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Understanding the impact of pandemics on long-term medication adherence: directly observed therapy in a tuberculosis treatment cohort pre- and post-COVID-19 lockdowns

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Abstract

Background The COVID-19 pandemic negatively impacted tuberculosis (TB) treatment services, including directly observed therapy (DOT) programs used to promote medication adherence. We compared DOT adherence embedded in a research study before and after COVID-19 lockdowns in South Africa.

Methods We analyzed data from 263 observational study participants undergoing drug susceptible (DS)-TB DOT between May 2017 to March 2022. Participants enrolled before October 2019 were considered 'pre-COVID-19' and those enrolled after September 2020 were considered 'post-COVID-19 lockdown groups. Negative binomial regression models were used to compare DOT non-adherence rates between the two lockdown groups. We then conducted a sensitivity analysis which only included participants enrolled in the immediate period following the first COVID-19 lockdown.

Results DOT non-adherence rate was higher in the post-COVID-19 lockdown group (aIRR = 1.42, 95% CI = 1.04–1.96; $p = 0.028$) compared to pre-COVID-19 lockdown period, adjusting for age, sex, employment status, household hunger, depression risk, and smoked substance use. DOT non-adherence was highest immediately following the initial lockdown (aIRR = 1.74, 95% CI = 1.17–2.67; $p = 0.006$).

Conclusion The COVID-19 lockdowns adversely effected adherence to TB DOT in the period after lockdowns were lifted. The change in DOT adherence persisted even after adjusting for socioeconomic and behavioral variables. We need a better understanding of what treatment adherence barriers were exacerbated by COVID-19 lockdowns to improve outcomes in post-pandemic times.

Trial registration ClinicalTrials.gov Registration Number: NCT02840877. Registered on 19 July 2016.

Keywords SARS-CoV-2, Adherence, *Mycobacterium tuberculosis*, Drug-susceptible TB, South Africa

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Background

South Africa, a high tuberculosis (TB) burden country, reported its first case of COVID-19 on March 5, 2020, and within three weeks, the country implemented a national lockdown with a five-level COVID-19 alert system [1, 2]. Higher alert levels were indicative of high COVID-19 spread coupled with low health system readiness, which led to the implementation of extreme restrictions of individual movement that required persons to stay home and the closure of schools and businesses. The highest two alert levels with the greatest restrictions (Level 4 and Level 5) were lifted at the end of May 2020, and decreased to Level 1 by September 2020 [see Additional file 1] [3]. The economic and emotional stresses of the early pandemic lockdowns were felt across South Africa and had persistent impacts on engagement with the healthcare system [2, 4, 5].

Medication non-adherence is a major driver of unfavorable TB treatment outcomes. Previous studies report that drivers of non-adherence include a lack of knowledge about TB treatment and the consequences of medication side effects, inadequate access to healthcare services, depression, and substance use (including alcohol use) [6–11]. In 1994, the World Health Organization (WHO) adopted the directly observed therapy (DOT), short-course strategy as a way to improve TB treatment adherence [12, 13].

With healthcare systems overwhelmed by COVID-19, South African services and resources for TB programs that supported treatment adherence were greatly diminished [4]. The impact of COVID-19 on TB programs was likewise seen in other countries, and resulted in fewer TB follow-up appointments, less observed medication ingestion in DOT programs, or stopping DOT programs altogether [4, 6]. Whether treatment adherence increased after the initial COVID-19 waves to pre-pandemic levels is not well-documented and there is little understanding of whether certain persons with TB disease were more adversely affected than others.

Our parent study, Tuberculosis Treatment and Alcohol Use Study (TRUST), provided an opportunity to have a granular view of how the COVID-19 lockdowns in South Africa impacted TB treatment adherence, which was monitored through a research DOT program [14]. In this study, all participants were assigned a community worker who visited them at their home for DOT for the six-month duration of their TB treatment. We aimed to compare DOT adherence and loss to follow-up (LTFU) rates of participants enrolled before and after the COVID-19 lockdowns, to assess whether DOT adherence rates observed after the initial lockdowns recovered to pre-pandemic levels, and to identify factors associated with non-adherence among those enrolled after the COVID-19 lockdown period.

Methods

Participants

We report on 263 participants enrolled into the TRUST cohort in Worcester, Western Cape Province, South Africa between May 2017, and March 2022. Study processes are described previously [14]. Participants were at least 15 years old, had microbiologic confirmation of *Mycobacterium tuberculosis* (smear, Xpert and/or culture positive) and were initiating outpatient treatment for pulmonary drug susceptible (DS)-TB with the standard four drug regimen. Exclusion criteria included rifampicin resistance, epilepsy medications, pregnancy, unknown HIV status, prior TB treatment in the past two years, and unable/unwilling to participate in DOT.

We classified participants into a pre-COVID-19 lockdown group (any participant enrolled before October 1, 2019) and a post-COVID-19 lockdown group (any participant enrolled after the study resumed on September 21, 2020). Participants enrolled between October 1, 2019, and March 31, 2020, were not included in this analysis because their DOT was interrupted by COVID-19 lockdowns. After study activities resumed, while the core DOT worker staff remained the same, there were notable changes in DOT procedures and protocols, including stricter PPE usage, enhanced cleaning, and conducting visits outside. This approach was generally well-received; though a few participants voiced concern over taking medication in view of their neighbors and efforts were made to make accommodation.

Measures

Participants completed interviewer-administered questionnaires and provided blood and sputum samples within one week of TB treatment initiation. Information on biological sex, age, race, employment, education, and history of incarceration were collected. High depression risk was defined as a Center for Epidemiological Studies Depression Score (CES-D) of ≥ 16 [15]. Moderate to severe hunger in the household was defined as a Household Hunger Scale (HHS) score of 2–6 [16]. Unhealthy alcohol use was defined as an Alcohol Use Disorders Identification Test (AUDIT) score ≥ 8 and/or a phosphatidylethanol (PEth) result > 49 ng/mL [17]. PEth is a biomarker of past 21-day alcohol consumption [18]. Tobacco use was defined as any self-reported current use, and smoked substance use was defined as self-reported current use and/or a positive urine drug screen for cannabis, methamphetamine, and/or methaqualone.

Body mass index (BMI) was categorized as severely underweight (< 16.5), underweight (16.5–18.5), normal

weight (18.5–24.9), overweight and obese (≥25) [19]. HIV status, CD4 count, and antiretroviral therapy (ART) information were extracted from medical records. Previous TB disease was collected via self-report and medical records. For all sputum specimens, a concentrated Ziehl-Neelsen (ZN) smear, acid-fast bacillus (AFB) presence and mycobacterial time-to-culture positivity (TTP) in days were prepared and examined [20–22]. Either a study radiologist or two TB physicians reviewed chest radiographs for cavitation (yes/no). Treatment outcomes, abstracted from the clinic medical records, were classified as favorable if the participants were cured or completed treatment, unfavorable if the participants were LTFU or died, and missing if the participant moved or transferred out [23].

The South African Medical Research Council, Boston University/Boston Medical Center, University of Cape Town, Stellenbosch University, and South African Western Cape Department of Health provided ethical approval for the study.

Adherence to DOT

All TRUST participants were assigned a community worker who performed DOT in person during the five workdays for the duration of their TB treatment. Details regarding the TRUST DOT program are described previously including the smart phone application that DOT workers used to record witnessed or reported medication ingestion [24]. We used adherence to DOT as a proxy for treatment adherence. Overall adherence was calculated as the number of observed doses by DOT worker divided by the total number of days where DOT was attempted during study enrollment for each participant. Weekly adherence to DOT was also calculated. Days where DOT workers did not attempt to contact participants (e.g., weekends and holidays) were excluded from adherence calculations. Although individuals in this cohort were primarily treated as outpatients, we considered the small number of hospitalization days to be observed doses ($n=452$).

We defined the DOT start date as the first DOT form recorded or two weeks after the participant's enrollment date. If the participant had a delay of more than two-weeks in starting DOT, participants ($n=3$) were considered 'non-adherent' for each day outside this two-week window. The DOT end date was defined according to the participant's treatment outcome or at the end of study participation if treatment outcome was missing [see Additional file 2]. DOT data was only included for the first six months (26 weeks) on treatment.

Statistical analyses

We stratified by COVID-19 lockdown groups and compared demographics, health status (BMI and HIV status), TB-related variables, including bacterial burden and treatment outcome, and substance use by examining the frequency (%) of categorical variables and median value (interquartile range [IQR]) of continuous variables. Chi-square and t-tests examined associations between variables and enrollment group.

A negative binomial regression (NBR) model was used to examine differences in the rate of non-adherence to DOT between the pre-COVID-19 and post-COVID-19 lockdown groups, with the log of the total number of possible DOT days as an offset. A sensitivity analysis was then conducted with participants in the pre-COVID-19 lockdown group and only participants in the post-COVID-19 lockdown group that were enrolled before May 30, 2021; this was closer to the initial lockdown and before South Africa's third COVID-19 wave and subsequent declaration of alert Level 2 with increased restrictions (Fig. 1B). Both models adjusted for age, sex, employment status, household hunger, depression risk, and smoked substance use, which are known to be associated with non-adherence [4, 6–8, 10]. All statistical analyses were performed using R (version 4.2.2), with significance set at $P<0.05$.

Results

Demographic, clinical, and microbiological characteristics reported at baseline for participants in both lockdown groups are summarized in Table 1. Compared to the pre-COVID-19 lockdown group, a greater proportion of participants in the post-COVID-19 lockdown group were unemployed (73.8% vs. 59.0%, $p=0.022$), severely underweight or underweight (31.2% or 42.5% vs. 23.5% or 34.4%, $p=0.049$) and had higher risk of depression (71.2% vs. 57.9%, $p=0.041$; Table 1). There was a non-significantly greater proportion of unfavorable treatment outcomes among participants in the post-COVID-19 lockdown group compared to the pre-COVID-19 lockdown group (13% vs. 7.3%, $p=0.146$; Table 1).

The unadjusted, median DOT non-adherence rate across both groups was 12.9% (IQR: 7.36%, 24.53%). The post-COVID-19 lockdown group had a slightly higher unadjusted, median DOT non-adherence rate compared to the pre-COVID-19 lockdown group [13.3% (IQR: 6.08%, 39.51%) vs. 12.9% (IQR: 7.82%, 21.44%)]. Immediately following the lockdowns, the overall DOT adherence rate was lower, but gradually increased and reached a similar rate that was observed before COVID-19 lockdown after the third COVID-19 wave in July 2021 (Fig. 1A). The adjusted DOT non-adherence rate was

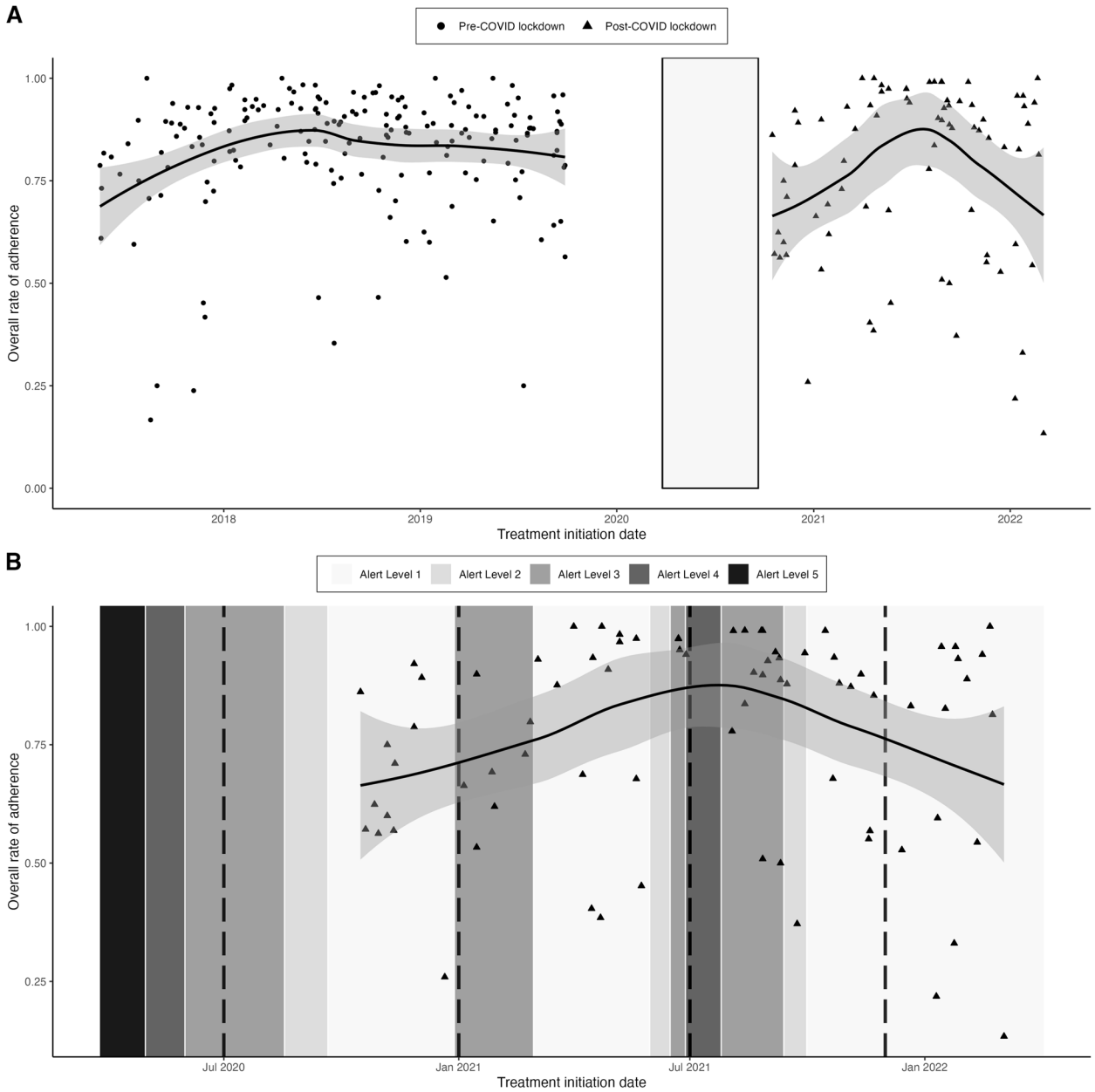

Fig. 1 **A** Overall rate of adherence to directly observed therapy (DOT) by enrollment group. Solid lines are weighted least squares regression line with local fitting and 95% confidence intervals, implemented with loess. Rectangle represents period that study enrollment was paused due to COVID-19 restrictions (March 26, 2020 – September 20, 2020). **B** Overall rate of adherence to directly observed therapy (DOT) for the post-COVID lockdown enrollment group during the pandemic. Rectangles represent the five-level COVID-19 alert system that determined the level of restrictions to be applied in South Africa [3], where darker rectangles represent higher alert levels and more restrictive measures to contain the virus. Solid lines are weighted least squares regression line with local fitting and 95% confidence intervals, implemented with loess. Dashed lines represent the national case count peaks of each wave [25]

higher in the post-COVID-19 lockdown group compared to the pre-COVID-19 lockdown group, after adjusting for age, sex, employment status, household hunger, depression risk, and smoked substance use (aIRR = 1.42, 95% CI = 1.04–1.96, $p = 0.028$; Table 2). We note that participants who experienced moderate-to-severe household hunger had a higher DOT non-adherence rate compared to those who experienced little to no household hunger, after adjusting for all other variables in the model (aIRR = 1.49, 95% CI = 1.08–2.06, $p = 0.010$; Table 2).

Table 1 Baseline demographics and clinical characterization by lockdown group (*N* = 263)

	Total sample (*N* = 263) *N* (%) or median (IQR)	**Pre-COVID-19 lockdown[a] (*N* = 183)** *N* (%) or median (IQR)	**Post-COVID-19 lockdown[b] (*N* = 80)** *N* (%) or median (IQR)	***p*-value**
Male sex	161 (61.2)	112 (61.2)	49 (61.2)	0.994
Age (years) categories				0.397
< 30	79 (30.0)	50 (27.3)	29 (36.2)	
30–39	66 (25.1)	45 (24.6)	21 (26.2)	
40–49	65 (24.7)	48 (26.2)	17 (21.2)	
> 50	53 (20.2)	40 (21.9)	13 (16.2)	
Mixed race ancestry	246 (93.5)	172 (94.0)	74 (92.5)	0.651
Education less than 9th grade	113 (43.0)	79 (43.2)	34 (42.5)	0.920
Unemployed	167 (63.5)	108 (59.0)	59 (73.8)	0.022
High risk of depression[c]	163 (62.0)	106 (57.9)	57 (71.2)	0.041
Moderate to severe household hunger[d]	115 (43.7)	76 (41.5)	39 (48.8)	0.278
History of incarceration (*N* = 262)	79 (30.2)	56 (30.6)	23 (29.1)	0.810
Health Status				
Body Mass Index[e]				0.049
Severely Underweight	68 (25.9)	43 (23.5)	25 (31.2)	
Underweight	97 (36.9)	63 (34.4)	34 (42.5)	
Normal Weight	83 (31.6)	63 (34.4)	20 (25.0)	
Overweight and Obese	15 (5.7)	14 (7.7)	1 (1.2)	
Living with HIV (*N* = 262)	71 (27.1)	53 (29.0)	18 (22.8)	0.302
CD4 count (*N* = 71)	269 (128, 510)	293 (155, 525)	182 (68, 424)	0.075
On ART (*N* = 71)	25 (35.2)	19 (35.8)	6 (33.3)	0.847
TB-related variables				
History of TB disease	99 (37.6)	74 (40.4)	25 (31.2)	0.157
Lung cavitation[f] (*N* = 262)				0.962
Yes	88 (33.6)	62 (34.1)	26 (32.5)	
No	168 (64.1)	116 (63.7)	52 (65.0)	
Unknown	6 (2.3)	4 (2.2)	2 (2.5)	
Baseline sputum culture TTP[g] (*N* = 211)	7 (5, 11)	7 (5, 11)	7 (5, 10)	0.810
Sputum concentrated ZN[h] (*N* = 261)				0.269
AFB negative	72 (27.6)	49 (27.1)	23 (28.8)	
Scanty	29 (11.1)	20 (11.0)	9 (11.2)	
+	45 (17.2)	27 (14.9)	18 (22.5)	
++	44 (16.9)	29 (16.0)	15 (18.8)	
+++	71 (27.2)	56 (30.9)	15 (18.8)	
Isoniazid resistance[i] (*N* = 237)	23 (9.7)	17 (10.1)	6 (8.8)	0.771

Table 1 (continued)

	Total sample (*N* = 263) *N* (%) or median (IQR)	Pre-COVID-19 lockdown[a] (*N* = 183) *N* (%) or median (IQR)	Post-COVID-19 lockdown[b] (*N* = 80) *N* (%) or median (IQR)	*p*-value
Unfavorable treatment outcome[j] (*N* = 255)	23 (9.0)	13 (7.3)	10 (13.0)	0.146
Alcohol, tobacco, and drug use variables				
Unhealthy alcohol use[k]	163 (62.0)	112 (61.2)	51 (63.8)	0.695
Tobacco use[l]	181 (68.8)	130 (71.0)	51 (63.8)	0.240
Smoked substance use[m]	143 (54.4)	98 (53.6)	45 (56.2)	0.686

Abbreviations: *AFB* Acid fast bacilli, *ART* Antiretroviral therapy, *AUDIT* Alcohol use disorders identification test, *CES-D* Center for epidemiological studies depression scale, *HHS* Household hunger scale, *IQR* Interquartile range, *PEth* Phosphatidylethanol, *TB* Tuberculosis, *TTP* Time to positivity, *ZN* Ziehl-Neelsen

[a] Pre-COVID-19 lockdown: participants enrolled in the study before October 1, 2019

[b] Post-COVID-19 lockdown: participants enrolled in the study after September 20, 2020

[c] Depression risk: at risk if CES-D score ≥ 16

[d] Household hunger: moderate to severe household hunger if total HHS score is between 2–6

[e] Body Mass Index: per NHLBI categories, Severely Underweight < 16.5, Underweight 16.5–18.5, Normal weight between 18.5-24.9, Overweight between 25.0-29.9 and Obese >30

[f] Presence of cavitary disease on baseline chest radiographs

[g] Baseline sputum culture TTP: culture time to positivity was considered available for patients with a non-contaminated study sample MGIT result. For sputum samples that were negative but not contaminated, they were set to a value of 42 days and right censored from that point on

[h] Sputum concentrated ZN: Observed with concentrated sputum smear microscopy

[i] Isoniazid resistance: assessed using Isoniazid Minimum Inhibitory Concentrations. Resistant if growth occurs at concentration > 0.1 μg/ml

[j] Unfavorable treatment outcomes: defined as death or loss to follow-up. Favorable treatment outcomes were defined as cured or treatment completed. Moved/transferred out of study area was considered missing

[k] Unhealthy alcohol use: participants with an AUDIT score of ≥ 8 or a PEth value > 49 ng/mL

[l] Tobacco use: self-reported currently smoking tobacco

[m] Smoked substance use: self-reported use or positive urine drug test for any of cannabis, methamphetamine, and/or methaqualone

Table 2 Comparison of directly observed therapy (DOT) non-adherence rates pre- and post-COVID-19 lockdowns (*N* = 263)

	aIRR	95% CI	*p* value
Lockdown group[a]			
Post-COVID-19 lockdown	1.42	1.04, 1.96	0.028
Pre-COVID-19 lockdown	—	—	
Age (years)			
> 50	0.92	0.59, 1.46	0.710
40–49	0.79	0.53, 1.17	0.232
30–39	1.01	0.68, 1.49	0.967
< 30	—	—	
Sex assigned at birth			
Male	0.84	0.62, 1.14	0.290
Female	—	—	
Employment status			
Unemployed	1.18	0.86, 1.59	0.302
Employed	—	—	
Household hunger[b]			
Moderate to severe	1.49	1.08, 2.06	0.010
Little to none	—	—	
Depression risk[c]			
High risk	0.82	0.59, 1.13	0.209
Low risk	—	—	
Smoked substance use[d]			
Yes	1.28	0.93, 1.75	0.125
No	—	—	

Abbreviations: *CES-D* Center for epidemiological studies depression score, CI Confidence interval, *IQR* Interquartile range, *IRR* Incidence rate ratio

[a] Pre-COVID lockdown: participants enrolled in the study before October 1, 2019, Post-COVID lockdown: participants enrolled in the study after September 20, 2020

[b] Household hunger: moderate to severe hunger in the household if total HHS score is between 2–6

[c] Depression risk: at risk if CES-D score ≥ 16

[d] Smoked substance use: self-reported use or positive urine drug test for any of cannabis, methamphetamine, and/or methaqualone

Compared to the pre-COVID-19 lockdown group, the adjusted DOT non-adherence rate in the post-COVID-19 lockdown group was even higher when we excluded participants that were enrolled later in the pandemic (those enrolled after May 30, 2020, $n = 45$) (aIRR = 1.74, 95% CI = 1.17–2.67, $p = 0.006$). Several confounders that we adjusted for in the sensitivity analysis model were also associated with higher DOT non-adherence rates; participants that were unemployed (aIRR = 1.45, 95% CI = 1.05–1.98, $p = 0.021$), experienced moderate to severe household hunger (aIRR = 1.74, 95% CI = 1.24–2.44, $p < 0.001$), and smoked substances (aIRR = 1.42, 95% CI = 1.02–1.98, $p = 0.035$) had significantly higher DOT non-adherence rates (Table 3).

Table 3 Comparison of directly observed therapy (DOT) non-adherence rates pre- and post-COVID-19 lockdowns: sensitivity analysis results (*N* = 217)

	aIRR	95% CI	*p* value
Lockdown group[a]			
Post-COVID-19 lockdown	1.74	1.17, 2.67	0.006
Pre-COVID-19 lockdown	—	—	
Age (years)			
> 50	1.13	0.70, 1.84	0.592
40–49	0.78	0.52, 1.18	0.238
30–39	1.12	0.74, 1.70	0.603
< 30	—	—	
Sex assigned at birth			
Male	0.75	0.54, 1.04	0.096
Female	—	—	
Employment status			
Unemployed	1.45	1.05, 1.98	0.021
Employed	—	—	
Household hunger[b]			
Moderate to severe	1.74	1.24, 2.44	< 0.001
Little to none	—	—	
Depression risk[c]			
High risk	0.80	0.58, 1.12	0.176
Low risk	—	—	
Smoked substance use[d]			
Yes	1.42	1.02, 1.98	0.035
No	—	—	

Abbreviations: CES-D Center for epidemiological etudies depression Score, *CI* Confidence interval, *IQR* Interquartile range, *IRR* Incidence rate ratio

[a] Pre-COVID lockdown: participants enrolled in the study before October 1, 2019; Post-COVID lockdown: participants enrolled in the study between September 21, 2020, and May 30, 2021 (before the third wave and Alert Level 2 implementation)

[b] Household hunger: moderate to severe hunger in the household if total HHS score is between 2–6

[c] Depression risk: at risk if CES-D score ≥ 16

[d] Smoked substance use: self-reported use or positive urine drug test for any of cannabis, methamphetamine, and/or methaqualone

Discussion

Even when supported by a DOT program with overall high medication adherence, we found that TB treatment adherence was significantly reduced in the period following the COVID-19 lockdowns. Participants who initiated TB treatment after the COVID-19 lockdowns were more often underweight, unemployed, and at high risk of depression compared to those who initiated TB treatment before the COVID-19 lockdowns, which reflects the pandemic-triggered economic and mental health crises, and increased barriers to accessing care. The adverse impact on TB treatment adherence was particularly notable during the continuation phase of treatment and

immediately following the initial COVID-19 lockdowns in South Africa. In the post-COVID-19 lockdown period (between September 2020 and May 2021), we observed a DOT non-adherence rate that was 1.7 times higher compared to pre-pandemic levels, even after adjusting for known mental health and socioeconomic factors associated with medication non-adherence. This demonstrates that the COVID-19 pandemic had considerable impacts on DOT-supported TB treatment adherence that extended beyond measured medication non-adherence risk factors. Despite the higher DOT non-adherence rates among participants enrolled after the COVID-19 lockdowns, we did not observe a significant difference in treatment outcomes between the two groups. However, this likely reflects the small sample size and lack of power to detect a difference between the two groups, as we found a higher proportion of participants in the post-COVID-19 lockdown group with unfavorable treatment outcomes.

While our study is unique in its use of community worker administered DOT, our finding of a significant reduction in TB treatment adherence after COVID-19 lockdowns is not unique. Reports from Iran, India, and Ethiopia have shown reduced TB treatment adherence and an increase in missed medication refill appointments after COVID-19 lockdowns [6, 11, 26, 27]. Kabbur et al. (2023) noted that in one region in India, only 2% of patients who were in a DOT program at the start of the pandemic were supervised while taking their TB treatment during COVID-19 lockdowns [26]. Similarly, our study DOT activities completely ceased during the initial COVID-19 lockdowns (from March to September 2020) and it is possible that post-lockdown findings may have been biased by increased stigma caused by our COVID-19 mitigation strategies.

Similar to other studies [28, 29], we found high depression risk, unemployment, and lower BMI among participants enrolled after COVID-19 lockdowns compared to those enrolled before the pandemic; however, we found no difference in bacterial or disease burden at baseline (presentation to TB care) between the two groups. During this early pandemic period (from September 2020 to March 2022), lower BMI likely reflects the increased food insecurity, rather than increased disease burden due to care engagement delays. Wang et al. (2021) found that patients with TB disease in China showed increased cavitation on chest X-ray and smear positivity during the pandemic when compared to pre-pandemic levels [30]. Similarly, a study in Spain found that patients with TB that presented to care in 2020 had increased lung involvement compared to before the COVID-19 pandemic [31]. An analysis done in the eThekwini district in South Africa found that there was a 45% reduction in TB investigations (diagnostic tests) and 40% reduction in confirmed TB cases in the initial lockdown period in 2020 [32]. Therefore, our sensitivity analysis that only included participants enrolled immediately following the initial lockdowns may conservatively capture the impact on disease severity at presentation. Additionally, patients with TB disease in South Africa often present with high disease burden, in part due to barriers to accessing care and the requirement of experiencing at least one TB symptom prior to testing. This may translate into a less detectable change in disease burden, which was already high before the pandemic.

Conclusion

While a major strength of our study was its use of DOT adherence data, this also has limitations. Adherence to DOT may not perfectly reflect treatment adherence, as doses were only counted if observed. Participants enrolled in our study may have also received support from the community worker that visited daily for DOT, which could have lessened the impact of the COVID-19 lockdowns compared to individuals with less regular monitoring and support. Our conclusions are also limited by the small sample size of the post-COVID-19 lockdown group, as we faced difficulties enrolling participants into the study after COVID-19 restrictions were gradually lifted. Additionally, the study's generalizability may be limited due to the specific context of South Africa and our inclusion criteria. Despite these limitations, it is clear that the COVID-19 pandemic had an adverse impact on TB treatment adherence that was most notable immediately following the initial lockdowns in South Africa. This change in TB treatment adherence may reflect the worsened health and economic status of individuals with TB disease, who experienced higher food insecurity, depression risk, and unemployment after the lockdowns. Further work is needed to better understand the barriers to TB treatment adherence (including economic factors) exacerbated by the COVID-19 lockdowns to improve treatment outcomes.

Abbreviations

TB	Tuberculosis
WHO	World Health Organization
DOT	Directly observed therapy
TRUST	Tuberculosis Treatment and Alcohol Use Study
LTFU	Loss to follow-up
DS-TB	Drug susceptible tuberculosis
CES-D	Center for Epidemiological Studies Depression Score
HHS	Household Hunger Scale
AUDIT	Alcohol Use Disorders Identification
PEth	Phosphatidylethanol
BMI	Body mass index
ART	Antiretroviral therapy
ZN	Ziehl-Neelsen
AFB	Acid-fast bacillus
TTP	Time-to-culture positivity

IQR	Interquartile range
NBR	Negative binomial regression
aIRR	Adjusted incidence rate ratio
ESP	End of study participation
IRB	Institutional Review Board
AE	Adverse Event

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-09994-7.

Additional file 1. Timeline of the national state of disaster alert levels specific to South Africa throughout the pandemic [3] Created with BioRender.com.

Additional file 2. Flow chart depicting how directly observed therapy (DOT) end date was determined based on treatment outcome (obtained from clinic they received care) or end of study participation (ESP) reason for all participants. Created with BioRender.com.

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Authors' contributions
VO and SM analyzed and interpreted the data. VO, SM, TCB, and KRJ were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was reviewed and approved by f our institutions' research ethics committees/institutional review boards: South African Medical Research Council Human Research Ethics Committee (protocol ID: EC011-5/2016), University of Cape Town Human Research Ethics Committee (reference number: 497/2016), Stellenbosch University Human Research Ethics Committee (protocol number: SU-BEE17-0001), and Boston University Institutional Review Board (IRB number: H-34970). Written, informed consent to participate in the study was obtained from all participants if ≥ 18 years of age or written individual consent and separate parental consent if < 18 years.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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