Interactions between COVID-19, HIV and TB: Effect on Disease Progression

HIV & Other Infectious Diseases Research Unit (HIDRU) Science Symposium, 14 March 2022

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Presentation Outline

• Magnitude of TB-HIV-COVID-19 disease burden
• Is HIV & TB associated with an increased risk of severe disease and death from COVID-19?
• Does COVID-19 co-infection alter PTB Clinical manifestation and disease progression?
• Do PLWHA/TB have impaired vaccine effectiveness?
• Impact of COVID-19 on the HIV & TB public health response
Colliding Syndemics: TB, HIV & COVID-19

**HIV**
- Globally: 1.5 million new cases, 680 000 deaths
- **South Africa:** 230 000 new cases (15%) 83 000 deaths (12%)

**TB**
- Globally: 10 million new cases, 1.5 million deaths
- **South Africa:** 328 000 new cases (3.3%) 61 000 deaths (4%)

**COVID-19**
- Globally: 418 million cases, 5.8 million deaths
- **South Africa:** 3.6 million cases, 97 520 thousand deaths
Is HIV & TB associated with an increased risk of severe disease and death from COVID-19?
Increased COVID-19 mortality in HIV & TB patients

- Population cohort study of adults attending public-sector facilities in Western Cape, SA
- Data collected between March - June 2020 (First wave wild-type strain)
- Among 3.5 million → 22 308 diagnosed with COVID-19 & 625 died
- HIV-associated COVID-19 mortality:
  - aHR 2.14 (CI: 1.70–2.70)
  - Mortality risk similar irrespective of viraemia (VL>1000 copies/mL) or CD4+ count <200 cells/µL
- TB-associated COVID-19 mortality:
  - Current aHR 2.70 [CI, 1.81–4.04]
  - Previous TB aHR 1.51 [CI, 1.18–1.93]
  - Similar mortality rates in rifampicin-sensitive and resistant TB
  - All deaths occurred in the intensive phase treatment
  - Covid-19 TB deaths occurred mainly among older people
Increased COVID-19 deaths in PLWHA: UK

HIV infection and COVID-19 death: a population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform


- Large scale population-based retrospective cohort study compared COVID death in HIV infected and uninfected
- Higher risk of COVID-19 death in people living with HIV after adjusting for age and sex, HR: 2.90
- Evidence of larger association of COVID-19 mortality among people of Black vs non-Black ethnicity: HR 4.31 vs 1.84
- No conclusive findings on the role of other co-morbidities, ART use, previous ADI’s, viral suppression and CD4 on COVID-19 mortality risk
Poor COVID-19 Outcomes & Higher Hospitalization among PLWHA: US

- Assessed outcomes in 3000 known PLWAH- COVID co-infected with matched COVID-infected HIV-ve controls
- Compared with COVID mono-infected, COVID-HIV co-infected patients:
  - Similar rates of COVID-19 diagnosis
  - Higher per population hospitalization rates
  - No difference in in-hospital mortality rates
  - Hospitalization risk increased by HIV disease: Stage 2 aRR 1.29 & Stage 3 aRR 1.69

PLWHA had increased risk for poor outcomes due to higher rates of severe disease requiring hospitalization. Risk of hospitalization increased with HIV disease progression
HIV an independent risk factor for in-hospital mortality in SA

- 219,265 admitted patients nationally, 23.3% COVID-19 mortality (March 2020 – March 2021)
- Predictors of COVID-19 in-hospital mortality included:
  - **Increasing age (strongest predictor OR 2.15 – 20.67)**
  - HIV infection (OR 1.34)
  - Current TB (OR 1.48), Current and past TB (OR 1.48)
  - Underlying NCD’s: hypertension, diabetes, cardiac/renal disease & malignancy within 5 years (OR ranged 1.07 – 2.21)
  - Treatment in the public health sector (OR 1.28)
  - Treatment in KZN (OR 1.41)
- PLWHA not on ART vs those on ART more likely to die in hospital (adjusted OR 1.45)
- Irrespective of HIV: Increase in number of comorbidities associated with increased COVID-19 in-hospital mortality risk
Effect of ART, CD4 cell count, and HIV viral load on COVID-19 in-hospital mortality

### ART status

<table>
<thead>
<tr>
<th>ART status</th>
<th>Case fatality ratio unimputed</th>
<th>Case fatality ratio (95% CI) imputed</th>
<th>Unadjusted OR (95% CI) imputed</th>
<th>p value</th>
<th>Adjusted OR (95% CI) imputed*</th>
<th>p value</th>
<th>Adjusted OR (95% CI) imputed*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV negative</td>
<td>30,697/137,986 (22.2%)</td>
<td>23.1% (22.9–23.3)</td>
<td>1 (ref)</td>
<td></td>
<td>1 (ref)</td>
<td></td>
<td>0.77 (0.72–0.82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HIV positive on ART</td>
<td>20,467/74,843 (27.3%)</td>
<td>24.6% (23.8–25.4)</td>
<td>0.85 (0.80–0.90)</td>
<td>&lt;0.0001</td>
<td>1.30 (1.22–1.39)</td>
<td>&lt;0.0001</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>HIV positive not on ART</td>
<td>19,259/59,413 (32.3%)</td>
<td>28.1% (25.2–31.1)</td>
<td>0.99 (0.86–1.15)</td>
<td>0.98</td>
<td>1.89 (1.65–2.1)</td>
<td>&lt;0.0001</td>
<td>1.45 (1.22–1.72)</td>
<td>&lt;0.0001</td>
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### CD4 count

<table>
<thead>
<tr>
<th>CD4 count</th>
<th>HIV negative 30,697/137,986 (22.2%)</th>
<th>23.1% (22.9–23.3)</th>
<th>1 (ref)</th>
<th></th>
<th>1 (ref)</th>
<th></th>
<th>1.06 (0.93–1.20)</th>
<th>0.37</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV positive CD4 count, ≥200 cells per μL</td>
<td>368,169/50,130 (21.8%)</td>
<td>19.7% (17.7–21.7)</td>
<td>0.64 (0.57–0.73)</td>
<td>&lt;0.0001</td>
<td>0.95 (0.83–1.08)</td>
<td>0.37</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>HIV positive CD4 count, &lt;200 cells per μL</td>
<td>380,108/50,130 (35.2%)</td>
<td>32.2% (29.9–34.5)</td>
<td>1.23 (1.09–1.38)</td>
<td>0.0003</td>
<td>2.19 (1.92–2.49)</td>
<td>&lt;0.0001</td>
<td>2.31 (1.82–2.93)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Viral load

<table>
<thead>
<tr>
<th>Viral load</th>
<th>HIV negative 30,697/137,986 (22.2%)</th>
<th>23.1% (22.9–23.3)</th>
<th>1 (ref)</th>
<th></th>
<th>1 (ref)</th>
<th></th>
<th>0.83 (0.76–0.90)</th>
<th>&lt;0.0002</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV positive viral load, &lt;1000 HIV RNA copies per mL</td>
<td>316,127/50,130 (24.8%)</td>
<td>24.7% (23.0–26.4)</td>
<td>0.86 (0.78–0.94)</td>
<td>0.0029</td>
<td>1.21 (1.11–1.32)</td>
<td>0.0002</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>HIV positive viral load, ≥1000 HIV RNA copies per mL</td>
<td>128,443/50,130 (28.9%)</td>
<td>25.2% (21.0–29.4)</td>
<td>0.85 (0.69–1.05)</td>
<td>0.13</td>
<td>1.88 (1.53–2.31)</td>
<td>&lt;0.0001</td>
<td>1.55 (1.20–2.01)</td>
<td>0.0029</td>
</tr>
</tbody>
</table>

### Comorbid condition

<table>
<thead>
<tr>
<th>Any individual HIV-positive individuals</th>
<th>Case fatality ratio unimputed</th>
<th>Case fatality ratio (95% CI) imputed</th>
<th>Adjusted OR (95% CI) imputed*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No comorbidity</td>
<td>341/2073 (16.4%)</td>
<td>15.6% (14.6–16.6)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>One comorbidity</td>
<td>384/1124 (25.2%)</td>
<td>23.2% (21.9–24.5)</td>
<td>1.34 (1.20–1.49)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Two comorbidities</td>
<td>292/932 (31.3%)</td>
<td>29.4% (27.7–31.0)</td>
<td>1.67 (1.48–1.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Three or more comorbidities</td>
<td>143/352 (40.6%)</td>
<td>41.9% (40.0–43.8)</td>
<td>2.46 (2.22–2.73)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- Increased risk of in-hospital COVID-19 mortality among PLWHA not on ART, CD4 < 200 cells/ul, VL > 1000, increasing co-morbidities
- Patients at high risk of mortality would benefit from vaccine prioritisation as well as early referral and treatment
Outcomes among PLWHA hospitalized with COVID-19: WHO Global Clinical Cohort Results

- Cohort of PLHWA from 24 countries admitted with SARS-COV-2,
- Assessed: hospital mortality and clinical severity
- Severe/critical cases definition: SpO2: <90%; respiratory rate: >30 b/min, received extracorporeal membrane oxygenation (ECMO); ICU admission, received an inotrope/vasopressor
- Mild/moderate case definition: SpO2: ≥90%; respiratory rate: ≤30 b/min
- 23.1% (3578/15 463) died, mean duration from hospital admission to death or discharge was 9.5 days

HIV independent risk factor for severe or critical illness at hospital admission and for in-hospital mortality
Disease severity & immune response in PLWHA

HIV status alters disease severity and immune cell responses in Beta variant SARS-CoV-2 infection wave

Farina Karim¹,², Inbal Gazy²,³, Sandile Cele¹,², Yenzekile Zungu¹, Robert Krause¹,², Mallory Bernstein¹, Khadija Khan¹,², Alex Sigal¹,²,⁶*

- Observational cohort (n= 236) study, from June 2020 – May 2021 in Durban South Africa
  - 93 people with HIV + COVID-19
  - Among HIV positive: 10% current TB and 31% previous TB
- Disease severity and immune cell changes in the first and second (501Y.V2 Beta variant) infection waves
  - During 1st wave: similar COVID-19 severity in HIV neg vs HIV pos, with some HIV modulation of SARS-CoV-2 immune responses.
  - During 2nd wave (new variant), higher disease severity was associated with ↑ supp.oxygen, ↓ CD4 counts, ↑ neutrophil to lymphocyte ratios (NLR) – stabilised after SARS-CoV-2 clearance in PLWH

- Immunocompromised PLWH have reduced serological response to SARS-CoV-2 infection
- Intra-host evolution in immunocompromised patients with advanced HIV unable to clear SARS-CoV-2 → emergence of variants
- HIV infection can synergize with the SARS-CoV-2 variant to change COVID-19 outcomes
Does COVID-19 co-infection alter PTB Clinical manifestation and disease progression?
Covid-19 & TB: Radiologic & clinical features in co-infected patients

- Impact of Covid-19 on TB clinical course and outcome modest
- 20 TB patients (19 PTB) diagnosed with Covid-19 within 30 days from TB diagnosis
- 63% cleared Covid-19 within 14 days & 5% (1/20) died
- Impact of Covid-19 on TB lesions on chest radiographs
  - 12 patients (63%) TB lesions improved
  - 1 patient with extrapulmonary TB - no change
  - 7 patients (35%) had worsening TB
- Covid-19 associated lesions on chest radiographs
  - 4 patients developed new onset pneumonia
  - 3 patients (15%) had mild-to-moderate interstitial thickening
  - 1 patient had ground glass pattern on CT
Covid-19 & TB: Impact on clinical course & outcome

• Matched cohort of 530 Covid-19 patients, 106 with confirmed previous or current active TB

• TB vs no TB co-infection with Covid-19
  ➔ RR: 2.2 fold higher mortality (p=0.001)
  ➔ 25% lower recovery (p=0.003)
  ➔ Shorter time-to-death (p=0.0031)
  ➔ Time-to-recovery longer in patients with TB (p=0.0046)

Survival analysis for time-to-death
Increased Covid-19 susceptibility in TB patients

Active or latent tuberculosis increases susceptibility to COVID-19 and disease severity

Yongyu Liu, Lijun Bi, Yu Chen, Yaguow Wang, Joy Fleming, Yanhong Yu, Ye Gu, Chang Liu, Lichao Fan, Xiaodan Wang, Moxin Cheng

Greater likelihood of severe symptoms

Greater rapidity of symptom onset

Greater likelihood of complications

Case-control study of 36 Covid-19 patients, 13 with MTB infection (IGRA pos)
COVID-19 infection among people living with DR-TB?

A positive COVID-19 test is associated with high mortality in RR-TB-HIV patients

E. Mohr-Holland,1,2 J. Daniels, B. Douglas-Jones, N. Mem, V. Scott,3 L. Trivino-Duran, C. Pfaff,4 J. Furin, P. Isaakidis

• Among 261 active RR-TB patients in Khayelitsha → Seventy-five (29%) received a SARS-CoV-2 test, 18 (24%) tested SARS-CoV-2 positive (median age 43 years, treated for RR-TB in hospital and >1 comorbidities)
• 61% of all RR-TB –COVID-19 co-infected patients died:
  – no significant clinical differences between those that died and survived
  – 4 were culture-negative at the time of death
• Among remaining 243 patients who were not tested for COVID or were negative, 6.6% died
  – mortality significantly higher among those who tested positive for COVID-19
  – Sicker patients offered testing for COVID-19
  – Possible pathological biological interactions between COVID-19 and RRTB leading to excess mortality
Is vaccine effectiveness impaired among PLWHA?
Is vaccine effectiveness impaired among PLWHA?

- **JnJ – viral vector vaccine**
  - 500 000 HCWs enrolled in the Sisonke trial
  - Similar neutralisation antibody response (Delta variant) following JnJ vaccination in well controlled PLWHA and HIV-negative participants, irrespective of past COVID infection
  - Reduced neutralization antibody response in non-vaccinated HIV infected participants
    - strongest reduction in HIV viraemic individuals

- **Pfizer and Moderna – mRNA vaccines**
  - Among 14 PLWHA, 5 (36%) received the Pfizer vaccine and 9 (64%) received the Moderna mRNA vaccine
  - At one month post vaccination:
    - First dose antibody titres: < 0.4 - > 250 units/ml
    - Second dose titres all > 250 units/ml
    - All participants had high titres of anti-RBD Ab’s on 2 dose vaccine with excellent HIV virologic control on ART
Is vaccine effectiveness impaired among PLWHA?

- **Oxford/AstraZeneca vaccine – viral vector vaccine**
  - 104 PLWHA in SA, on ART >3 months, VL<1000c/ml
  - Antibody responses similar in HIV positive and HIV-negative people 28 and 42 days after the first dose
  - No difference in the frequency of adverse reactions between people with and without HIV

- **Sinopharm vaccine – inactivated vaccine**
  - 42 HIV-1 infected individuals v 28 healthy individuals
  - Vaccine was safe, immunogenic in PLWH who are stable on ART
  - Comparable AB responses + T cell responses in PLWH vs with those in healthy individuals
COVID-19 JnJ Vaccine effectiveness in HIV infected HCWs in South Africa

Although VE was seen against death in HCW living with HIV, this was reduced in comparison to HCW without HIV at an effectiveness of 65% (95% CI 3-93)

- HCWs were vaccinated over 3 months (17 February - 17 May 2021)
- VE assessed in Matched cohorts

Source: Bekker et al., 2022. Sisonke Trial – Preprint
Impact of COVID-19 on the HIV & TB public health response
Potential COVID-19 Collateral Damage

- COVID-19 impact on the health system is likely to be far more substantial and long-lasting in countries with high TB and HIV incidence
- Modelling data:
  - Disrupted drug supplies $\rightarrow$ surge in drug resistance $\rightarrow$ increased costs of treatment
  - Reversing gains and successes in managing tuberculosis and HIV achieved in the last 10 years

- Excess of 6 million TB deaths by 2025
  - Decreased diagnosis, treatment initiation, and successful treatment completion
- Increased HIV mortality by 40% in 2025
  - A 6-month disruption of ART delivery for HIV could result in up to half a million additional deaths yearly
Covid-19 impacted HIV services

The impact of the COVID-19 lockdown on HIV care in 65 South African primary care clinics: an interrupted time series analysis


- Lockdown reduced patient attendance at health facilities in South Africa:
  - 57%* (n=339) apprehensive to visit clinics/hospital during lockdown

- HIV testing ↓ 47.6% in April 2020

- ART initiations ↓ 46.2% in April 2020

- No marked change in ART medicine collections

*The Ask Afrika COVID-19 Tracker
COVID-19 Impact on TB and HIV Mortality

Pre-COVID-19:
- Substantial reduction in HIV associated TB mortality in SA
- HIV Death rates unchanged since 2014
  – TB commonest cause of death in PLWHA

COVID-19:
- Global reduction in finding, treating and preventing TB
- Increased TB mortality → 100 000 additional TB deaths in 2021 alone

Summary

• HIV appears to be a significant independent risk factor for severe or critical illness at hospital admission and in-hospital mortality.
• Risk of COVID-19 hospitalization increases with HIV disease stage, not on ART, CD4 < 200 cells/ul, VL > 1000, increasing co-morbidities, increasing age.
• Changes in the virus may make infection with some variants substantially different in disease course, immunologic modulation, and effect on PLWH relative to ancestral SARS-CoV-2 strains or other variants.
• Preliminary data show Covid-19 in TB is more severe, with higher mortality, more complications.
• VE is maintained against death and reduced against hospitalization, and for in-hospital ICU/critical care among PLWHA compared to HIV uninfected.
Funders