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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

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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

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Is HIV & TB associated with an increased risk of severe disease and death from COVID-19?

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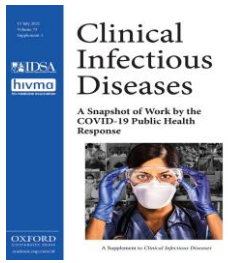
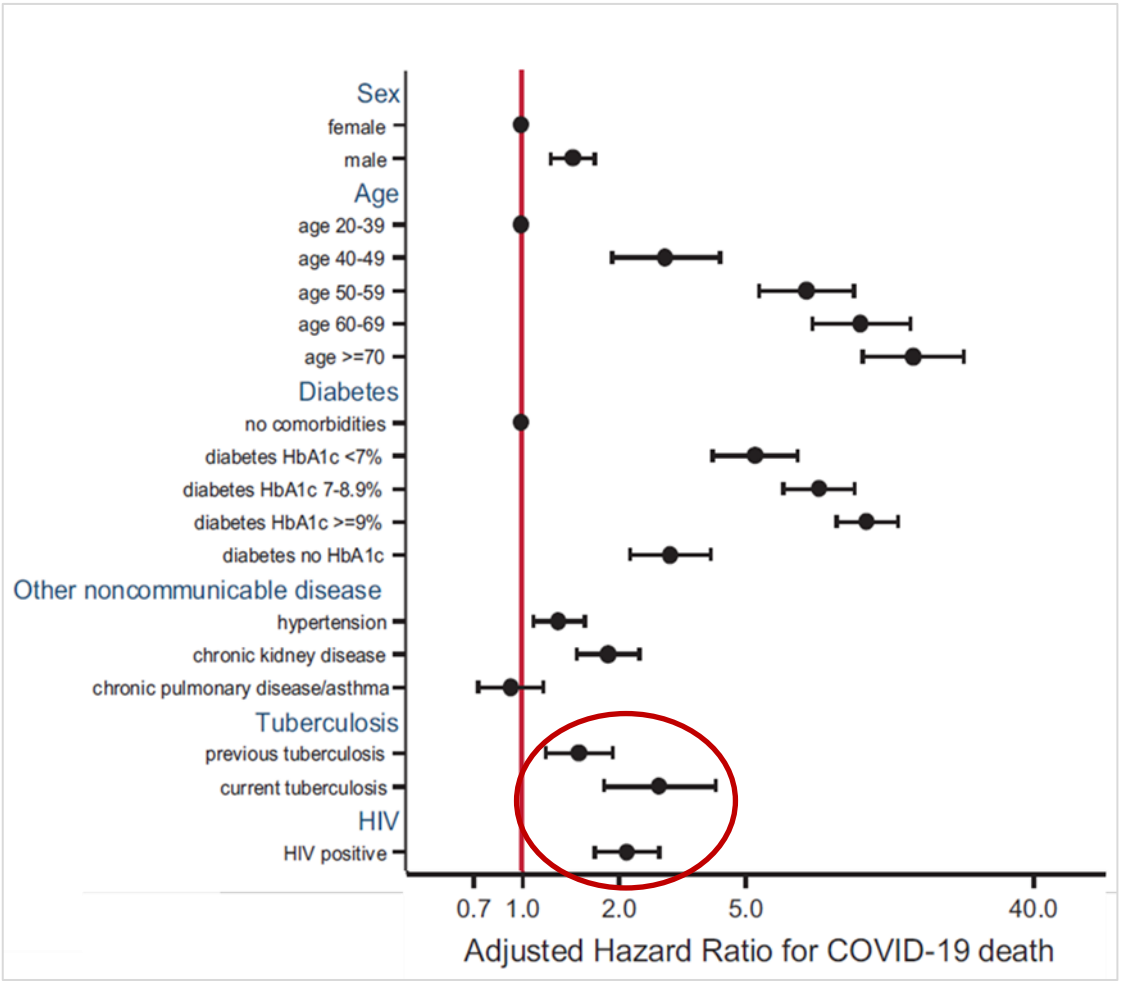
Increased COVID-19 mortality in HIV & TB patients



Risk Factors for Coronavirus Disease 2019 (COVID-19) Death in a Population Cohort Study from the Western Cape Province, South Africa

Western Cape Department of Health in collaboration with the National Institute for Communicable Diseases, South Africa

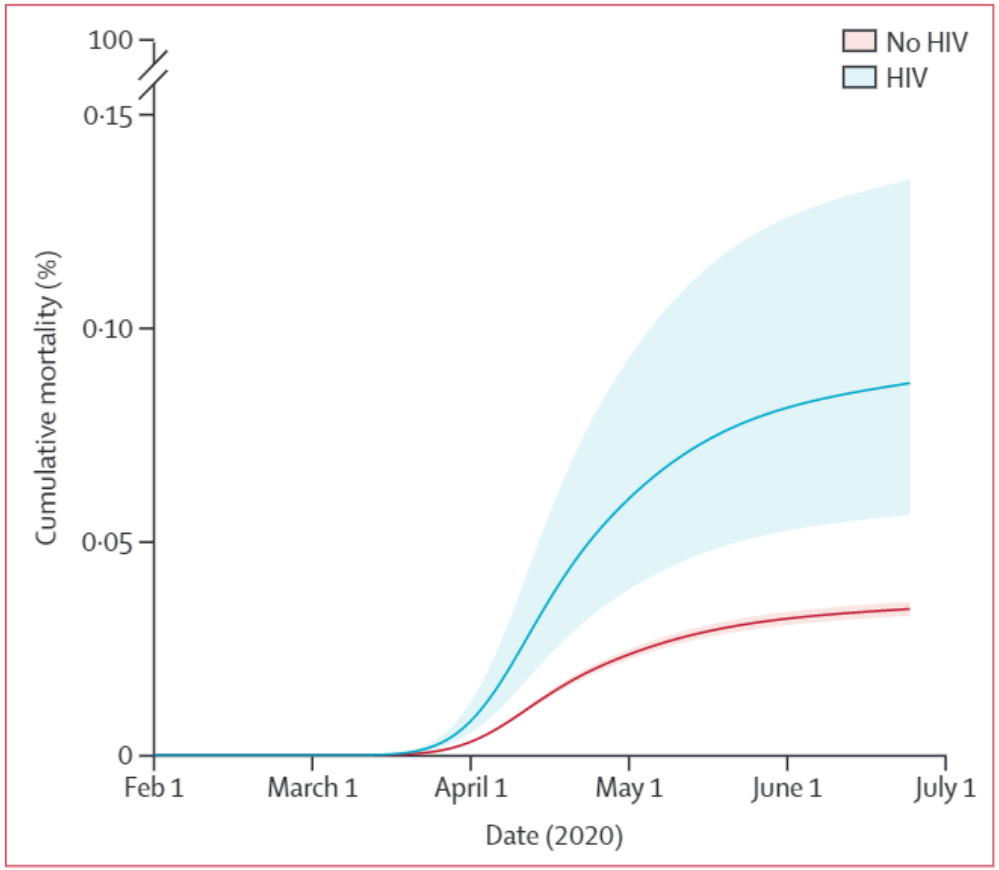


- Population cohort study of adults attending public-sector facilities in Western Cape, SA
- Data collected between March - June 2020 (First wave wild-type strain)
- Among 3.5 million → 22 308 diagnosed with COVID-19 & 625 died
- HIV-associated COVID-19 mortality:
  - aHR 2.14 (CI: 1.70–2.70)
  - Mortality 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

Krishnan Bhaskaran, Christopher T Rentsch, Brian MacKenna, Anna Schultze, Amir Mehrkar, Chris J Bates, Rosalind M Eggo, Caroline E Morton, Sebastian C J Bacon, Peter Inglesby, Ian J Douglas, Alex J Walker, Helen I McDonald, Jonathan Cockburn, Elizabeth J Williamson, David Evans, Harriet J Forbes, Helen J Curtis, William J Hulme, John Parry, Frank Hester, Sam Harper, Stephen J W Evans, Liam Smeeth, Ben Goldacre**



- 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

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Poor COVID-19 Outcomes & Higher Hospitalization among PLWHA: US

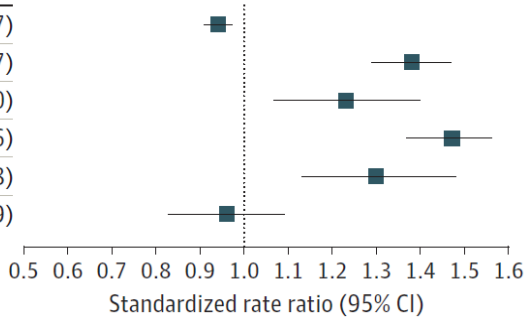
Original Investigation | Infectious Diseases

COVID-19 Outcomes Among Persons Living With or Without Diagnosed HIV Infection in New York State

James M. Tesoriero, PhD; Carol-Ann E. Swain, PhD; Jennifer L. Pierce, BS; Lucila Zamboni, PhD; Meng Wu, PhD; David R. Holtgrave, PhD; Charles J. Gonzalez, MD; Tomoko Udo, PhD; Johanne E. Morne, MS; Rachel Hart-Malloy, PhD; Deepa T. Rajulu, MS; Shu-Yin John Leung, MA; Eli S. Rosenberg, PhD

Summary of COVID-19 Diagnosis, Hospitalization, and in-Hospital Deaths in those with and without diagnosed HIV Infection

Outcome	Unadjusted: PLWDH rate per 1000	Unadjusted: Non-PLWDH rate per 1000	Unadjusted: Rate ratio (95% CI)	Standardized rate ratio (95% CI)
Diagnosed with COVID-19, per population	27.7	19.4	1.43 (1.38-1.48)	0.94 (0.91-0.97)
Hospitalized with COVID-19, per population	8.3	3.2	2.61 (2.45-2.79)	1.38 (1.29-1.47)
In-hospital death with COVID-19, per population	1.9	0.8	2.55 (2.22-2.93)	1.23 (1.07-1.40)
Hospitalized with COVID-19, per diagnosis	299.9	163.5	1.83 (1.72-1.96)	1.47 (1.37-1.56)
In-hospital death with COVID-19, per diagnosis	69.3	38.7	1.79 (1.56-2.05)	1.30 (1.13-1.48)
In-hospital death with COVID-19, per hospitalization	231.0	236.6	0.98 (0.85-1.12)	0.96 (0.83-1.09)



- Assessed outcomes in 3000 known PLWHA-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

Risk factors for COVID-19-related in-hospital mortality in a high HIV and tuberculosis prevalence setting in South Africa: a cohort study

Waasila Jassat, Cheryl Cohen, Stefano Tempia, Maureen Masha, Susan Goldstein, Tendesayi Kufa, Pelagia Murangandi, Dana Savulescu, Sibongile Walaza, Jamy-Lee Bam, Mary-Ann Davies, Hans W Prozesky, Jonathan Naude, Ayanda T Mnguni, Charlene A Lawrence, Hlengani T Mathema, Jarrod Zamparini, John Black, Ruchika Mehta, Arifa Parker, Perpetual Chikobvu, Halima Dawood, Ntshengedzeni Muvhango, Riaan Strydom, Tsholofelo Adelekan, Bhekizizwe Mdlovu, Nirvasha Moodley, Eunice L Namavhandu, Paul Rheeder, Jacqueline Venturas, Nombulelo Magula, Lucille Blumberg, DATCOV author group

- 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

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Effect of ART, CD4 cell count, and HIV viral load on COVID-19 in-hospital mortality

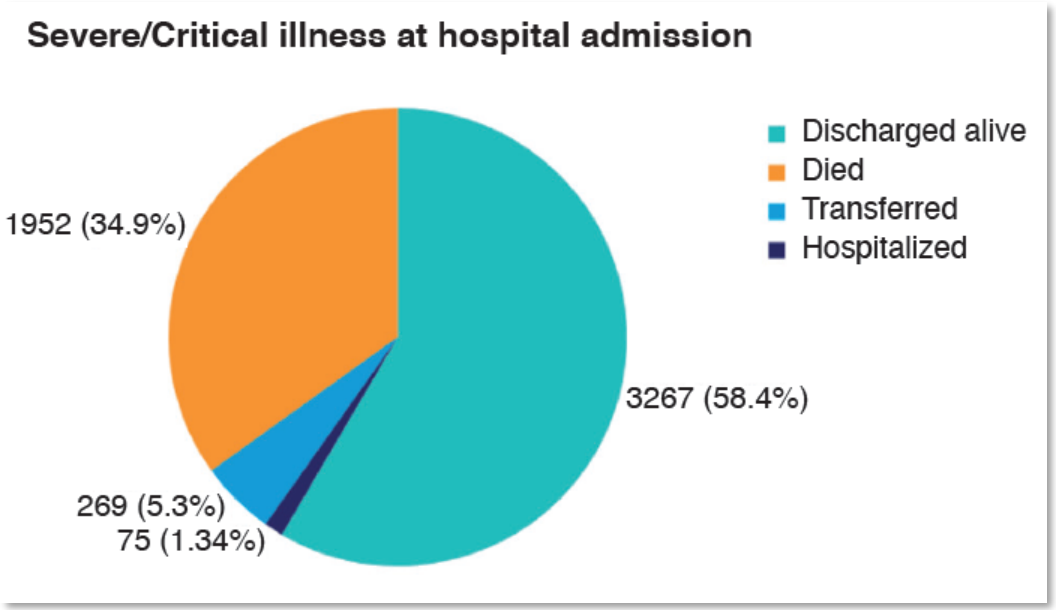
	Case fatality ratio unimputed	Case fatality ratio (95% CI) imputed	Unadjusted OR (95% CI) imputed	p value	Adjusted OR (95% CI) imputed*	p value	Adjusted OR (95% CI) imputed*	p value
ART status								
HIV negative	30 697/137 986 (22·2%)	23·1% (22·9–23·3)	1 (ref)	..	1 (ref)	..	0·77 (0·72–0·82)	<0·0001
HIV positive on ART	2046/7484 (27·3%)	24·6% (23·8–25·4)	0·85 (0·80–0·90)	<0·0001	1·30 (1·22–1·39)	<0·0001	1 (ref)	..
HIV positive not on ART	192/594 (32·3%)	28·1% (25·2–31·1)	0·99 (0·86–1·15)	0·98	1·89 (1·60–2·23)	<0·0001	1·45 (1·22–1·72)	<0·0001
CD4 count								
HIV negative	30 697/137 986 (22·2%)	23·1% (22·9–23·3)	1 (ref)	..	1 (ref)	..	1·06 (0·93–1·20)	0·37
HIV positive CD4 count, ≥200 cells per µL	368/1690 (21·8%)	19·7% (17·7–21·7)	0·64 (0·57–0·73)	<0·0001	0·95 (0·83–1·08)	0·37	1 (ref)	..
HIV positive CD4 count, <200 cells per µL	380/1080 (35·2%)	32·2% (29·9–34·5)	1·23 (1·09–1·38)	0·0023	2·19 (1·92–2·49)	<0·0001	2·31 (1·82–2·93)	<0·0001
Viral load								
HIV negative	30 697/137 986 (22·2%)	23·1% (22·9–23·3)	1 (ref)	..	1 (ref)	..	0·83 (0·76–0·90)	0·0002
HIV positive viral load, <1000 HIV RNA copies per mL	316/1273 (24·8%)	24·7% (23·0–26·4)	0·86 (0·78–0·94)	0·0029	1·21 (1·11–1·32)	0·0002	1 (ref)	..
HIV positive viral load, ≥1000 HIV RNA copies per mL	128/443 (28·9%)	25·2% (21·0–29·4)	0·85 (0·69–1·05)	0·13	1·88 (1·53–2·31)	<0·0001	1·55 (1·20–2·01)	0·0029

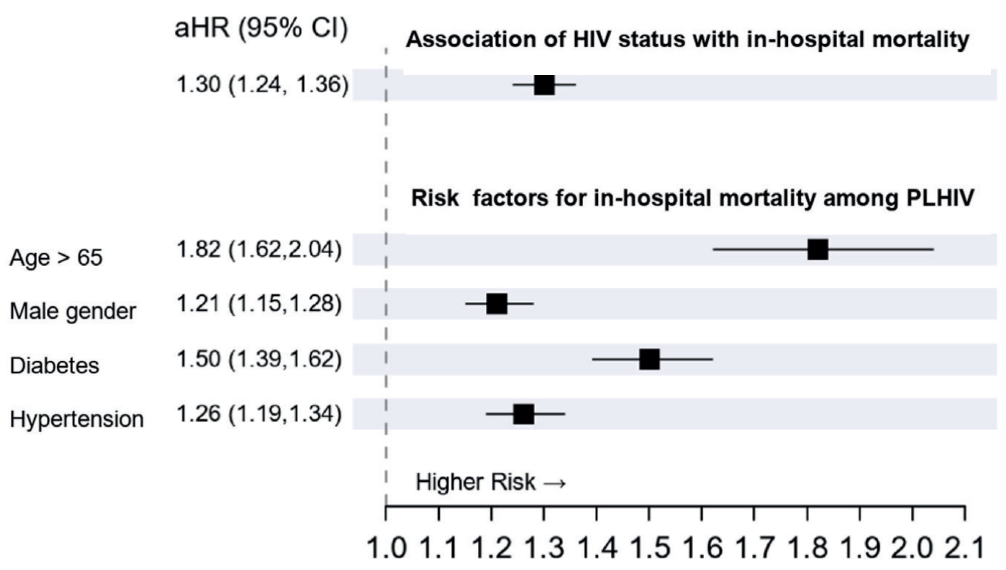
	Case fatality ratio unimputed	Case fatality ratio (95% CI) imputed	Adjusted OR (95% CI) imputed*	p value
Any individual				
HIV-positive individuals				
Comorbid condition				
No comorbidity	341/2073 (16·4%)	15·6% (14·6–16·6)	1 (ref)	..
One comorbidity	384/1524 (25·2%)	23·2% (21·9–24·5)	1·34 (1·20–1·49)	<0·0001
Two comorbidities	292/932 (31·3%)	29·4% (27·7–31·0)	1·67 (1·48–1·90)	<0·0001
Three or more comorbidities	143/352 (40·6%)	41·9% (40·0–43·8)	2·46 (2·22–2·73)	<0·0001

- **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

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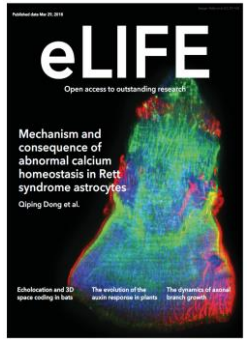
Disease severity & immune response in PLWHA

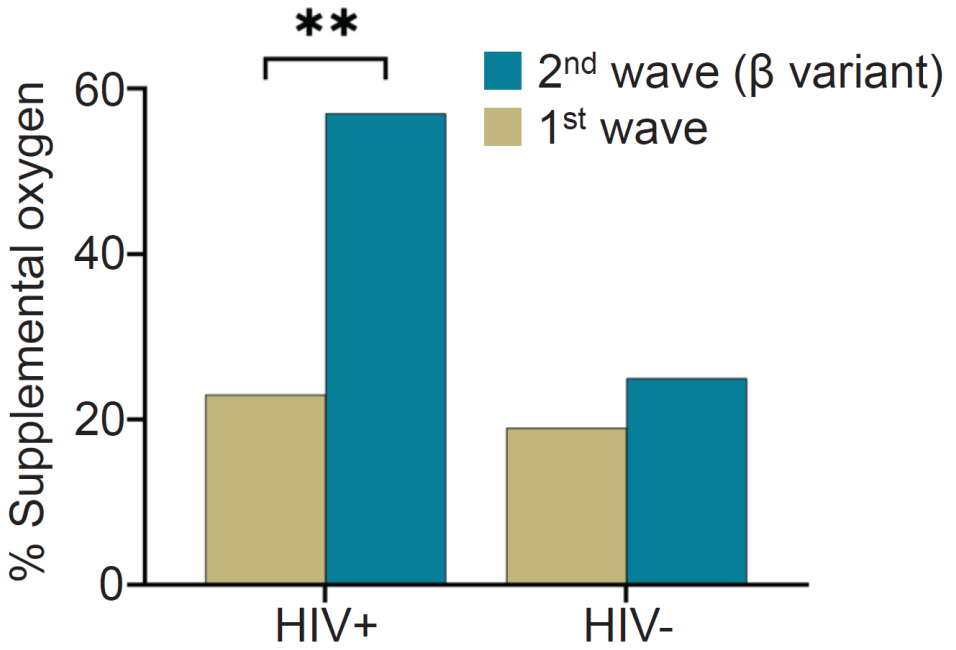


HIV status alters disease severity and immune cell responses in Beta variant SARS-CoV-2 infection wave

Farina Karim[1,2], Inbal Gazy[2,3], Sandile Cele[1,2], Yenzekile Zungu[1], Robert Krause[1,2], Mallory Bernstein[1], Khadija Khan[1,2]..... Alex Sigal[1,2,6*]

- 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?

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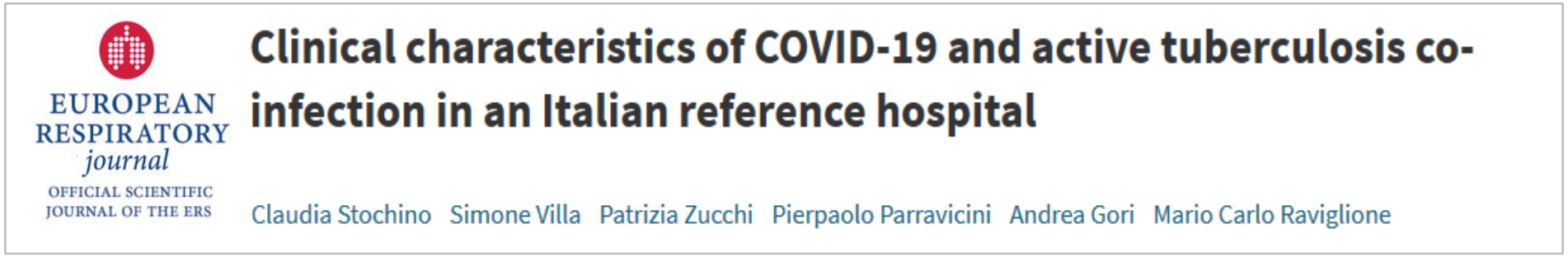
Covid-19 & TB: Radiologic & clinical features in co-infected patients



- **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

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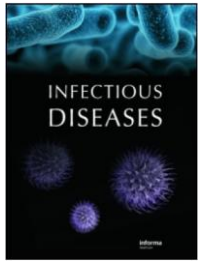
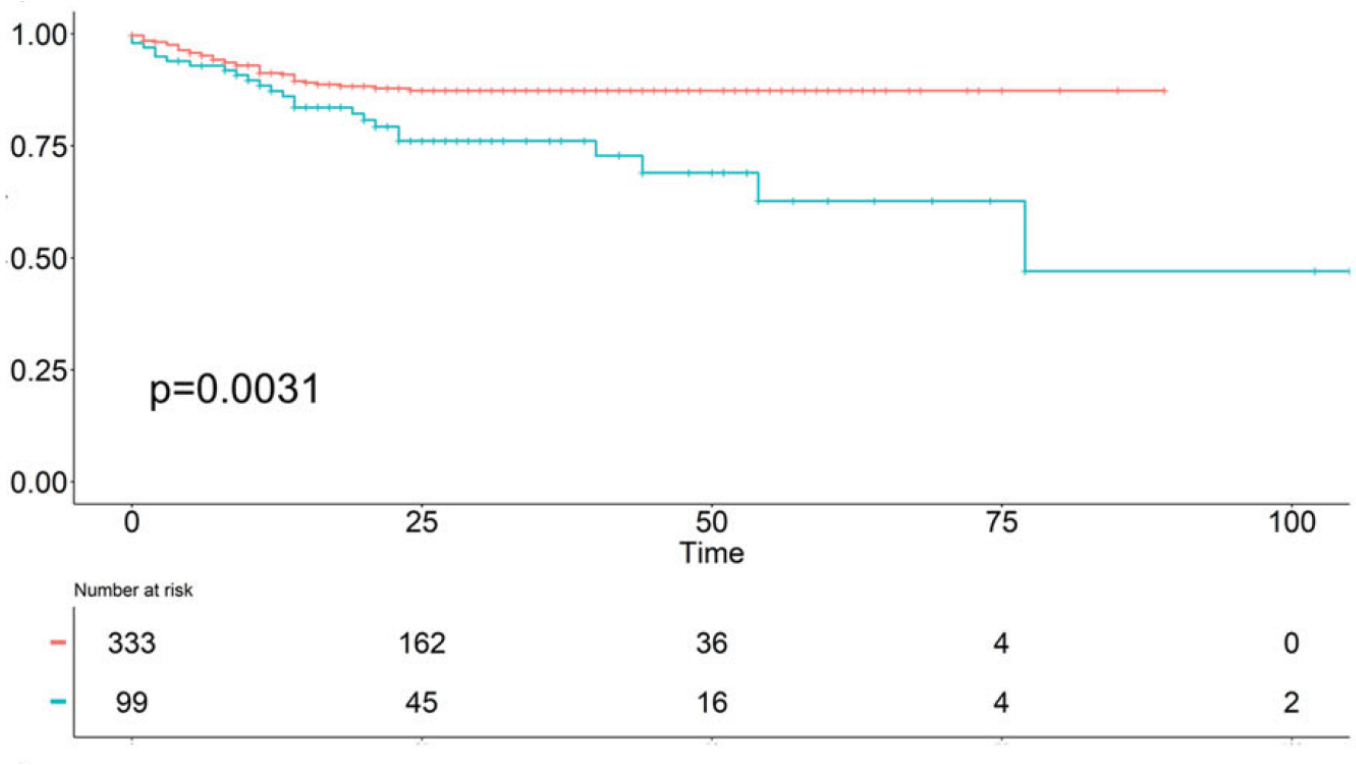
Covid-19 & TB: Impact on clinical course & outcome



Previous and active tuberculosis increases risk of death and prolongs recovery in patients with COVID-19

Karla Therese L. Sy[a,b], Nel Jason L. Haw[c*] and Jhanna Uy[c,d*]



Survival analysis for time-to-death

- 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)

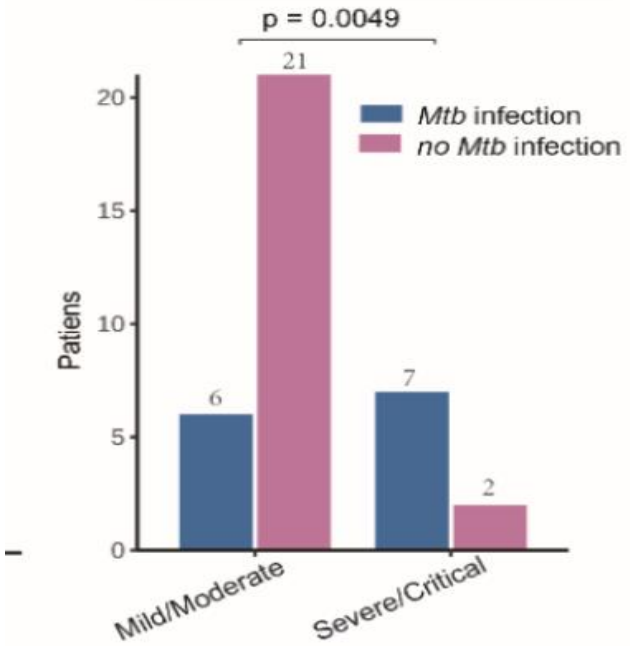
Increased Covid-19 susceptibility in TB patients

medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

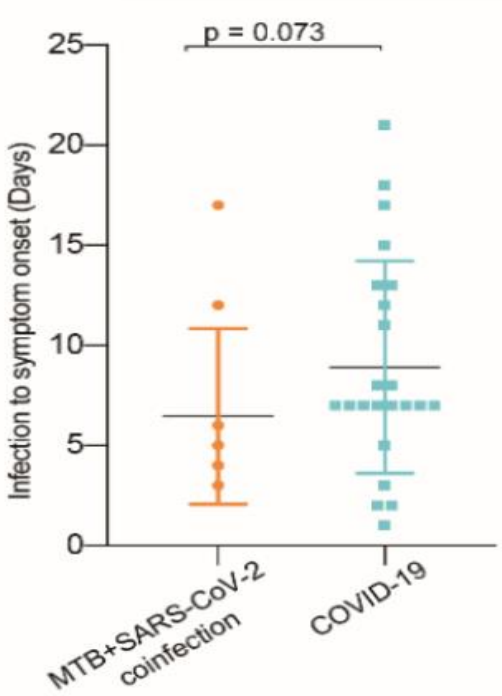
Active or latent tuberculosis increases susceptibility to COVID-19 and disease severity

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

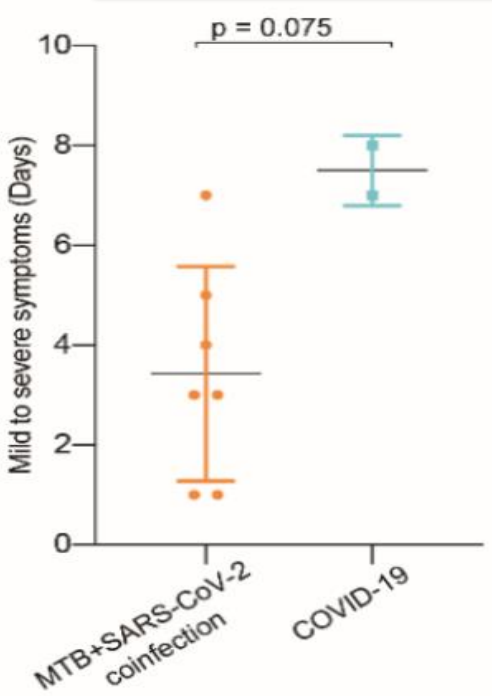
Greater likelihood of severe symptoms



Greater rapidity of symptom onset



Greater likelihood of complications



Case-control study of 36 Covid-19 patients, 13 with MTB infection (IGRA pos)

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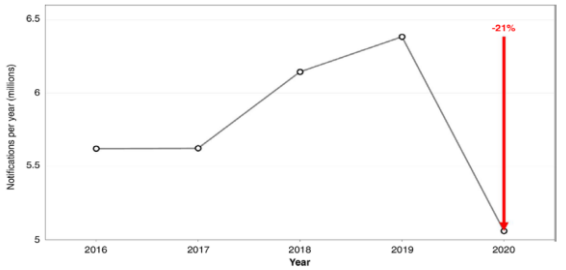
COVID-19 infection among people living with DR-TB?

The International Journal of Tuberculosis and Lung Disease

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[1], N. Mema,[1] V. Scott,[31] L. Trivino-Duran,[1] C. Pfaff,[1] J. Furin,[4] P. Isaakidis[2]



A 21% decrease in TB case notification

- 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

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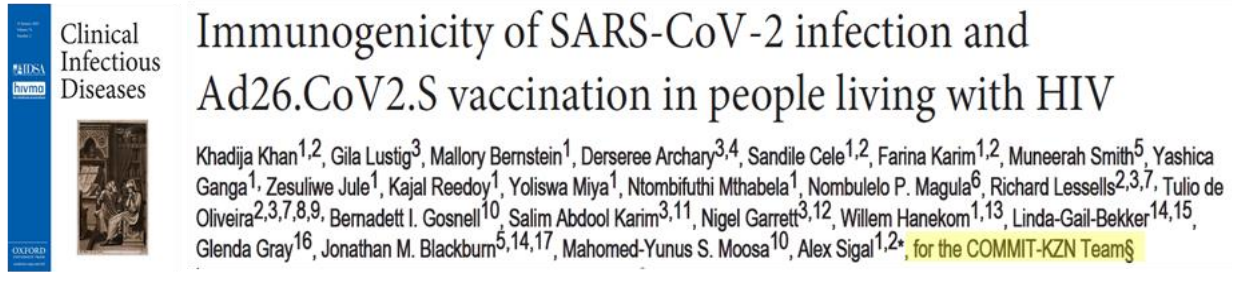
Is vaccine effectiveness impaired among PLWHA?

Is vaccine effectiveness impaired among PLWHA?



Clinical Infectious Diseases

Immunogenicity of SARS-CoV-2 infection and Ad26.CoV2.S vaccination in people living with HIV

Khadija Khan[1,2], Gila Lustig[3], Mallory Bernstein[1], Derseree Archary[3,4], Sandile Cele[1,2], Farina Karim[1,2], Muneerah Smith[5], Yashica Ganga[1], Zesuliwe Jule[1], Kajal Reedoy[1], Yoliswa Miya[1], Ntombifuthi Mthabela[1], Nombulelo P. Magula[6], Richard Lessells[2,3,7], Tulio de Oliveira[2,3,7,8,9], Bernadett I. Gosnell[10], Salim Abdool Karim[3,11], Nigel Garrett[3,12], Willem Hanekom[1,13], Linda-Gail-Bekker[14,15], Glenda Gray[16], Jonathan M. Blackburn[5,14,17], Mahomed-Yunus S. Moosa[10], Alex Sigal[1,2*], for the COMMIT-KZN Team§

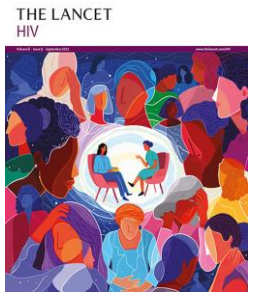
Safety and antibody response to two-dose SARS-CoV-2 messenger RNA vaccination in persons with HIV

Jake A. Ruddy[a], Brian J. Boyarsky[a], Justin R. Bailey[b], Andrew H. Karaba[b], Jacqueline M. Garonzik-Wang[a],

- **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?



Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 in people living with and without HIV in South Africa: an interim analysis of a randomised, double-blind, placebo-controlled, phase 1B/2A trial

Shabir A Madhi, Anthonet L Koen, Alane Izu, Lee Fairlie, ...Penny L Moore, Gaurav Kwatra*, on behalf of the Wits VIDA COVID team†*

- **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

Immunogenicity of an inactivated SARS-CoV-2 vaccine in people living with HIV-1: a non-randomized cohort study

Yanmeng Feng,[a,#] Yifan Zhang,[b,c,d,#] Zhangyufan He,[b,d,#] Haojie Huang,[e] Xiangxiang Tian,[b,c,d] Gang Wang,[d] Daihong Chen,[d] Yanqin Ren,[b] Liqiu Jia,[b] Wanhai Wang,[c] Jing Wu,[b] Lingyun Shao,[b] Wenhong Zhang,[b,f,g,h] Heng Tang,[a,] and Yanmin Wan,[b,g,i,*]*

- **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

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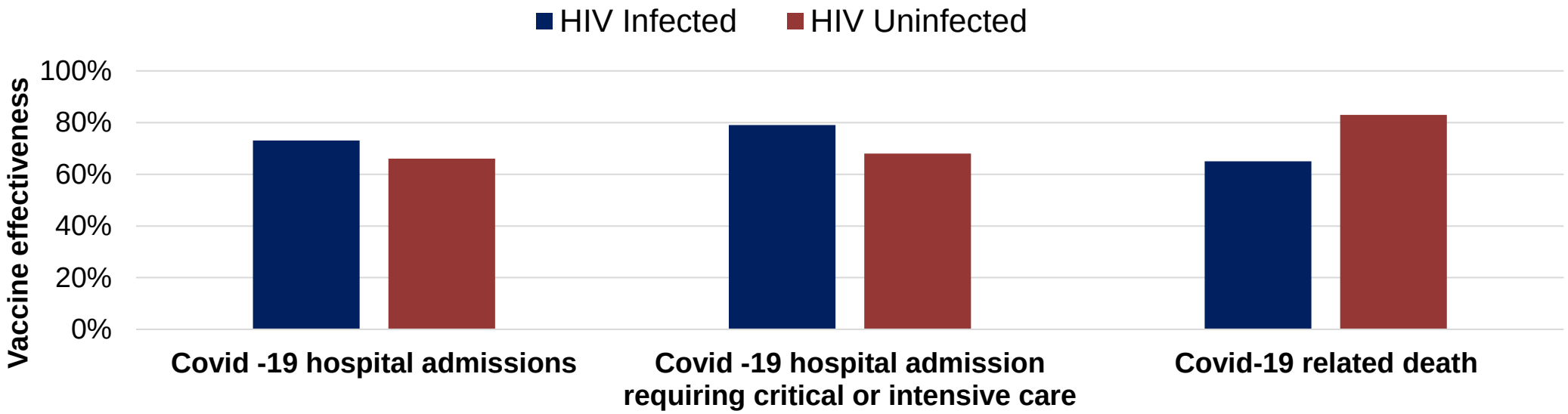
COVID-19 JnJ Vaccine effectiveness in HIV infected HCWs in South Africa



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

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)

Source: Bekker et al., 2022. Sisonke Trial – Preprint

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Impact of COVID-19 on the HIV & TB public health response

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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:

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

- Disrupted drug supplies → surge in **drug resistance** → increased costs of treatment
- Reversing gains and successes in managing tuberculosis and HIV achieved in the last 10 years

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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

Jienchi Dorward, Thokozani Khubone, Kelly Gate, Hope Ngobese, Yukteshwar Sookrajh, Siyabonga Mkhize, Aslam Jeewa, Christian Bottomley, Lara Lewis, Kathy Baisley, Christopher C Butler, Nomakhosi Gxagxisa, Nigel Garrett

- **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*

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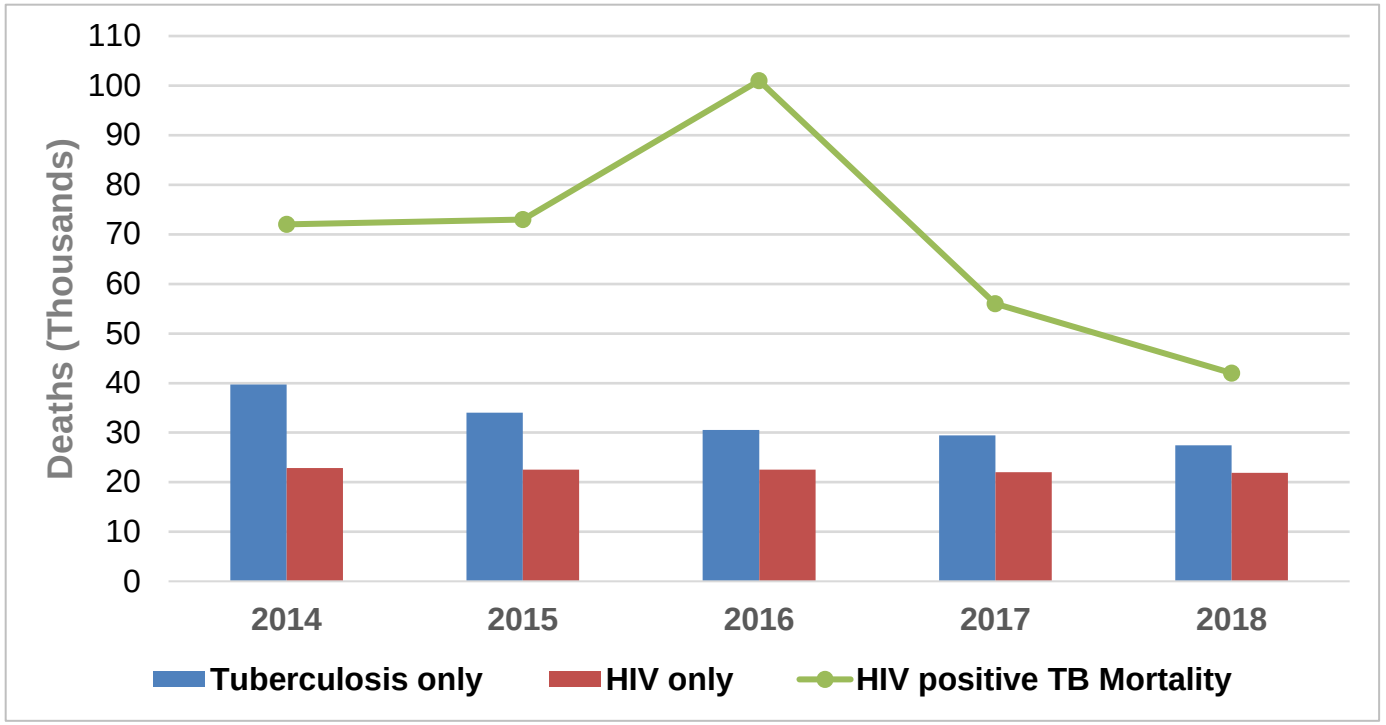
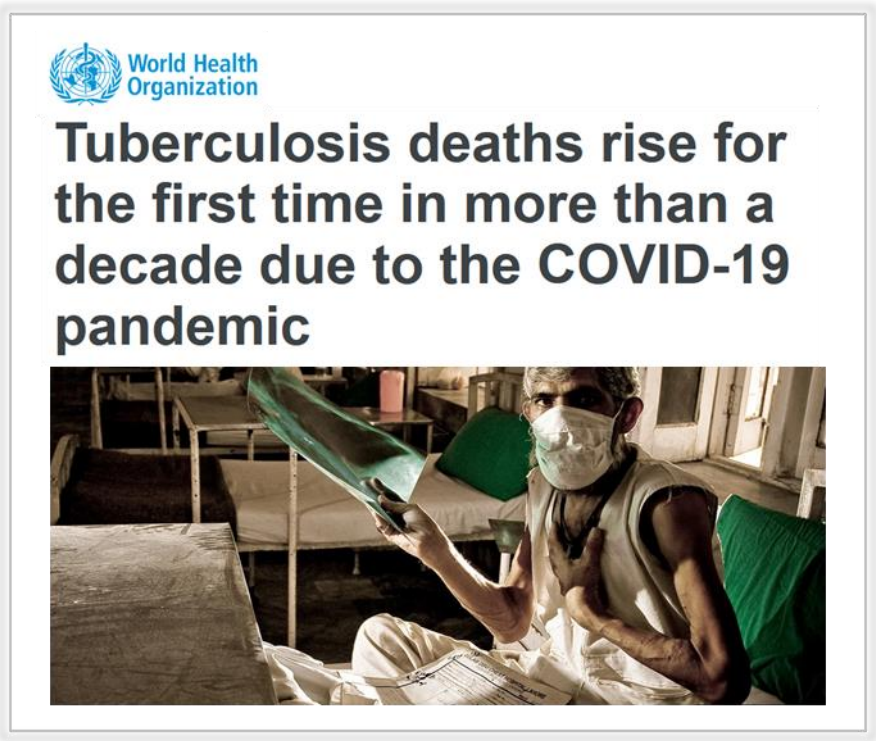
COVID-19 Impact on TB and HIV Mortality





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**

Statistics SA 2018 – 2021 Report

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

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