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**Risk Factors for Recurrent Tuberculosis among HIV Patients who are on Anti-Retroviral Treatment
in Rural Northeast, South Africa.**

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Background

- Tuberculosis (TB) is a chronic infectious disease caused by the bacterium *Mycobacterium tuberculosis*.
- Although it mostly affects the lungs, it can also affect other organs such as the brain, kidneys, and bones.
- TB is one of the top 10 global causes of mortality, raising serious public health concerns (WHO).
- In 2020, an estimated 10 million people were diagnosed with TB and 1.5 million died from the disease.
- South Africa is one of the countries with a high burden of TB, accounting for three percent of cases worldwide.

Background cont'd

- Recurrent tuberculosis (TB) refers to *a new episode of TB disease occurring in patients who were successfully treated and declared cured*, as defined by the World Health Organization and the US National Tuberculosis Surveillance System.
- This can happen due to ***reactivation of a pre-existing infection*** or ***reinfection with a new strain***.
- Recurrent tuberculosis is a major factor in the global burden of TB, especially in high-prevalence areas and among individuals living with HIV.

Background cont'd.

- Research has demonstrated a strong connection between TB and HIV epidemics, with HIV-positive individuals at higher risk of experiencing recurrent TB.
- Studies have shown that recurrent TB cases make up a significant portion (5-30%) of the global TB burden.
- According to Fischinger et al. (2021), the majority of TB cases in South Africa are recurrent cases, caused by relapse or reinfection.

Problem Statement

- Despite advances, TB remains a major cause of death in South Africa.
- Recurrent TB exacerbates the challenge, complicating treatment and leading to drug-resistant strains.
- Recurrent TB imposes significant social and economic burdens, including prolonged illness and increased healthcare costs.
- In high TB prevalence areas like rural northeast South Africa, the coexistence of TB and HIV significantly contributes to recurrent TB cases.
- By analysing the underlying causes and risk factors contributing to TB recurrence, targeted interventions and strategies can be developed to address the unique challenges faced by affected populations.

Justification

- There is a global concern about TB recurrence in patients that were successfully treated for TB, especially its role in multi-drug resistant TB .
- The occurrence of recurrent TB in rural northeast, South Africa poses a serious threat to public health as it undermines the progress made in TB control efforts.
- Patients who experience recurrent TB face prolonged illness, increased healthcare costs, and potentially adverse treatment outcomes.
- Addressing the problem of recurrent TB in rural northeast, South Africa is crucial for improving individual health outcomes, reducing the burden of drug-resistant TB, and safeguarding the health and well-being of the entire community.

Research Question, Aim and Study Objectives

RESEARCH QUESTION

What are the risk factors for the recurrence of tuberculosis after successful treatment among HIV patients who are on anti-retroviral treatment in rural northeast, South Africa?

AIM

To determine the risk factors for the recurrence of tuberculosis in HIV patients who are on anti-retroviral treatment in rural northeast, South Africa.

OBJECTIVES

1. To determine the incidence rate of recurrent TB among HIV patients who are on ART in rural northeast, South Africa
2. To determine the time to another TB episode after successful TB treatment in HIV patients who are on ART in rural northeast, South Africa
3. To identify risk factors for TB recurrence after successful treatment among HIV patients who are on ART in rural northeast, South Africa

Methods

Study design:

- This was a retrospective cohort by using clinical data of HIV patients receiving antiretroviral treatment between 1st January 2014 and 31st December 2022 at Agincourt research area in rural northeast, South Africa.

Study site:

- The study was conducted in rural northeast, South Africa. The study area has South Africa's second-highest HIV prevalence rate.

Study population:

- HIV patients on ART who received a TB diagnosis (pulmonary TB or extrapulmonary TB) at least once during the study period (1st January 2014 – 31st December 2022) and were at least 18 years old made up the study population.

Methods cont'd

Data collection:

- Data was sourced from the Agincourt Health and Demographic Surveillance System (HDSS) clinic link study.
- The data is collected by trained field workers.

“Every HIV patient has a clinical file that is created upon first registration at an ART clinic and is updated at each clinic visit. Following the clinic visit, visit-level information from the patient file is entered into an electronic database”

Data analysis:

- Stata 17 SE to clean and analyse the data.
- Descriptive statistics (Frequency and Percentage Distributions) were carried out.
- Tests for normality were conducted on continuous variables (weight, CD4 count at baseline, and duration of previous TB treatment)
- Data was found not normally distributed, therefore, median and interquartile range (IQR) were presented.

Methods cont'd.

Data analysis cont'd:

- ***Cox regression model*** was fitted (to investigate factors associated with the recurrence of TB in individuals over time, after successful treatment).
- The fitness of the cox regression model was investigated using the ***Cox-Snell residual plot***
- ***Kaplan-Meier curves*** were used to visualize and compare group-specific recurrence probabilities of TB over time (To determine the time to another episode of TB from successful TB treatment)
- Outcome status defined as 'Recurrent' or 'Not-recurrent,' coded as 1 or 0, respectively.
- The recurrence time was defined as the duration from the treatment to the occurrence of TB recurrence.

Results

1. Characteristics of the study population for recurrent TB among HIV patients on ART

- The study was conducted on **4,802 HIV patients** in rural northeast South Africa who were receiving Antiretroviral Therapy (ART) and had previously been treated for tuberculosis.
- 396 patients experienced recurrent TB, while 4,406 did not during the study period.
- The majority of patients were female (72.4%), with a median weight of 66 kgs.
- Age distribution showed that the largest group was aged 30-39 years (34.5%), followed by 18-29 years (24.7%), 40-49 years (23.1%), 50-59 years (11.0%), and 60 years and above (6.6%).
- The majority of patients were in WHO HIV stage one (84.7%), with fewer in stages two, three, and four.

Results cont'd

2. TB Recurrence

- Recurrence rate of 3.0 per 100 person years (**95% CI: 2.7 – 3.3**).
- Total time at risk was 131.4 person years.
- Recurrence rate higher in men (**4.3 per 100 person years**) compared to women (**2.6 per 100 person years**).
- Higher recurrence rates observed in patients aged 40-49 years (**3.3 per 100 person years**) and 30-39 years (**3.2 per 100 person years**).

Results cont'd.

2. TB Recurrence cont'd

- Patients at stage 3 (**8.7 per 100 person years**) and stage 4 (**8.4 per 100 person years**) had higher recurrence rates.
- Patients without comorbidities had a higher recurrence rate (**3.1 per 100 person years**) than those with comorbidities (**2.6 per 100 person years**).
- Non-adherence to TB medication associated with higher recurrence rate (**3.8 per 100 person years**).
- Non-adherence to HIV medication also slightly increased recurrence rate (**3.3 per 100 person years**) compared to adherent patients (**3.0 per 100 person years**).

Results cont'd..

Factor	Categories	Number	Recurrent cases	Follow-up (10 ² py)	Recurrence rate (10 ² py) (95% CI)	Logrank P-val
Overall		4,802	396	131.4	3.0 (2.7 – 3.3)	
Sex	Male	1,326	143	33.6	4.3 (3.6 – 5.0)	<0.001
	Female	3,472	253	97.8	2.6 (2.3 – 2.9)	
Age	18 – 29	1,188	97	34.3	2.8 (2.3 – 3.4)	0.55
	30 – 39	1,657	147	46.1	3.2 (2.7 – 3.8)	
	40 – 49	1,110	95	29.1	3.3 (2.7 – 4.0)	
	50 – 59	527	36	14.0	2.6 (1.9 – 3.6)	
	60+	319	21	8.0	2.6 (1.7 – 4.0)	
WHO Stage (HIV)	Stage 1	3,186	204	83.8	2.4 (2.1 – 2.8)	<0.001
	Stage 2	286	28	9.1	3.1 (2.1 – 4.5)	
	Stage 3	263	66	7.9	8.4 (6.6 – 10.7)	
	Stage 4	28	6	0.7	8.7 (3.9 – 19.4)	
Comorbidities	Comorbidities	881	72	27.4	2.6 (2.1 – 3.3)	0.09
	No comorbidities	3,921	324	104.1	3.1 (2.8 – 3.5)	
Poor Adherence to TB medication	Yes	4,390	25	6.6	2.6 (2.1 – 3.3)	0.02
	No	412	371	124.8	3.1 (2.8 – 3.5)	
Poor Adherence to HIV medication	Yes	4,227	41	12.3	3.3 (2.5 – 4.5)	0.17
	No	575	355	119.1	3.0 (2.7 – 3.3)	

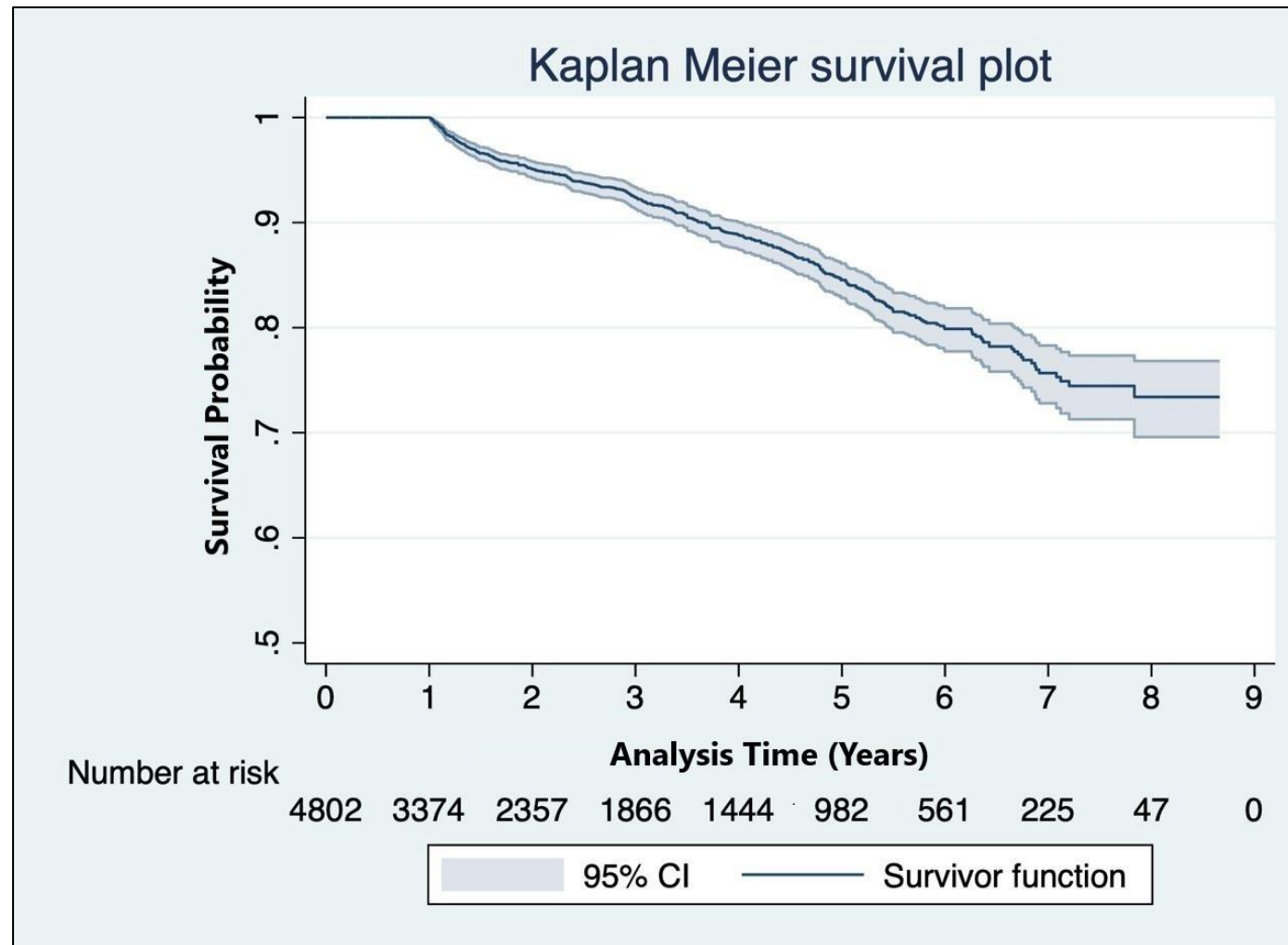
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Results cont'd...

3. Time to another TB episode after successful treatment

- Study calculated time to subsequent TB episodes for recurrent cases.
 - i. Minimum time to another TB episode: **0.02 years (7 days)**.
 - ii. Median time to another TB episode: **1.93 years**.
 - iii. Maximum time to another TB episode: **8.66 years**.
- Shows variation in time of TB recurrence.
- Some experience recurrence shortly after initial episode, while others experience a longer interval.

Results cont'd....



Results cont'd.....

4. Risk factors for recurrent TB among HIV patients who are on ART in rural northeast SA

- Male patients were 73% more likely to experience recurrent TB than female patients.
- Patients with increased weight had a lower risk of recurrent TB.
- Patients at WHO HIV stages three and four had higher likelihood of recurrent TB compared to stage one.
- Patients with low CD4 count were more likely to have recurrent TB.
- Longer duration of TB treatment increased risk of TB recurrence.
- Patient non-adherence to TB medication led to higher likelihood of recurrent TB.

Results cont'd.....

5. Factors associated with recurrent TB in HIV patients on ART in rural South Africa

- Male patients were 48% more likely to experience recurrent TB.
- Patients at WHO stage 3 were 2.53 times more likely to have recurrent TB.
- Low CD4 count at baseline increased likelihood of recurrent TB.
- Longer duration of TB treatment was associated with higher risk of recurrence.
- Other factors such as age, weight, comorbidities, poor medication adherence were not statistically significant in multivariate analysis.

Results cont'd....

Variables	Crude HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Sex Female Male	ref 1.73 (1.41 – 2.12)	- <0.001	1.48 (1.12 – 1.96)	0.007
Weight (5kgs)	0.91 (0.87 – 0.95)	<0.001	0.97 (0.92 – 1.02)	0.22
Age 18 – 29 30 – 39 40 – 49 50 – 59 60+	ref 1.14 (0.88 – 1.47) 1.19 (0.90 – 1.59) 0.93 (0.63 – 1.36) 0.96 (0.60 – 1.53)	- 0.33 0.22 0.70 0.85	0.80 (0.58 – 1.10) 0.83 (0.57 – 1.23) 0.72 (0.42 – 1.24) 1.01 (0.54 – 1.88)	0.17 0.36 0.24 0.97
WHO stage (HIV) Stage 1 Stage 2 Stage 3 Stage 4	ref 1.17 (0.79 – 1.73) 3.29 (2.49 – 4.34) 3.62 (1.61 – 8.16)	- 0.45 <0.001 <0.002	1.09 (0.71 – 1.68) 2.53 (1.81 – 3.54) 0.68 (0.09 – 4.98)	0.68 <0.001 0.71
CD 4 Count (10 Cells/mm ³)	0.98 (0.98 – 0.99)	<0.001	0.99 (0.98 – 0.99)	<0.001
Duration of previous TB treatment (months)	0.96 (0.93 – 0.98)	<0.001	0.95 (0.92 – 0.98)	0.001
Comorbidities No comorbidities Comorbidities	ref 0.80 (0.62 – 1.03)	- 0.09	0.73 (0.49 – 1.09)	0.13
Poor Adherence to TB medication No Yes	ref 1.60 (1.07 – 2.40)	- 0.02	1.40 (0.76 – 2.60)	0.29
Poor Adherence to HIV medication No Yes	ref 1.25 (0.91 – 1.73)	- 0.17	1.38 (0.85 – 2.24)	0.19

Conclusions and Recommendations

- **Gender Disparity**: Male patients were found to be at a higher risk of experiencing recurrent TB compared to female patients, *emphasizing the need for targeted interventions to address this gender disparity and improve TB outcomes among male individuals.*
- **HIV WHO Stage**: Patients at more advanced stages of HIV (WHO stage three and stage four) were at a significantly higher risk of TB recurrence, *highlighting the importance of early HIV diagnosis and effective management to prevent disease progression.*
- **Baseline CD4 Count**: Maintaining a higher baseline CD4 count was associated with a lower likelihood of TB recurrence, *underscoring the importance of early initiation of ART and adherence to HIV treatment to reduce the risk of TB recurrence.*
- **Duration of TB treatment**: Patients with a longer duration of TB treatment were found to be at a higher risk of recurrence, *indicating the need for continuous monitoring and support during and after TB treatment to prevent future recurrences.*

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