–0.86) or 350–499 cells per μL (aOR 0.79, 95% CI 0.70–0.88), detectable plasma HIV-RNA (aOR 0.61, 95% CI 0.53–0.70) or a previous SARS-CoV-2 diagnosis (aOR 0.58, 95% CI 0.51–0.65). Vaccine coverage was likely to increase with increasing age groups (40–64 years (aOR 3.01, 95% CI 2.75–3.30), 65–74 years (aOR 3.77, 95% CI 3.01–4.77), and ≥75 years (aOR 5.77, 95% CI 3.27–8.24)), and was associated with male sex (aOR 1.39, 95% CI 1.12–1.72). We also observed a higher odds of vaccine coverage among PLWH with mild socioeconomic deprivation (aOR 1.21, 95% CI 1.08–1.35), MSM (aOR 1.43, 95% CI 1.26–1.62) and those with comorbid conditions (one comorbidity (aOR 1.28, 95% CI 1.16–1.43), two comorbidities (aOR 1.58, 95% CI 1.39–1.78), three comorbidities (aOR 1.58, 95% CI 1.36–1.84), or four or more comorbidities (aOR 1.58, 95% CI 1.37–1.83)) (Table 2).

Table 2. Factors associated with SARS-CoV-2 vaccine coverage among people living with HIV in Catalonia in multivariable logistic regression.

Characteristics		OR	aOR [a]
Sex	Female	1.00 (ref)	1.00 (ref)
	Male	1.25 (1.15–1.37)	1.39 (1.12–1.72)
Age category, y	16–39	1.00 (ref)	1.00 (ref)
	40–64	3.25 (3.02–3.50)	3.01 (2.75–3.30)
	65–74	4.98 (4.08–6.13)	3.77 (3.01–4.77)
	≥75	6.08 (4.17–9.19)	5.08 (3.27–8.24)
Country of origin	Spain	1.00 (ref)	1.00 (ref)
	Outside Spain	0.51 (0.48–0.55)	0.64 (0.59–0.70)
Socioeconomic deprivation	Least deprived	1.00 (ref)	1.00 (ref)
	Mildly deprived	1.22 (1.11–1.34)	1.21 (1.08–1.35)
	Most deprived	0.94 (0.87–1.02)	0.97 (0.88–1.07)
HIV transmission route	Male heterosexual	1.00 (ref)	1.00 (ref)
	Female hetero/homo/bisexual	0.81 (0.72–0.93)	1.14 (0.88–1.48)
	PWID	1.09 (0.95–1.25)	0.87 (0.74–1.03)
	MSM	0.99 (0.89–1.09)	1.43 (1.26–1.62)
	Other	0.79 (0.67–0.94)	1.06 (0.87–1.30)
CD4 count (cells/μL) category	≥500	1.00 (ref)	1.00 (ref)
	350–499	0.82 (0.74–0.91)	0.79 (0.70–0.88)
	200–349	0.77 (0.68–0.87)	0.74 (0.64–0.86)
	<200	0.89 (0.82–0.98)	0.92 (0.83–1.02)
HIV RNA viral load	Undetectable	1.00 (ref)	1.00 (ref)
	Detectable	0.49 (0.44–0.54)	0.61 (0.54–0.69)
Number of comorbidities	0	1.00 (ref)	1.00 (ref)
	1	1.51 (1.38–1.65)	1.28 (1.16–1.43)
	2	2.02 (1.82–2.24)	1.58 (1.39–1.78)
	3	2.31 (2.04–2.63)	1.58 (1.36–1.84)
	≥4	2.52 (2.25–2.82)	1.58 (1.37–1.83)

SARS-CoV-2 diagnosis	No previous SARS-CoV-2 diagnosis	1.00 (ref)	1.00 (ref)
	Previous SARS-CoV-2 diagnosis	0.56 (0.51–0.63)	0.58 (0.51–0.65)

Abbreviations: PLWH, people living with HIV; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, Coronavirus disease 2019; PWID, people who inject drugs; MSM, men who have sex with men; [a] Model adjusted for sex, age, country of origin, socioeconomic deprivation, HIV-exposure group, CD4 levels, HIV RNA viral load, chronic comorbidities, and previous SARS-CoV-2 diagnosis.

3.4. SARS-CoV-2 Outcomes among Vaccinated and Unvaccinated People Living with HIV

SARS-CoV-2 diagnosis (437 (9.5%) vs. 323 (3.5%), $p < 0.001$), associated hospitalisations (10 (2.3%) vs. 0 (0%), $p < 0.001$), intensive care unit admissions (6 (1.4%) vs. 0 (0%), $p < 0.001$), and deaths (10 (2.3%) vs. 0 (0%), $p < 0.001$) were higher among the unvaccinated PLWH compared with the vaccinated (Table 3).

Table 3. SARS-CoV-2 diagnosis and associated clinical outcomes among people living with HIV vaccinated and unvaccinated against COVID-19 (27 December 2020–11 July 2021).

	Total n = 13,662	**Unvaccinated PLWH n = 4596**	**Vaccinated PLWH n = 9066**	
	n (%)	**n (%)**	**n (%)**	***p***
SARS-CoV-2 diagnosis	616 (4.5)	437 (9.5)	179 (2.0)	<0.001
COVID-19 hospital admissions	10 (1.6)	10 (2.3)	0 (0)	<0.001
COVID-19 ICU admissions	6 (1.0)	6 (1.4)	0 (0)	<0.001
COVID-19 deaths	10 (1.6)	10 (2.3)	0 (0)	<0.001

Abbreviations: PLWH, people living with HIV; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, Coronavirus disease 2019; ICU, intensive care unit.

4. Discussion

While our study in this large cohort of PLWH revealed that a majority (66.6%) of the population had received a SARS-CoV-2 vaccine as of 11 July 2021, coverage in some specific groups might not be optimal. We observed lower uptake among those with a CD4 cell count of >200 cells per μL, detectable plasma HIV-RNA, previous SARS-CoV-2 diagnosis, and migrants. Furthermore, SARS-CoV-2 diagnoses, associated hospitalisations, ICU admissions, and deaths were lower among vaccinated PLWH compared with the unvaccinated.

Astounding evidence establishes vaccines as one of the most successful and cost-effective health interventions ever [23]. In the case of COVID-19, the vaccines offer promising prospects to beat a pandemic that has threatened overall stability globally and caused overwhelming morbidity and mortality [24–27].

The government of Spain set out a vaccination strategy that sought to vaccinate those most vulnerable to SARS-CoV-2 first and met its goal of fully vaccinating at least 70% of the total population by 31 August 2021 [28]. Even though the vaccine rollout started slowly in the first few months in Spain due to a severe vaccine shortage, the procurement of more vaccines by the government, the introduction of mass vaccination centres, and the resolution of logistical barriers accelerated the vaccine uptake steadily from April/May 2021, with the vaccination peak in Spain coinciding with the observed vaccination peak in our cohort. The peak period also coincides with the vaccination period for people aged 40–59 years in Catalonia and Spain [28]. This age group contributes to more than half of the overall PISCIS cohort and that could be an additional reason explaining the peak in vaccinations in June among our population. The 66.6% vaccination coverage observed in our cohort as of 11 July 2021 is similar to that in the Catalonian general population, with a coverage of 67.7% (at least one dose) as of the same week [29].

Regardless of the fairly comparable coverage between the general population and PLWH in Catalonia, almost all persons aged 60 years and above in Spain had received at least one vaccine dose against SARS-CoV-2 as of 14 July 2021 (98.1%) [29], but that was not the case in our cohort (overall 80%). PLWH aged 60 years and above were called from their respective primary care centres and subsequently from the HIV units in the various hospitals, suggesting that the suboptimal coverage in this group is because of hesitancy.

Existing studies have identified migrants as a vulnerable group for COVID-19 in the general population [30] and among PLWH [3]. Not unexpectedly, we found a lower vaccination uptake in this group. Migrants face systemic healthcare access barriers and are affected by varying social determinants of health, which could hamper their access to SARS-CoV-2 vaccines. Some studies have also found higher vaccine hesitancy and low vaccination coverage among migrants and other ethnic minority groups [31]. This finding is concerning and calls for action and further investigation to understand the low acceptance and barriers to healthcare and vaccine access among migrants living with HIV.

We anticipated that all PLWH with CD4 levels <200 cells per μL would be vaccinated by 11 July 2021, because this group is prioritised for vaccination in Spain due to their vulnerability to COVID-19 [14]. In our cohort, however, a third of the population had not received the vaccine as of this date despite being prioritised in public health strategies. We were also concerned to find that unsuppressed HIV viraemia was associated with lower vaccination coverage. Non-HIV suppression and lower CD4 cell counts are associated with drug abuse, social determinants, poor treatment, and follow-up compliance, and hence poor health care in general, and could explain why coverage was lower in these groups. A study from Catalonia identified detectable plasma HIV RNA as a risk factor for poor COVID-19 prognosis [3]. Given the increased risk for COVID-19-associated morbidity and mortality in these clinical groups, addressing SARS-CoV-2 vaccination barriers in these subpopulations is crucial.

Our study revealed that PLWH with a previous SARS-CoV-2 diagnosis were less likely to be vaccinated. As of 11 July 2021, the vaccination protocol for persons less than 65 years of age previously infected with SARS-CoV-2 in Spain was a single dose six months after the confirmed SARS-CoV-2 diagnosis [14]. This could explain why the vaccine coverage is lower among previously infected people.

The lower rates of SARS-CoV-2 diagnosis, associated hospital admissions, ICU admissions, and deaths among vaccinated PLWH compared with the unvaccinated is an important indication of the benefits achieved with SARS-CoV-2 vaccines in this population. Further studies assessing vaccine effectiveness among PLWH and the effect of vaccination on poor clinical outcomes in real-world settings are vital.

Our multicentre cohort study had some limitations. Given the importance of clinical variables in understanding the subgroups with suboptimal vaccination coverage, we excluded patients who had not used the public healthcare system in Catalonia in the past 18 months. We therefore could be over-estimating the vaccination coverage in our population. We also do not have information on individuals who were vaccinated outside the Catalonia autonomous region because, in Spain, the 17 Autonomous Communities are responsible for offering integrated healthcare services to the regional population and managing their public healthcare system. Another important limitation of our study was our inability to evaluate the immunological response to vaccines among PLWH over time and in specific clinical groups such as those with CD4 cells less than 200 cells/mm^3 and unsuppressed HIV viremia. Vaccination reception can be influenced by level of education, income, and religious beliefs. We were limited by our inability to control for these factors due to the nature of cohort studies among human populations.

In conclusion, our study reveals that a majority (66.6%) of PLWH in our cohort had received at least one dose of a SARS-CoV-2 vaccine as of 11 July 2021 and significantly lower SARS-CoV-2 diagnosis, associated hospitalisations, and deaths were observed among vaccinated PLWH compared with the unvaccinated, mirroring what happened in the general population. Nevertheless, non-Spanish origin, a CD4 cell count >200 cells per μL, detectable

plasma HIV-RNA, and a previous SARS-CoV-2 diagnosis were associated with lower vaccination coverage, suggesting that vaccine strategies towards PLWH have been driven by general criteria and not taking specific vulnerability factors into account. Our data confirm the benefits of the SARS-CoV-2 vaccine also to PLWH and reinforce the need to proactively identify PLWH at risk for under-vaccination and to design targeted public health strategies to improve vaccine uptake in these specific socio-demographic and clinical groups.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/microorganisms10081666/s1, Table S1: Baseline characteristics of people living with HIV in Catalonia according to reception of a single dose or full vaccination (December 2020–July 2021); Table S2: Eleven groups of the most prevalent chronic comorbidities among people living with HIV in Catalonia with corresponding International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9/10-CM) codes. Table S3: Baseline characteristics of people living with HIV in Catalonia according to SARS-CoV-2 vaccine status (27 December–July 2021).

Author Contributions: Conceptualisation, D.K.N., J.R.-U., J.M.L. and Y.D.; methodology, D.K.N., J.R.-U., J.M.L. and Y.D.; formal analysis, J.R.-U., J.M.L., S.M., J.A. and Y.D.; investigation, D.K.N., J.R.-U. and J.M.L.; resources, D.K.N. and J.R.-U.; data curation, S.M., J.A., the PISCIS Study Group and Y.D.; writing—original draft preparation, D.K.N. and J.R.-U.; writing—review and editing, D.K.N., J.R.-U., A.B., M.G.-M., A.I., P.S., G.N., A.O. and J.M.L.; visualisation, Y.D.; supervision, J.R.-U., J.C., J.M.M. and J.M.L.; project administration, D.K.N., J.R.-U. and J.M.L.; funding acquisition, J.R.-U. and J.M.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Fundació La Marató de TV3, grant number 202117-30-31. The Fundació La Marató de TV3 had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Institutional Review Board Statement: The Institutional Review Board of Germans Trias i Pujol Hospital, Badalona, Spain has approved the PISCIS cohort study (EO-11-108). Patient-level information obtained from PADRIS was anonymised and deidentified before the analysis.

Data Availability Statement: The study protocol is available from Reyes-Urueña (e-mail: jmreyes@iconcologia.net). Statistical code for the analysis can be requested from Yesika Diáz, Sergio Moreno, and Jordi Aceiton (ydiazr@iconcologia.net, smorenof@iconcologia.net, jaceiton@igtp.cat). The data for this study are available at the Centre for Epidemiological Studies of Sexually Transmitted Diseases and HIV/AIDS in Catalonia (CEEISCAT), the coordinating centre of the PISCIS cohort and from each of the collaborating hospitals upon request via https://pisciscohort.org/contacte/.

Acknowledgments: We want to thank the Public Data Analysis for Health Research and Innovation Program of Catalonia (PADRIS) and the Programme for the Prevention, Control and Care for HIV, Sexually Transmitted Diseases and Viral Hepatitis (PCAVIHV) of the Ministry of Health, Government of Catalonia for their support. The PISCIS Study Group: Esteve Muntada, Anna Esteve, Francisco Fanjul, Vicenç Falcó, Hernando Knobel, Josep Mallolas, Juan Tiraboschi, Adrià Curran, Joaquín Burgos, Boris Revollo, Maria Gracia, Maria del Mar Gutierrez, Javier Murillas, Francisco Homar, Jose V. Fernández-Montero, Eva González, Joaquim Peraire, Lluís Force, Elena Leon, Miquel Hortos, Ingrid Vilaró, Amat Orti, David Dalmau, Àngels Jaen, Elisa De Lazzari, Leire Berrocal, Lucía Rodríguez, Freya Gargoulas, Toni Vanrell, Jose Carlos, Josep Vilà, Marina Martínez, Bibiana Morell, Maribel Tamayo, Jorge Palacio, Juan Ambrosioni, Montse Laguno, María Martínez-Rebollar, José L. Blanco, Felipe Garcia, Berta Torres, Lorena de la Mora, Alexy Inciarte, Ainoa Ugarte, Iván Chivite, Ana González-Cordon, Lorna Leal, Antoni Jou, Eugènia Negredo, Maria Saumoy, Ana Silva, Sofia Scévola, Paula Suanzes, Patricia Alvarez, Isabel Mur, Melchor Riera Jaume, Mercedes García-Gasalla, Maria À. Ribas, Antoni A. Campins, María Peñaranda, María L. Martin, Helem Haydee, Sònia Calzado, Manel Cervantes, Marta Navarro, Antoni Payeras, Carmen Cifuentes, Aroa Villoslada, Patrícia Sorní, Marta Molero, Nadia Abdulghani, Thaïs Comella, Rocio Sola, Montserrat Vargas, Consuleo Viladés, Anna Martí, Elena Yeregui, Anna Rull, Pilar Barrufet, Laia Arbones, Elena Chamarro, Cristina Escrig, Mireia Cairó, Xavier Martinez-Lacasa, Roser Font, Lizza Macorigh, Juanse Hernández.

Conflicts of Interest: J.M.M. reported receiving a personal 80:20 research grant from Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, for 2017–2023 and consulting honoraria and/or research grants from Angelini, Contrafect, Genentech, Gilead Sciences, Jansen, Lysovant, Medtronic, MSD, Novartis, Pfizer, and ViiV Healthcare, outside the submitted

work. A.I. reported that his institution received grants from Gilead Sciences and MSD, and he personally received consultation fees from Gilead Sciences, ViiV Healthcare, and Thera Technologies; honoraria for lectures and presentations from Gilead Sciences, MSD, Jansen, and ViiV Healthcare; travel support for attending meetings from Gilead Sciences, Jansen, and ViiV Healthcare. J.M.L. has received honoraria from Gilead Sciences, Janssen-Cilag, and ViiV Healthcare outside of the present work. P.S. has received speaking fees from Merck Sharp & Dome, Janssen-Cilag, Gilead Sciences, and ViiV Healthcare; consulting honoraria from Merck Sharp & Dome; travel support for attending meetings from Gilead Sciences and Angelini Pharma; and a grant from ViiV Healthcare outside of the submitted work. For the remaining authors, no conflicts of interest were declared. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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4. DISCUSSION

In this chapter, the major findings of this doctoral dissertation, the impact of SARS-CoV-2 on HIV from both clinical and public health, are discussed. The chapter briefly summarizes key aspects to improve both the clinical management and public health response with regards to HIV/SARS-CoV-2 co-infection among HIV vulnerable populations and PLWH; SARS-CoV-2 outcomes between PLWH and the general HIV-negative population; risk factors of severe COVID-19 among PLWH; the potential effect of tenofovir; and SARS-CoV-2 vaccination among PLWH. The chapter also comments on the significance of these findings, their implications on Public Health, and limitations of the thesis. Lastly, recommendations and directions for future research studies vital to address the remaining challenges.

4.1. Overall discussion

The COVID-19 pandemic and the measures taken to curb its transmission unintendedly affected key HIV care and testing services. Physicians and other health care workers who would usually provide HIV care were involved in treating COVID-19 patients whilst some HIV centers across the globe were converted to COVID-19 quarantine and treatment centers. When preparing for the next pandemic, it will be crucial to find contingency plans to handle similar situations. In some settings, different eHealth and telemedicine approaches were employed to minimize the effect of the breakdown in key health services. Regarding testing for example, in Catalonia, the "testate" program [223] permitted the request for HIV and other infectious diseases testing right from home to deal with the possible closure of testing centers at the heights of the pandemic. The pandemic also revealed the importance of robust surveillance systems that capture epidemiological, microbiological, clinical, vaccination, and mortality. The impact of SARS-CoV-2 on HIV remained unclear partly because of the lack of large and quality data that capacitates the analysis and generation of important new knowledge. All earlier reported data were case studies or cohort studies involving very few patients. Steps should be taken to make existing surveillance registries of PLWH similar if not universal across countries to make data sharing easier and posit us to understand important trends among PLWH who remain vulnerable to different infections because of their compromised immune systems.

The comparison of COVID-19 outcomes between PLWH and the general HIV-negative population demonstrated that HIV itself might not be a risk factor for SARS-CoV-2 acquisition or the development of a poor prognosis. Hospital and ICU admissions were similar in the two populations with lower mortality observed among PLWH. The initial warnings of the potential risk of HIV-infected persons to COVID-19 was a good call due to uncertainties regarding the role of impaired immune function in SARS-CoV-2 infection and clinical prognosis. Nevertheless, PLWH with HIV viral suppression, high CD4 cell count, and receiving ART might have outcomes similar to that of the HIV general population. Testing was however lower in this population despite their potential higher risk. Even though in Catalonia, HIV positivity was not criteria for SARS-CoV-2 testing, there is a possibility that this group is being left out

of important health and social programs as observed in other contexts [224,225]. The higher test positivity rate found among PLWH shows their higher exposure to SARS-CoV-2. Given the importance of timely diagnosis vis-à-vis disease outcomes and the potential risk of severe outcomes from some sub-populations, it will be essential for public health testing strategies in times of pandemics to target potentially vulnerable populations like PLWH.

The different sociodemographic, immunological, and clinical characteristics associated with a SARS-CoV-2 infection or a severe outcome could provide knowledge on the interaction between HIV and SARS-CoV-2. The inconsistency in existing data could mean that the effect of SARS-CoV-2 is different in varying sub-populations of PLWH. Both low CD4 and detectable HIV viraemia are indicators of poor HIV treatment outcomes [226,227]. Our studies showing that both populations are more prone to severe COVID-19 is disturbing considering this group is also at a higher risk for other opportunistic infections [228,229]. COVID-19 prevention strategies among PLWH should therefore be focused on this population. Targeted intervention for prevention and management should employ a syndemic approach as this group of PLWH have been reported to face other social determinants of health including homelessness, lower socioeconomic levels, and more prevalent alcoholism and smoking [230,231]. All these factors could increase their exposure to SARS-CoV-2 diagnosis and severe clinical outcomes. Other non-HIV-related variables that were found to be associated with severe COVID-19 were older age and the presence of chronic comorbidities. These have been also reported in the general population since the early days of the pandemic. With the majority of PLWH ageing and a substantial number of newly diagnosed cases in Europe being among relatively older individuals, away from COVID-19, HIV management should integrate practices to curb that promote quality of life and healthy aging among elderly PLWH. One observation in our studies that has also been observed in previous pandemics [232] is how migrants are disproportionately affected. Migrants were more likely to get a SARS-CoV-2 infection, severe COVID-19, or not receive a SARS-CoV-2 vaccine compared to the host Spanish population. Migrants have an increased risk of infectious diseases due to structural barriers, socioeconomic inequalities, and linguistic barriers which limit their access to healthcare services [233,234]. Other reports have evidently demonstrated that migrants are more likely to be diagnosed with late HIV which can affect their CD4 levels and viral load at baseline making them prone to a poorer prognosis. The current COVID-19 pandemic has affected migrants and ethnic minorities in different countries [235–239]. However, unlike in other settings, universal access to health services is free and universally accessible to all. There is therefore the need to unravel the unequal effect of the pandemic on these two populations.

Since the emergence of SARS-CoV-2 variants that can escape vaccine immunity, finding therapy options for SARS-CoV-2 became even more important. TDF/FTC has been postulated as a potential treatment option showing protective effects in large cohort studies. Our analysis showed protection from TDF/FTC in unadjusted analysis but after adequate adjustments for residual confounding, the

association diminished. Similar reports have been found in HIV-negative individuals where these confounders do not exist. The findings show the importance of confounding in observational studies. The validity of such studies depends on the ability to limit potential confounding. The findings suggest that TDF/FTC users had baseline characteristics that reduce their risk of SARS-CoV-2 infection and severe COVID-19. Switching of ART regimen of HIV patients to include TDF/FTC is currently not warranted until a well-designed RCT reveals new evidence.

In the absence of widely available precise medicines to manage COVID-19, the vaccines available have significantly improved our immunity to SARS-CoV-2 protecting populations from severe diseases, offering health systems and world economies to restart, and reducing the risk of poor outcomes from emerging variants. Spain has met the WHO mid-2022 targets for global vaccination coverage [240] but our analysis highlighted that some key sub-populations among PLWH could be missing out. We found that vaccination coverage was lower among PLWH with CD4 cell count >200 cells/μL, detectable plasma HIV-RNA, previous SARS-CoV-2 diagnosis, and migrants. It will be important for HIV units to implement strategies that target these populations with low uptake especially those who have a high risk of severe COVID-19 outcomes. National and regional vaccination needs to be updated regularly as new data and knowledge unfold.

4.2. Thesis strengths

This dissertation addresses the interplay between SARS-CoV-2 in HIV, a topic of vital importance with equivocal data reported to date. Continued research adjusted for potential confounders was, therefore, crucial to address vital unanswered questions regarding HIV and SAR-CoV-2 infection. PLWH, at the beginning of the COVID-19 pandemic, was considered a vulnerable group for both SARS-CoV-2 infection and severe outcomes compared to the general HIV-negative population. Even though subsequent reports from large studies suggested increased mortality among PLWH, these studies were limited by important confounding factors and the involvement of only hospitalised patients. Reports on testing at the beginning of the pandemic among PLWH were lacking as data usually focused on hospitalised patients possibly masking the knowledge of the true effect of the pandemic in this population. Understanding the vulnerability presented by SARS-CoV-2 on HIV amidst speculated protection from some ART regimens and the impact of HIV markers is critical to inform clinical practice and enhance public health response. Therefore, this dissertation represents vital work on the clinical and public health impact of SARS-CoV-2 on HIV and the potential benefits of tenofovir-based ART and vaccination against SARS-CoV-2 diagnosis and severe COVID-19.

Leveraging data from the PISCIS cohort and the PADRIS, we have been able to determine that PLWH were not prioritised for SARS-CoV-2 testing despite their potential susceptibility highlighting how this population could be affected by other social determinants of health. PLWH also presented with higher test positivity rates compared to the HIV-negative general population which makes the situation more worrying and shows that future public health strategies should target this population when planning interventions for pandemic management. Hospitalizations, ICU admissions, and mortality were however not higher among PLWH compared to the general population showing that higher rates of poor COVID-19 outcomes might be influenced by severe COVID-19 risk factors including comorbid conditions and the variations in other health determinants in the populations studied.

The thesis has also brought some clarity to the matter regarding the impact of specific HIV markers, CD4 count, and plasma HIV viral load on COVID-19 severity. The study found that low CD4 count (<200 cells per μL) and detectable plasma HIV viral load were associated with worse outcomes from HIV/SARS-CoV-2 co-infection. Notably, low CD4 count (<200 cells per μL) was not associated with severe outcomes among patients with HIV virologic suppression. The findings from our study were vital in prioritising PLWH with immunosuppression and unsuppressed HIV viremia for vaccination against SARS-CoV-2 and clinical management of COVID-19 in Catalonia and across Spain [241].

Additionally, the dissertation establishes that ART regimen of PLWH should not be altered to include tenofovir because of speculated protective effects. We found that tenofovir recipients have intrinsic characteristics associated with more benign SARS-CoV-2 infection outcomes and reported protective effects from other studies are not as a result of antiviral activity from tenofovir but from factors that were

not adequately adjusted for in these observational studies. Also, even though findings from this dissertation show that SARS-CoV-2 vaccination coverage among PLWH mirrored the uptake in the general population, coverage was significantly lower among PLWH of non-Spanish origin, those with a CD4 cell count of >200 cells per μL, detectable plasma HIV-RNA, and previous SARS-CoV-2 diagnosis suggesting that vaccination programs for PLWH have been driven by general criteria and not taking into account specific vulnerability factors.

The studies have illuminated how health inequalities have been amplified by the COVID-19 pandemic with increased diagnosis, disease severity, and lower uptake among migrants compare to the indigenous Spanish PLWH. Beyond the results presented in this dissertation, the methodology employed in the tenofovir study provides an essential contribution to current literature on the effect of tenofovir on SARS-CoV-2 outcomes. The PISCIS-PADRIS cohort offered a unique opportunity to employ propensity-score matching techniques and further adjustments to reduce residual confounding whilst maintaining a good power to perform the analysis. The results show that failure to evaluate potential confounding factors can bias observational study results and lead to erroneous inferences.

4.3. Thesis limitations

Specific limitations in the analyses for chapters three to six are included within each chapter. However, after summarising this dissertation research, there are some general limitations that can be addressed in future research.

To begin, our analyses are limited by the constraints inherent to the use of electronic medical records. However, PISCIS and PADRIS data undergo robust data quality control measures and standardised criteria are used to identify cases. Also, variables that were likely to suffer from documentation errors were excluded from the analyses. Furthermore, the sample sizes of the studies are relatively large and should mitigate any data pollution arising from documentation errors.

Secondly, the PISCIS cohort utilises longitudinal, population-based data on PLWH receiving care from 16 HIV units in Catalonia. The data collected does not include information on some factors that could influence exposure to SARS-CoV-2 like occupation, household size, and conditions at the place of work. Given the objectives of this dissertation, this information is vital. To mitigate the potential influence of the absence of SARS-CoV-2 exposure variables, we included the socioeconomic deprivation variable in our study. Socioeconomic deprivation was an ecological variable classified according to the socioeconomic level index created by the AQuAS based on the basic health area (ABS) of residence in Catalonia [242]. The place of residence, however does not always predict the socioeconomic level of an individual.

There are important variables that were absent from our databases. Smoking and BMI were notably absent from our study data. Other studies have found an association between these factors and COVID-19 severity. We were not able to appropriately control for these variables in our analyses.

Estimates of SARS-CoV-2 testing and diagnosis in this dissertation could be an underestimation of actual figures. In the early days of the pandemic in Spain, access to testing was based on the presence of signs and symptoms of COVID-19, nature of jobs (priority given to workers in geriatric care homes and health facilities), age, presence of comorbidities, and contact tracing. Asymptomatic COVID-19 cases therefore could have gone undiagnosed. Also, only cases that were diagnosed through the Catalan Health System will be captured in our databases. People who tested for SARS-CoV-2 in private facilities including pharmacies and other autonomous communities in Spain were not captured. Testing policies and restrictions in Spain could impact the reported burden of SARS-CoV-2 among PLWH inferring that only those with moderate to severe disease were reported at the beginning of the pandemic.

Additionally, in the PLWH study population, female patients were under-represented making it challenging to extrapolate the findings of this study to other contexts with a high HIV burden among women. Finally, comparative assessments of SARS-CoV-2 testing, outcomes, and vaccination will be

stronger in matched analysis between PLWH and the general HIV-negative population of Catalonia which is lacking in the studies from chapters three and six.

Beyond these limitations, the data presented and the analyses included in this dissertation have significant implications and important findings for public health and clinical care. These are further discussed below in the next section.

4.4. Implications for public health

SARS-CoV-2 testing was lower among people living with HIV compared to the general HIV-negative population during the early stages of the pandemic in Catalonia, Spain. PLWH, despite their speculated vulnerability to SARS-CoV-2 during the early days of the pandemic in Spain, were not prioritised for SARS-CoV-2 testing. This population is also affected by other social and structural determinants which limit their access to health services. Testing in times of public health emergencies is important for potentially vulnerable populations to timely manage cases and prevent poorer clinical course and reduce mortality risk. There are logistical challenges during such times with limited diagnostic testing to assess and prevent the spread of infections within high-risk communities. Delayed diagnosis of SARS-CoV-2 has been associated with severe COVID-19 clinical outcomes [243]. Currently (March 1, 2022), rapid SARS-CoV-2 antigen tests are widely available in pharmacies across Spain with the government regularizing their pricing and offering free tests to some groups to ensure wider access [244,245]. Measures on testing during public health emergencies should be inclusive to reach high-risk populations such as PLWH.

Regardless of the lower testing observed, the analyses in this dissertation found a higher test positivity among PLWH. The incidence of SARS-CoV-2 among PLWH differs across study populations, which is probably driven by variation in access to testing and the prevalence of SARS-CoV-2 risk factors. Epidemiological surveillance reporting sociodemographic, biological, and clinical information should be enhanced globally to be able to robustly answer such important questions timely.

Available information suggests that current EMA-recommended vaccines are not less safe for use in PLWH. Additionally, there are currently no reports of pharmacological interactions between ART and SARS-CoV-2 vaccines [156]. The vaccine coverage in Catalonia among PLWH was similar to that reported in the general population. With emerging evidence reporting a higher risk of worse outcomes from COVID-19 among PLWH, efforts should have been made to reach higher coverage than the reported. Worryingly, some subpopulations including migrants and those with detectable HIV plasma viral load were under-vaccinated. These groups have been identified as high-risk populations for severe COVID-19 and public health policies on vaccination among PLWH should be restrategised to ensure equitable access to such sub-populations. Additionally, the findings of poorer outcomes among unvaccinated PLWH demonstrate that access to vaccinations in this population will help to minimize the risk of SARS-CoV-2 infection and severe COVID-19.

4.5. Implications on clinical care

It was unknown at the beginning of the current pandemic whether PLWH are at greater risk of acquiring SARS-CoV-2 infection or severe clinical outcomes. There were conflicting reports on the vulnerability on PLWH receiving tenofovir and those with advanced immunosuppression (i.e., <200 cells/mm^3).

In the first study, we observed similar rates of hospitalization and ICU admission, and lower deaths between PLWH and the general HIV-negative population. This suggests that the reported increased risk of severe clinical outcomes from HIV/SARS-CoV-2 infection might not be due to HIV per se but as a result of the disproportionate burden of chronic comorbidities and other negative health determinants associated with severe COVID-19. It is recommended that PLWH follow all applicable recommendations as the general population to prevent acquisition of SARS-CoV-2, such as practicing social or physical distancing, wearing masks consistently, avoiding crowded areas, and using proper hand hygiene.

This dissertation also demonstrated that chronic comorbidities, detectable HIV viraemia, and immunosuppression are at an increased risk of severe outcomes. These factors have also been associated with poor prognosis of different co-conditions [246,247]. It is therefore important that efforts towards meeting the 90-90-90 targets are intensified to ensure that PLWH in care, take their ART medications and attain suppressed HIV viraemia. Also, measures should be put in place for timely diagnosis of other chronic comorbidities and given full consideration in clinical management. PLWH with comorbid conditions, detectable HIV viraemia, and advanced immunosuppression should also be prioritised for COVID-19 risk reduction, including vaccination and clinical management.

The speculation of probable benefits from tenofovir has lacked convincing evidence with prior studies lacking the ability to adjust for residual confounders. It has remained a key unanswered question with some researchers postulating a possible switch of ART regimen among PLWH to include tenofovir, especially TDF. We did not observe a significant association between the use of tenofovir and SARS-CoV-2 diagnosis or severe COVID-19. Clinical care of PLWH co-infected with SARS-CoV-2 receiving tenofovir should not be different from those not on tenofovir. SARS-CoV-2 preventive measures should also remain the same for both tenofovir users and non-users.

5. MAIN CONCLUSIONS

1. PLWH in Catalonia, Spain at the early phases of the pandemic, tested less for SARS-CoV-2 compared to the general HIV-negative population but reported higher positivity rates. In terms of hospital and ICU admissions, the rates were similar in the two populations. Mortality was lower among PLWH compared to the general population. Given the potential vulnerability of PLWH to other infections, pubic health strategies should target such groups and further research including matched analysis will be vital to understand the susceptibility of PLWH to SARS-CoV-2.

2. Among PLWH, the risk of a SARS-CoV-2 diagnosis was higher among migrants, having ≥4 chronic comorbidities, and MSM. Among PLWH co-infected with COVID-19, those with CD4 count <200 cells per μL, detectable plasma HIV viral load, older age, non-Spanish origin, and neuropsychiatric, autoimmune, respiratory, and metabolic disease had a higher risk of severe outcomes. Lower CD4 was associated with severe COVID-19 but notably, not among those with undetectable viral load. HIV in essence might not be a risk factor for SARS-CoV-2 acquisition or poor outcomes but PLWH with detectable HIV viraemia, chronic comorbidities, and some subpopulations could be at increased risk of severe outcomes from COVID-19. These groups should be prioritized in clinical management and considered a target group for SARS-CoV-2 prevention programs including vaccination.

3. We found no significant assoication between tenofovir, either as TAF/FTC or TDF/FTC and a reduced SARS-CoV-2 diagnosis or poorer COVID-19 outcomes including hospital and ICU admissions or death among PLWH. Significant differences existed until the models were adjusted for possible residual confounders evidencing potential intrinsic characteristics of TDF/FTC making them less prone to SARS-CoV-2 infections and severe outcomes. Treatment approaches and control measure of PLWH against SARS-CoV-2 should not be changed until well-designed randomized clinical trials reveal new contrary evidence.

4. SARS-CoV-2 vaccination coverage among PLWH in Catalonia mirrored the observed coverage in the general population but coverage was significantly lower among those with detectable HIV viremia, CD4 >200, previous SARS-CoV-2 díagnosis, and migrants. SARS-CoV-2 diagnosis, hospitalizations, ICU admissions, and associated mortality were higher among unvaccinated PLWH compared to those vaccinated. Vaccine strategies for PLWH should not be driven by general national vaccination policies but take into account specific vulnerability factors. There is a need take actions that can identify under-vaccinated populations and to improve vaccine uptake in these specific socio-demographic and clinical groups.

6. RECOMMENDATIONS

Further research and action will be vital to strengthen current evidence and better understand the interplay between SARS-CoV-2 and HIV including the impact of vaccination on specific HIV groups. The scientific knowledge generated will be essential to guide clinical management and advise policies regarding SARS-CoV-2 treatment and vaccination among PLWH. The knowledge produced will also assist efforts to strategically design interventions that can improve the health of PLWH amidst the COVID-19 global threat. The following are some of the clinical and policy recommendations and future research directions emerging from this dissertation.

6.1. Clinical and policy recommendations

- There is an urgent need to build resilient health systems that ensure that PLWH is able to stay linked to their local HIV units even in the times of health crises like COVID-19 and establish robust epidemiological surveillance that enhances our ability to monitor the two infections assiduously.

- Testing in times of public health emergencies should be enhanced to reach vulnerable populations including PLWH.

- HIV itself might not be a risk factor for SARS-CoV-2 infection or severe COVID-19 but PLWH with chronic comorbidities, detectable viraemia, and advanced immunosuppression could be at an increased risk to pooer outcomes and should therefore be priotised in the clinical management of COVID-19 and vaccination against SARS-CoV-2.

- Treatment of PLWH should not be modified to include tenofovir until well-designed randomized control trials reveal different evidence as a significant association between TAF or TDF and SARS-CoV-2 was not established. PLWH receiving tenofovir should follow prescribed SARS-CoV-2 preventive measures as adhered to by the general population.

- SARS-CoV-2 vaccination coverage among PLWH in Catalonia was similar to the observed in the general population but sub-populations like migrants and those with unsuppressed HIV viraemia had reduced uptake. These populations are at an increased risk of severe COVID-19 and targeted public health strategies should be implemented to improve vaccine uptake in these specific socio-demographic and clinical groups.

- Efforts should be made to address health inequalities among migrants living with HIV having suffered a higher risk of SARS-CoV-2 diagnosis, severe COVID-19, and lower vaccination coverage.

6.2. Future research directions

This thesis has addressed several noteworthy gaps of interest regarding HIV and SARS-CoV-2 co-infection, yet, as with all research, there are further research areas that can be addressed, buidling on from these findings. Some of these may be partially addressed via ongoing research which has emerged as part of this dissertation and literature on this topic is growing exponentially over time, given the huge public health urgency. With access to diverse and updated data, key unanswered questions could be answered timely.

- Emerging data from observational cohorts from the USA and Europe presented conflicting reports on COVID-19 severity in PLWH compared to the HIV-negative population [88,159,162,163,248]. These studies have however involved only hospitalised patients and were limited by the inability to adjust for important confounders [88,159,162,163,248]. A recent study from Yang *et al* [249] provided a better analysis in a study from the USA involving 1,436,622 adults with COVID-19, of which 13,170 were PLWH. In this study, PLWH had higher odds of COVID-19 mortality (adjusted odds ratio 1.29, 95% CI 1.16–1.44) and hospital admission (1.20, 1.15–1.26). The study however had relevant limitations. CD4 cell count, HIV RNA viral load, BMI, and smoking were not accurately measured across various study sites. Large proportions of data on CD4 cell count and viral load were also missing. These variables have been identified as risk factors for severe clinical outcomes from COVID-19 [250] and hence their adequate control in the analysis is vital. Additionally, the risk of infection and poor outcomes could vary among MSM, PWID, and other HIV exposure risk groups. This information was not reported in this study. Comparing the impact of SARS-CoV-2 among PLWH and the general population taking into account the limitations in the study from Yang *et al* and adjusting additionally for vaccination status will improve our understanding of whether PLWH are at elevated risk of adverse COVID-19 outcomes.

- The study from chapter four of this dissertation identified that PWID are at a reduced risk of SARS-CoV-2 diagnosis which is contrary to reports from other studies in the general population [251,252]. Some researchers have shown that the current pandemic has disproportionately affected PWID [251,252] conceivably as a result of cardiorespiratory conditions associated with the long-term use of drugs [252]. It is therefore imperative to investigate the observed reduced risk of SARS-CoV-2 diagnosis from our study.

- Furthermore, the COVID-19 pandemic has underpinned existing social and racial injustice and inequity bringing it to the forefront of public health. Minority groups have been affected more by the COVID-19 pandemic [253–255]. Similar findings were found in this dissertation. Whilst

we collaborate with key stakeholders to advocate for structural changes, it is vital to investigate the mechanisms of these disparities, especially in the context of Catalonia where health care access is free.

- Regarding vaccination, the strategies used in Catalonia and Spain were based on age, presence of comorbidities, and occupation. Comparing the coverage between PLWH and the HIV-negative general population in age- and comorbidities-matched analysis will provide enhanced evidence. The assessed potential benefits from article 5 do not adjust for possible confounding factors and this will be necessary for subsequent studies to provide a stronger knowledge of the potential benefits of SARS-CoV-2 vaccination in this population. Sub-populations that were identified with lower vaccine uptake should be studied for possible vaccine hesitancy. Existing evidence shows that PLWH have a fragile immune response to hepatitis B [256], and yellow fever vaccination [257], and people with low CD4 cell counts have diminished antibody titres to diphtheria, tetanus, and poliomyelitis [258]. Emerging data from SARS-CoV-2 vaccination among PLWH is showing diminished responses from those with lower CD4 cell counts [259,260]. There is therefore a need to investigate immunogenicity according to CD4 cell count and their impact on the immune response to vaccination in PLWH.

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ANNEXES

Annex 1: Additional article

HIV and SARS-CoV-2 Co-infection: Epidemiological, Clinical Features, and Future Implications for Clinical Care and Public Health for People Living with HIV (PLWH) and HIV Most-at-Risk Groups

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Current HIV/AIDS Reports (2022) 19:17–25

Current HIV/AIDS Reports (2022) 19:17–25
https://doi.org/10.1007/s11904-021-00596-5

THE GLOBAL EPIDEMIC (S VERMUND, SECTION EDITOR)

HIV and SARS-CoV-2 Co-infection: Epidemiological, Clinical Features, and Future Implications for Clinical Care and Public Health for People Living with HIV (PLWH) and HIV Most-at-Risk Groups

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Accepted: 9 December 2021 / Published online: 3 February 2022

Abstract

Purpose of Review The purpose of this review is to use the currently available clinical and epidemiological data, to identify key aspects to improve both the clinical management and public health response to SARS-CoV-2/HIV co-infection among HIV vulnerable populations and people living with HIV (PLWH).

Recent Findings While at the beginning of the COVID-19 pandemic, the lack of robust information on SARS-CoV-2/HIV co-infection, prevented a clear picture of the synergies between them, currently available data strongly support the importance of common structural factors on both the acquisition and clinical impact of these infections and the relevance of age, comorbidities, and detectable HIV viral load as associated worse prognostic factors among PLWH.

Summary Although more information is needed to better understand the biological, clinical, and epidemiological relationship between both infections, a syndemic approach to prevent SARS-CoV-2 among HIV high-risk groups and PLWH, targeting these populations for SARS-CoV-2 vaccines and protocolizing early identification of PLWH with worse COVID-19 prognosis factors, is crucial strategies to decrease the overall impact of SARS-CoV-2 /HIV co-infection.

Keywords HIV · AIDS · SARS-CoV-2 · COVID-19 · Co-infection · Epidemiology · Clinical guidelines · Impact · Synergia · Sindemia

Introduction

As we make efforts to grapple with HIV, the novel COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been an unprecedented threat to global health, challenging the robustness of health systems and the overall economy as a whole. Since the first case was reported in Wuhan, China, in 2019, infections are approaching 200 million and claimed more than 4 million lives as of July 22, 2021 [1]. Older age and the presence of chronic comorbidities like hypertension, diabetes, obesity, chronic respiratory disease, chronic kidney disease, cardiovascular disease, and malignancies are currently linked with a higher risk of severe disease and mortality [2–5]. On the other hand, as it happens with many other transmissible infections, COVID-19 vulnerability is also associated to social and structural determinants like poverty, population density, and lack of access to health services, creating a syndemia of social and health problems [6].

In this context, HIV most-at-risk populations share many structural factors for SARS-CoV-2 acquisition

This article is part of the Topical Collection on *The Global Epidemic*

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amidst the existing controversy regarding the susceptibility of people living with HIV (PLWH) to SARS-CoV-2 infection and severity of the co-infection. PLWH have higher susceptibility to other infections including respiratory infections due to their aberrant humoral and T-cell-meditated immune responses [7]. Moreover, with PLWH aging [8], having higher prevalence of chronic comorbidities [9], and presenting with other risk factors of severe COVID-19 such as smoking [10], this population might have an increased risk of poorer COVID-19 outcomes.

Although there are antecedents of two previous coronavirus epidemics, the severe acute respiratory syndrome (SARS) in 2003 and the Middle East respiratory syndrome (MERS) in 2013 [11], there is little to learn from these experiences regarding the incidence and clinical severity of HIV co-infection with these two coronaviruses. Currently available data do not suggest higher SARS-CoV-2 infection rates among PLWH [12–15] and although initial studies assessing the severity of COVID-19 among PLWH showed no clear evidence of poorer outcomes [16], emerging data are reporting higher risk of morbidity [13] and mortality [17–20] among some HIV-SARS-CoV-2 co-infected patients, particularly those with lower CD4 cell counts and those with unsuppressed HIV viraemia [21–23]. Some researchers have also speculated lower risk of infection and severe outcomes among HIV/SARS-CoV-2 co-infected patients because of the potential protection from some antiretroviral therapy (ART) regimens [12, 24, 25] and have even suggested that immunosuppression could restrict the development of COVID-19-related cytokine storm [26, 27].

Finally, governments across the globe implemented strict measures to reduce mobility of persons and limit social activities in order to control the transmission of SARS-CoV-2. These measures disrupted daily human lives and inadvertently hampered the delivery of key preventive and clinical HIV services [28].

The inconsistency of clinical data regarding the impact of SARS-CoV-2 on HIV and the scarcity of population-based data sources which reports both infections highlights the importance of robust information systems with sociodemographic, biological, and clinical data to respond to the increasing number of questions needed to be answered to better articulate an effective response and to improve both clinical and public health guidelines on HIV-SARS-CoV-2 co-infections.

We have reviewed the association of HIV and SARS-CoV-2 and its implications for HIV services from both a clinical and public health perspective, with a particular emphasis on the European context. Moreover, we explain how the COVID-19 pandemic has disrupted HIV prevention and treatment services, creating huge challenges to the continuity of essential healthcare activities. Finally, we highlighted topics where further research is required such as vaccination.

Epidemiology of HIV and SARS-CoV-2

Estimates from the UNAIDS show that as of the end of 2020, there were 37.6 million (estimate range, 30.2–45.0 million) people were living with HIV with 1.5 million new cases and 690,000 deaths in 2020 only [29]. Since it was identified in 1980s in the World Health Organization (WHO) European Region, the HIV epidemic remains an on-going public health problem in the region with over 2 million people living with the infection by the end of 2019 [30]. In 2019, there were 136,449 reported new cases in the region representing a crude rate of 15.6 per 100,000 persons of newly diagnosed infections [30]. Late diagnosis remains a challenge in the region as 31% of newly diagnosed persons presented with advanced HIV (CD4 < 200 cells/mm^3) [30].

The COVID-19 pandemic first hit Europe on January 24, 2020, with the first three cases reported in France [31]. As of July 22, 2021, the region had reported 33,956,561 cases and 742,847 deaths [32]. France, UK, Italy, Spain, Germany, and Poland have been hugely affected in the European region in terms of number of confirmed cases and deaths [32]. The European monitoring of excess mortality for public health action (EuroMOMO) network reported excess mortality estimates in the initial stages of the COVID-19 pandemic in Europe. By the 18th week after the pandemic commenced in Europe, the cumulative excess mortality in all ages was 185,287 deaths. People aged ≥ 85 years contributed most to the excess mortality (48%) and was least among 15–44 year olds (1%) [33].

Across Europe, the incidence of COVID-19 among PLWH ranges from 0.3 to 5.7% person years [12, 14, 22, 34, 35]. Two studies have assessed the prevalence of HIV among hospitalized COVID-19 patients in Europe being between 0.26 and 1.0% [20, 36]. In a pooled analysis, PLWH were identified to be more susceptible to SARS-CoV-2 infection with a risk ratio (RR) of 1.24 (95% confidence interval [95% CI] 1.05–1.46); the prevalence of HIV among hospitalized COVID-19 patients in this analysis was however not significantly different than the background population (RR = 1.22, 95% CI 0.61–2.65) [37]. Nevertheless, because diagnostic rates are a function of the screening criteria, it is likely that — particularly at the beginning of the pandemic — diagnostic rates among PLWH were overestimated because testing was based on symptoms, age, comorbidities, or epidemiological criteria.

HIV/SARS-CoV-2 co-infected patients in Europe were 38–56 years which is about a decade younger than the reported average age in the general population [20] and predominantly males [12, 14, 20, 22, 34, 35]. COVID-19

diagnosed PLWH were more likely to belong to a low socioeconomic class [17] and likely to be of black ethnicity [17, 20]. Mortality rates among HIV/SARS-CoV-2 co-infected patients in Europe have ranged from 1.9 to 29.0% [12, 14, 20, 21, 34–36, 38–42].

An essential aspect of any infectious disease control and prevention measure is quality epidemiological surveillance, timely and accurate enough to identify cases and patterns of transmission to guide early and effective preventive interventions. Both in the USA [43] and Europe [44], retrospective analysis of influenza monitoring sentinel networks suggested that SARS-CoV-2 was circulating earlier than the first cases were officially recognized and therefore a high percentage of these infections remaining undiagnosed. A study from Wuhan, China, reported that if public health measures had begun 3 weeks earlier, cases could have been reduced by 95% [45].

Robust population-based programmatic and surveillance data, including epidemiological, microbiological, clinical, and syndromic information are crucial to understand the distribution and dynamics of SARS-CoV-2 and its impact in key populations such as PLWH. Unfortunately, at the beginning of the COVID-19 pandemic, many national information systems were not prepared to face an integrated approach of the needs emerged by the SARS-CoV-2 infection. Systematizing the use of microbiological methods to identify SARS-CoV-2 infection among PLWH is imperative not only to have a better picture of the epidemiological pattern of the co-infection, but also to identify individuals at risk of worse clinical outcomes promptly.

Potential Impact of Antiretrovirals on SARS-CoV-2 Infection Risk and Outcomes

Since the beginning of the COVID-19 pandemic, the possibility that some antiretroviral drugs might be active against SARS-CoV2 was considered. However, with the evidence available so far, the antiretroviral treatment should not be modified to treat SARS-CoV-2, since no proven activity of any antiretroviral drug has been consistently documented. Some studies are ongoing to bring light to this issue. The association of tenofovir disoproxil (TDF) use and a potentially lower COVID-19 infection rate has sparked much debate. In studies from Spain [12] and South Africa [18], TDF was associated with lower SARS-CoV2 infection incidence rates.

However, selection biases were present in both studies since it is unlikely to provide TDF to PLWH with known comorbidities such as cardiovascular risk factors or kidney disease, which have been identified as risk factors for COVID-19 and poor outcomes. Therefore, PLWH treated with TDF would probably be preferentially younger and with no known comorbidities, entailing an intrinsic lower risk for SARS-CoV-2 infection. In the South African study, receipt of TDF (vs. zidovudine) was associated with reduced COVID-19 mortality even after adjusting for renal disease, viral suppression, and antiretroviral treatment duration, but again, other non-adjusted factors (prior virologic failure, tuberculosis) could be associated with zidovudine use [18]. A third study in subjects with chronic hepatitis B (without HIV infection) has also reported significantly lower rates of severe COVID-19, intensive care unit (ICU) admission, ventilatory support, and fewer days in the hospital in those receiving TDF vs entecavir [46]. However, again, people taking TDF had significantly lower comorbidity rates. Finally, TDF/FTC PrEP users presented a higher seroprevalence to SARS-CoV-2 than the control group, with no significant differences in clinical manifestations [47]. Similarly, a matched case–control comparison in the PREVENIR-ANRS French study with middle-aged HIV-negative people who did or did not use TDF/FTC PrEP found no evidence that TDF may help ward off SARS-CoV-2 infection [48].

HIV protease-inhibitors (mainly lopinavir/ritonavir) have been used early during the pandemic to treat COVID-19 but, currently, no study supports their use.

Potential Impact of Comorbidities on SARS-CoV-2 Infection

Although some studies have reported HIV infection as a risk factor for poor outcome, there is no clear evidence for a more severe disease course of SARS-CoV-2 infection in PLWH on active ART and with good cellular immunity (CD4 cell count) levels. Among hospitalized COVID-19 patients, most studies reported a younger age of PLWH vs. HIV-negative patients, with higher rates of comorbidity [14, 23, 35]. These comorbidities are consistently associated with poorer outcomes in PLWH with well-controlled HIV infection and constitute the underlying bias in all series reported.

On the other hand, larger cohort studies suggested poorer outcomes for PLWH not only in the presence of comorbidities, but also in those with low CD4 cell count (< 200 cells/mm^3) [18, 23]. This would be consistent with the poorer COVID-19 outcomes seen in other immunocompromised hosts. In addition, severe COVID-19 has been also described in PLWH with concomitant opportunistic infections, such as tuberculosis and/or *Pneumocystis jirovecii* [49].

Thus, PLWH have a higher risk for severe COVID-19 outcomes in two clinical contexts: (i) uncontrolled HIV infection and/or advanced immunodeficiency, or (ii) additional comorbidities.

Outcomes (Hospitalization, Intensive Care Unit, and Mortality) and Determinants

In studies including outpatients, overall rates of ICU admission ranged between 3 and 22% for PLWH [50]. When only hospitalizations were reported, ICU admission for PLWH ranged between 17 and 33% [50]. Severity of COVID-19 illness increases with age and comorbidities, as it does in the general population. Multimorbidities have been reported in nearly two-thirds of patients co-infected with HIV and SARS-CoV-2 [23, 50].

Despite the existing debate, clinical data from 37 countries reported to the WHO Global Clinical Platform for COVID-19 indicate that HIV infection is a significant independent risk factor for severe/critical COVID-19 presentation at hospital admission and in-hospital mortality [19]. Mortality in hospitalized PLWH with COVID in the UK showed an adjusted hazard ratio (aHR) of 1.69 (95% CI 1.15–2.48; $p = 0.008$) [20], whereas, in primary care alone, after adjustment for age, gender, ethnicity, smoking, and obesity among other variables, the aHR was 2.59 (1.74–3.84; $p < 0.0001$). Most deceased PLWH had other comorbidities [17]. Similar results were found in Western Cape, South Africa, in multivariate analysis with PLWH having a risk of death with COVID-19 of 2.14 (1.70–2.70) [18]. However, global mortality varied considerably across studies, depending on the design. Mortality was as high as 24% in the UK series (only hospitalizations) [20], as low as 2% in a series from France [41], and 3.6% in the South African cohort study [18] with a higher number of patients and the inclusion of outpatients, but also a more severely immunosuppressed population.

A recent analysis from the PISCIS Cohort Study in Catalonia (Spain) identified HIV co-infected patients with detectable HIV viral load, lower CD4 cell counts, older age, chronic comorbidities, and migrants as those with higher risks of severe outcomes [22]. Of note, lower CD4 cell counts were a risk factor to severe COVID-19 only among patients with detectable viral load in stratified analysis.

European Guidelines on Clinical Management

Clinical and radiological COVID-19 presentation is no different in PLWH to typical reports in the general population [23, 50].

The European AIDS Clinical Society and several National HIV/AIDS Societies have provided general recommendations for the management of PLWH with COVID-19 [51]. Essentially, the diagnostic approach and overall management should follow those indicated for the general population. Differential diagnosis should include other respiratory diseases such as *Pneumocystis jirovecii* and tuberculosis, particularly in severely immunocompromised PLWH.

However, when treating COVID-19 in PLWH, specific issues must be addressed. The first is to consider and check for drug-drug interactions between COVID-19 treatments and ARV drugs. The second is to consider the potential overlapped toxicities of ARVs and SARS-CoV-2 therapies, such as liver or kidney toxicity of remdesivir with specific ARV drugs.

For PLWH with severe immune depletion and other types of immunosuppressed individuals (solid transplant recipients, onco-hematologic patients), prolonged SARS-CoV-2 replication and shedding have been reported, which may require longer isolation periods. However, no specific recommendation for testing and isolation has been provided yet for PLWH.

Finally, emerging data is showing that long COVID will have a great impact in the burden of disease both in developed and low- and middle-income countries (LMIC) [52]. Given the huge symptomatic spectrum and the lack of knowledge about its pathophysiological mechanism, PLWH exposed to SARS-CoV-2 should be monitored to clarify if they are at higher risk of experiencing some features of long COVID syndrome.

SARS-CoV-2 Vaccination Among PLWH

There is limited information of the immunogenicity and reactogenicity of commercially available COVID-19 vaccines in PLWH. Studies analyzing the response of PLHIV to COVID-19 vaccines are needed to define the potential advantages and disadvantages of some types of vaccines (adenovirus-based vs. mRNA vs. recombinant spike vaccines) or the need for additional vaccine doses to achieve full protective immunity in immunosuppressed HIV-infected patients. The latter is an important point because it is well known that the immune damage to B-cell compartments and antibody generation caused by HIV infection can decrease the humoral response as it has been demonstrated to other vaccines (e.g., influenza or pneumococcal vaccines) [53, 54]. Therefore, dysfunctional B-cell memory lymphocytes and follicular helper T-cell activity could potentially decrease humoral responses to neo-antigens such as SARS-CoV-2 protein spike.

Data on PLWH included in approved phase 2/3 vaccine trials so far is limited. Regarding mRNA vaccines, in the Moderna and Pfizer trials [55, 56], only 0.6% and 0.5% of participants were PLWH respectively. The HIV sub-study

results of these trials have not been published yet. However, in another small study in 12 PLWH (seven women, five men), the Pfizer vaccine induced, between 7 and 17 days after the second vaccine dose, a robust humoral and cellular immune responses comparable to that seen in 17 healthy donors (seven women, 10 men) [57]. Regarding the adenovirus-based vaccines, the safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine [58] were evaluated in 54 individuals in a single-arm open-label vaccination substudy. All participants were men (most white) on ART, with undetectable plasma HIV viral loads (< 50 copies/mL), and CD4 counts of more than 350 cells/mm^3 (median 700 cells/mm^3). No serious adverse events occurred. Anti-spike IgG responses peaked at day 42 and were sustained until day 56 with no correlation with CD4 cell count or age. Compared with HIV-negative participants, the study found no differences in magnitude or persistence of SARS-CoV-2 spike-specific humoral or cellular responses. Finally, using the recombinant spike protein, the NVX-CoV2373 vaccine phase 2b trial [59] performed in South Africa included 6% of PLWH. The vaccine efficacy in PLWH was lower than in non-HIV-individuals (52% vs. 60%).

Immunosuppressed PLWH should be considered a risk group in which early COVID-19 vaccination would be advised as supported by European AIDS Clinical Society (EACS) Guidelines [51]. PLWH with low CD4 counts (below 200 cells/μL or even below 350 cells/μL) are at higher risk of developing severe COVID-19 [22] and could be considered as a priority group for COVID-19 vaccination. Therefore, we urgently need studies that analyze the efficacy and safety of vaccines in these immunosuppressed patients, in patients without ART, in women, and in different races. In addition, we should also know the duration of the immune response since some PLWH may need additional doses of vaccines.

Finally, since there is evidence that HIV adenovirus-based vaccines increased the risk of acquiring HIV [60–62], further information is also needed to better understand the appropriateness of using the adenovirus type 5 vectored vaccines among HIV most-at-risk groups.

Impact of SARS-CoV-2 Pandemic in HIV Most-at-Risk Groups and PLWH

Aside the direct risks to physical health, the psychological impact of COVID-19 could also be detrimental to mental well-being as elevated levels of stress and anxiety are further exacerbated by the ongoing uncertainty of the situation [63]. Key populations among PLWH experience particular forms of exclusion, criminalization, inequality, and discrimination that render them particularly vulnerable to COVID-19 [64]. This burden can affect the physical, emotional, and social well-being of PLWH and interfere with the reception of effective healthcare and access to HIV treatment [65].

A survey of older PLWH in Miami, USA, found that participants reported increased stress associated with their sense of social isolation and fragile economic situation [66]. PLWH who reported higher levels of anxiety and depression also reported losing their jobs during the pandemic [67]. Another study has described that psychological stress might be a predictor of COVID-19 burden (financial and social burden) and COVID-19 risk (health factors associated with an increased risk of severe health outcomes due to COVID-19) [67]. Additionally, COVID-19 burden and COVID-19 risk were predictors of depression and sleep problems [68]. Lesbian, gay, bisexual, transgender, and intersex (LGTBI) people reported an elevated risk of domestic and family violence, increased social isolation, difficulties in accessing crucial HIV treatment, and gender-affirming health services [67, 69].

The impact of COVID-19 on sexual behavior among gay and bisexual men living with HIV has been described in three studies which reported changes in sexual behaviors, including avoiding close physical contact and reducing or ceasing sex with casual partners [70, 71]. There is also a reported increase in recreational drugs such as marijuana and methamphetamine (up to 8%), and alcohol consumption and binge drinking [70–72].

Impact on Health Services, Access to Diagnosis, and Treatment

In addition to the health emergency caused by the COVID-19, the pandemic has threatened the excellence in ART delivery in well-resourced countries which could potentially result in reduction in adherence and decreased healthcare retention [73, 74]. It is estimated that a significant proportion of PLWH could access usual care because many HIV/AIDS prevention and control centers around the world have been converted into COVID-19 treatment centers and the perceived fear of contracting COVID-19 has made this group situation more vulnerable [75].

Vital HIV care resources including healthcare personnel have been channeled into curbing the COVID-19 pandemic [76]. A high percentage of community-based testing services have stopped or dramatically decreased their activity [77] and many HIV care centers worldwide were repurposed for the fight against COVID-19 denying PLWH the possibility of accessing crucial ART. [75]

During these periods, drug guarantee and distribution strategies were adopted by several countries; however, there are still uncertainties regarding the situation of assistance to PLWH in countries where the economy was highly affected. A study evaluating the impact of the pandemic on care for

this population as well as on the provision of treatment found that no country, among the 19 participants, reported the closure of HIV care services; however, the functioning was normal in 6 countries (31.6%) and in 11 of them (57.9%), care was shared between HIV and COVID-19. Furthermore, the rechanneling of health professionals, especially HIV specialists, to the COVID-19 response caused the exhaustion of many HIV care teams [77].

For this reason, recommendations for management and prevention of COVID-19 among PLWH emphasize the need for continuity of HIV care, including uninterrupted access to ART, routine vaccinations, and the use of telehealth means to access care, as long as it follows the general COVID-19 preventive guidelines. Also, continuous monitoring of the impact of the pandemic on this population is encouraged, so that it is possible to systematize evidence to support the reorganization of assisting services for PLWH. Regarding prevention services, the pandemic has challenged the functioning of HIV prevention services such as free access to condoms and HIV pre-exposure prophylaxis (PrEP) and calls for innovative approaches going forward [78].

In Europe, some HIV prevention and diagnosis services have incorporated self-sampling and self-testing approaches [77]; nevertheless, applicability of these strategies may not be easy as they require good information technology and mailing systems, which is not the case in many LMIC. On the other hand, steady access to clinical care may be facilitated by means of telemedicine. But again, in light of the COVID-19 pandemic, as it has been described from an experience in the USA, it is likely that economic, geographic inequities, and the digital divide will prevent some PLWH from accessing care via this route due to lack of necessary technology (e.g., computer, smartphones) or stable internet access, especially among older PLWH [79].

Conclusions

In this review, we have highlighted some aspects of the SARS-CoV-2/HIV co-infection from both a public health and clinical perspective. Although at the beginning of the COVID-19 pandemic the lack of integrated epidemiological surveillance and programmatic data prevented to have a clear picture of the overlapping distribution of both infections and its determinants, from a public health perspective, currently available data confirms the role of common structural determinants in both their acquisitions and clinical impact. Public health weakness, drug use, mental health, stigma, social marginalization, and other structural determinants all disproportionally increase the exposure to both HIV and SARS-CoV-2.

From a clinical perspective, data suggest that PLWH taking effective ARV treatment are not at higher risk of acquiring SARS-CoV-2. Moreover, there is no current evidence suggesting that TDF could reduce the risk of SARS-CoV-2 infection or severe COVID-19 outcomes in PLWH, and both clinical and radiological features of COVID-19 in PLWH are similar to those without HIV infection. Nevertheless, HIV-associated comorbidities, low CD4 (< 200 cells) cell counts, and in particular unsuppressed HIV viraemia are associated with poorer COVID-19 clinical outcomes and death among PLWH. In such a context, PLWH should be considered a priority target group for SARS-CoV-2 vaccinations and further information is needed to identify potential advantages or disadvantages of the different commercially available vaccines and vaccination schedules to be used into this population.

The SARS-CoV-2 pandemic has not only impacted PLWH, particularly disrupting access to ARV treatments, but also HIV most-at-risk groups — including men who have sex with men (MSM), sexual workers (SW), and people using drugs (PUD) — decreasing access to HIV prevention and early diagnosis and linkage programs. Under the current uncertain epidemiological scenario, both clinical services offering medical care to PLWH and community programs offering services to vulnerable groups should be adapted to the evolving COVID-19 pandemic and the corresponding mitigation scenarios to prevent disruption of the HIV continuum of care among these populations. Systematization of SARS-CoV-2 testing among PLWH is basic not only to better understand the epidemiological co-infection pattern, but also to identify PLWH co-infected with SARS-CoV-2 with worse prognostic factors, as soon as possible. Integration of SARS-CoV-2 testing strategies in HIV testing programs should therefore be considered. With this regard, alternative approaches like telemedicine, self-sampling, and self-testing technologies have been used in both developed and LMIC with promising results and they should be scaled up.

Integrated information systems including epidemiological, microbiological, clinical, vaccination and mortality data should be reinforced and maintained to monitor the impact of COVID among PLWH and HIV most-at-risk-groups. The use of longitudinal clinical data from PLWH, population-based SARS-CoV-2 diagnosis data as well as ecological approaches to include structural indicators, seems crucial to increase the knowledge and improve the practices of SARS-CoV-2/HIV co-infection from both a clinical and public health perspective.

Funding JM Miró received a personal 80:20 research grant from Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, during 2017–2021.

Declarations

Conflict of Interest JM Miró has received consulting honoraria and/or research grants from AbbVie, Angelini, Contrafect, Cubist, Genentech, Gilead Sciences, Jansen, Lysovant, Medtronic, MSD, Novartis, Pfizer, and ViiV Healthcare, outside the submitted work. Josep Mª Llibre, Juan Ambrosini, Juliana Reyes, Fabiola Ganem, Daniel Nomah, and Jordi Casabona declare they do not have any conflict of interest.

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and immunogenicity of the ChAdOx1 nCoV-19 vaccine in 54 individuals with HIV. The conclusions were that in virologically suppressed white men on ART and more than 350 cells/mm^3, the magnitude and persistence of SARS-CoV-2 spike-specific humoral or cellular responses at short term (2 months) were similar to that seen in HIV-negative participants. In addition, vaccination was safe without any serious adverse events.

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Annex 2: Dissemination of doctoral thesis results

1. **Oral presentation:** Characterization of COVID-19 among HIV-infected persons. 2020 European Researchers' Night (La Nit de la Recerca). November 27, 2020. Barcelona, Spain.

2. **Flash talk presentation:** Sociodemographic, clinical, and immunological factors associated with SARS-CoV-2 diagnosis and severe COVID-19 outcomes in people living with HIV. III Can Ruti PhD Day. June 22, 2021. Badalona, Spain.

3. **Oral presentation:** Unsuppressed plasma HIV-RNA is associated with worse COVID-19 outcomes among people living with HIV. 11th International AIDS Society Conference on HIV Science. Date: July 18-21, 2021.

4. **Online news article in AIDSMAP**: Lower CD4 count and unsuppressed HIV raise the risk for severe COVID-19. https://www.aidsmap.com/news/jul-2021/lower-cd4-count-and-unsuppressed-hiv-raise-risk-severe-covid-19. July 20, 2021.

5. **Online news article in NATAP**: Lower CD4 count and unsuppressed HIV raise the risk for severe COVID-19. https://www.natap.org/2021/IAS/IAS_48.htm . July 20, 2021.

6. **Online article on IGTP news:** CEEISCAT researchers coordinate a project identifying the risk factors for severe covid-19 for people living with HIV. http://www.germanstrias.org/news/293/ceeiscat-researchers-coordinate-a-project-identifying-the-risk-factors-for-severe-covid-19-for-people-living-with-hiv . October 18, 2021.

7. **Online news article in IDBELL:** A study identifies risk factors for severe COVID-19 in HIV patients. https://idibell.cat/en/2021/10/a-study-identifies-risk-factors-for-severe-covid-19-in-hiv-patients/ . October 26, 2021.

8. **Poster presentation:** A population-based assessment of SARS-CoV-2 testing, test positivity, and clinical severity between the general population and people living with HIV in Catalonia, Spain (March-December 2020). 18th European AIDS Conference. October 27-30, 2021, London, United Kingdom.

9. **Presentation:** HIV and SARS-COV-2 co-infection: clinical and public health perspectives. Technical session, Centre for Epidemiological Studies of Sexually Transmitted Disease and HIV/AIDS in Catalonia (CEEISCAT). November 10, 2021. Badalona, Spain.

10. **Oral presentation:** A population-based assessment of SARS-CoV-2 testing, test positivity, and clinical severity between the general population and people living with HIV in Catalonia, Spain (March-December 2020). XII Congreso Nacional de GeSIDA. November 29 – December 2, 2021. Malaga, Spain.

11. **Oral poster presentation:** Sociodemographic, clinical, and immunological factors associated with SARS-CoV-2 diagnosis and severe COVID-19 outcomes in people living with HIV. XII Congreso Nacional de GeSIDA. November 29 – December 2, 2021. Malaga, Spain.

12. **Poster presentation:** Impact of tenofovir on SARS-CoV-2 infection among people living with HIV. The 29th Conference on Retroviruses and Opportunistic Infections (CROI). February 12-16, 2022.

Annex 3: Other studies

During my stay at the Centre for Epidemiological Studies of Sexually Transmitted Disease and HIV/AIDS in Catalonia (CEEISCAT) as a doctoral student, I collaborated in other studies which are related to the current thesis.

1. Sentís A, Prats-Uribe A, López-Corbeto E, Montoro-Fernandez M, **Nomah DK**, de Olalla PG, Mercuriali L, Borrell N, Guadalupe-Fernández V, Reyes-Urueña J, Casabona J; Catalan HIV and STI Surveillance Group. The impact of the COVID-19 pandemic on Sexually Transmitted Infections surveillance data: incidence drop or artefact? BMC Public Health. 2021 Sep 7;21(1):1637. doi: 10.1186/s12889-021-11630-x.

2. Sentís A, Montoro-Fernandez M, Lopez-Corbeto E, Egea-Cortés L, **Nomah DK**, Díaz Y, Garcia de Olalla P, Mercuriali L, Borrell N, Reyes-Urueña J, Casabona J; Catalan HIV and STI Surveillance Group. STI epidemic re-emergence, socio-epidemiological clusters characterisation and HIV coinfection in Catalonia, Spain, during 2017-2019: a retrospective population-based cohort study. BMJ Open. 2021 Dec 13;11(12):e052817. doi: 10.1136/bmjopen-2021-052817.

3. Jamarkattel S, **Nomah DK**, Moreno S, Díaz Y, Aceitón J, Bruguera A, Llibre JM, Saumoy M, Homar F, Fanjul F, Miro JM, Casabona J, Reyes-Urueña J. Mortality and causes of death in people living with HIV (PLHIV) from 2010-2020: An analysis of the PISCIS cohort. The 24th International Workshop on HIV observational databases and hepatitis (IWHOD). Abstract 114. March 24-26, 2022. Sevilla, Spain.

4. **Nomah DK**, Bruguera A, Diaz Y, Moreno S, Aceiton J, Llibre J.M, Falcó V, Imaz A, Fanjul F.J, Peraire J, Deig E, Domingo P, Miró JM, and Casabona J, and the PISCIS study group. COVID-19 outcomes and vaccination coverage among migrants living with HIV in Catalonia, Spain: a propensity score-adjusted analysis using the prospective PISCIS cohort. (Abstract EPC441). the 24th International AIDS Conference. Date: July 29-August 2, 2022. Montreal, Canada.

Annex 4: Funding, awards, and scholarships

- Article 1, 2, and 3 were funded by Fundació 'La Caixa' (grant number: COVIHCAT), 2020.

- Article 4 was funded by Fundació La Marató de TV3, grant number 202117-30-31, 2021.

- Received scholarship from the International AIDS Society (IAS) to attend the 2021 International AIDS Society Conference on HIV Science (Berlin/Virtual).

- Scholarship to attend the International Summer School on Advanced Methods in Global Health organized by University of Barcelona/ISGlobal, September 2021.

- Received scholarship to attend the 18th European AIDS Conference (EACS), October 27-30, 2021, London, United Kingdom/virtual.

- Article 2 selected among the top 10 studies in HIV science for the year 2021 at the 2021 GeSIDA conference in Malaga, Spain.

- Received scholarship from the International AIDS Society (IAS) to attend the 2022 International AIDS Society Conference on HIV Science (Montreal/Virtual).

Annex 5: Master thesis supervision

Student name: Francis Quist

Program: Masters in clinical research and international health track, University of Barcelona, Spain.

Thesis title: Determinants of hypertension and diabetes among Sub-saharan African (Ghanaian) migrants in the Greater Barcelona region.

Year: 2020-2021

Student name: Yi-Hua Pan

Program: Masters in Infectious Diseases and One Health, Université de Tours-Universitat Autonoma de Barcelona- Medizinische Hochschule Hannover.

Thesis title: The impact of the COVID-19 pandemic on people living with HIV (PLWH). An interrupted time-series analysis of the impact of the COVID-19 pandemic on HIV care services and SARS-CoV-2 breakthrough infection among people living with HIV Catalonia, Spain: PISCIS cohort study.

Year: 2022

Annex 5: PISCIS investigators

The PISCIS Cohort Study Group

Coordinating Centre: Centre for Epidemiological Studies of Sexually Transmitted Diseases and AIDS in Catalonia (CEEISCAT)

Project coordinator: Juliana Reyes-Urueña

Field coordinator: Andreu Bruguera Riera

Data protection and technical support: Esteve Muntada

Data management and statistical analysis: Sergio Moreno, Yesika Díaz, Jordi Aceitón.

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