Public Health Bulletin
South Africa

Linkage to care in rifampicin-resistant diagnosed tuberculosis cases in Gauteng, South Africa, 2022–2023

Nomathamsanqa Ndhlovu[1*], Modipadi Mugivhi[2], Themba Ngwenya[2], Kgomotso Dinake[2], Shaheed Omar[3]

[1]Division of Public Health Surveillance and Response, National Institute for Communicable Diseases, a division of the National Health Laboratory Service, Johannesburg, South Africa
[2]Drug-Resistant Tuberculosis sub-directorate, HIV and AIDS, Sexually Transmitted Infections, Tuberculosis (HAST) directorate, Gauteng Department of Health, Johannesburg, South Africa
[3]Centre for Tuberculosis, National Institute for Communicable Diseases, a division of the National Health Laboratory Service, Johannesburg, South Africa

*Corresponding author: Nomathamsanqa Ndhlovu, nomathamsanqan@nicd.ac.za

PHBSA.2025;3(2):58-78

Summary

Tuberculosis (TB) is one of the leading causes of death by an infectious disease in South Africa. Timeous linkage of rifampicin-resistant (RR) TB patients to care is key in reducing TB transmission and fatalities. The target for TB linkage to care is 95%, according to the South African National Strategic Plan, and the current target for time to treatment initiation is seven days. Additionally, South Africa, together with other member states of the World Health Organization, have adopted the goal to end the global TB epidemic by 2035. Monitoring linkage-to-care indicators is essential to measure progress towards these targets and to assess the effects of programme interventions. Data on laboratory-confirmed RR-TB Results for Action, combined with feedback on patient linkage-to-care for RR-TB patients in Gauteng province, South Africa, from 2022 to 2023, was utilised. The data were obtained from the Centre for TB at the National Institute for Communicable Diseases, a division of the National Health Laboratory Service, and the Gauteng Department of Health HIV and AIDS, Sexually Transmitted Infections, Tuberculosis (HAST) programme. A descriptive analysis of linkage-to-care variables and the differences by district was conducted. Gauteng recorded 867 RR-TB cases in 2022 and 895 cases in 2023. In 2022, the treatment initiation rate was 83% (721/867), while 7% (63/867) died before treatment initiation, 1% (10/867) refused treatment, 2% (17/867) moved out of the province and 6% (56/867) were initial loss to follow-up (iLTFU). In 2023, the initiation rate improved to 89% (798/895), where 6% (55/895) died before treatment initiation, 1% (4/895) refused treatment, 0% (0/895) moved out and 4% (38/895) were iLTFU. Less than 1% of patients (seven in 2022 and seven in 2023) were initiated on TB treatment more than 60 days after diagnosis. Although an improvement in treatment initiation was noted over the two years, strengthening tracing, patient trust, regular analysis of the data collected on linkage to care, and other programme initiatives are imperative to decrease the number of patients that are not linked to care and to achieve the TB elimination goals.

Introduction

Tuberculosis (TB) is caused by infection with *Mycobacterium tuberculosis.*[1,2] Globally, over ten million people develop TB annually, with an incidence of 134 per 100 000 people recorded in 2023.[2] Males and those in the 25–34 year-age group account for the largest proportion of TB cases.[2] South Africa had a TB incidence of 427 cases per 100 000 people in 2023 and is one of the 30 high-burden countries for TB and drug-resistant (DR) TB globally.[2,3] Drug-susceptible (DS) TB is a result of infection with a strain of *M. tuberculosis* that is susceptible to all TB drugs[4], while DR-TB occurs when a person is infected by a strain of *M. tuberculosis* that is resistant to one or more of the drugs used in TB treatment. One of these drugs is rifampicin, and resistance to rifampicin treatment in TB patients is categorised as rifampicin-resistant (RR) TB.[5,6] This type of resistance is particularly concerning, as the incidence rate of RR-TB was 21 per 100 000 people for South Africa in 2023 and 20 per 100 000 people for Gauteng province in 2015.[3,7]

In South Africa, TB is the sixth leading cause of death.[8] Mortality in undertreated TB patients, including DR-TB patients, is higher (OR: 4.9 CI: 2.47–9.78) compared to TB patients receiving appropriate treatment, and the case fatality rate in HIV-negative, untreated smear-positive pulmonary TB patients is estimated at 70%.[9,10] South Africa has adopted targets to ensure patient linkage to care and to

decrease TB mortality.[11] The National Strategic Plan (NSP) for South Africa's target for TB linkage to care is 95%, and the current target for time-to-treatment initiation is seven days.[11,12] However, treatment coverage in South Africa for TB overall was recorded at 78% in 2023, 87% for DS-TB in 2017, and 78% for RR-TB patients in Gauteng in 2021.[2,13,14] The lower treatment coverage for DR-TB is likely due to travel to treatment initiation sites and longer treatment regimens prior to 2023, increasing deterrence.[5,6,15] Moreover, the median time to treatment for RR-TB decreased from 44 days in 2011 to 22 days in 2013 following the introduction of Gene-Xpert Nucleic-Acid Amplification Tests (NAAT).[16]

South Africa has been using NAAT to rapidly diagnose RR-TB for over a decade.[17] These tests provide results within 40 hours from laboratory receipt for most patients, supporting a shorter time to treatment initiation.[6,18] The Centre for TB (CTB) at the National Institute for Communicable Diseases (NICD), a division of the National Health Laboratory Service (NHLS), shares all public-sector positive RR-TB NAAT results with programme managers weekly, as Results For Action (RFA), to improve time to treatment initiation and linkage to care. Following diagnosis of RR-TB, further drug susceptibility tests are conducted (National DR-TB Reflex testing) to determine treatment regimens according to the drug resistance profile of a patient.[6]

The TB recovery plan for South Africa post COVID-19, pillar 2, emphasises the importance of strengthening linkage to care and access to treatment, which corresponds to objectives in the NSP for TB in South Africa.[12] The plan highlights impactful interventions that will be prioritised to meet these objectives.[12] Examples of these interventions include providing text messages for all tested individuals, improving information system interoperability, and training healthcare workers on treatment regimens and new TB guidelines.[11]

Gauteng province has introduced several programme interventions to meet the goals from the END TB strategy[19] and to improve linkage to care. Ongoing evaluation of indicators such as treatment initiation rates, time to treatment initiation, and initial loss to follow-up (iLTFU) amongst RR-TB patients is important to determine whether these interventions have led to improved linkage to care.

The aim of this surveillance project was to describe the RR-TB cases diagnosed in Gauteng between 2022 and 2023 and to assess patient linkage to care.

Methods

Study design and setting

A descriptive study was carried out by analysis of secondary data. The study utilised RR-TB RFA obtained from CTB at the NICD and treatment initiation feedback information from the TB managers in Gauteng.

Study setting and population

All individuals of any age tested at a public facility with a positive TB NAAT and an RR-TB detected in Gauteng in 2022 and 2023 were included in the study. Patients who had a second positive test within the same year were considered duplicates and were excluded from the study. Therefore, only one episode of RR-TB per person was considered per year.

Data collection

The CTB designed an automated alert system through the Corporate Data Warehouse (CDW), hosted by the NHLS, to send out positive RR-TB NAAT results to stakeholders weekly. The weekly RFA includes RR-TB NAAT results for all public health facilities in all provinces, including Gauteng. The data include the following information:

- Patient name;
- Facility where patient specimen was collected;
- Health district of facility;
- Sub-district of facility;
- Type of specimen collected;
- Date the specimen was collected;
- Review date of results at the facility;
- Episode number of the test;
- Patient address (if available); and
- Patient folder number.

The provincial DR-TB office consolidates the weekly RR-TB RFA into one continuous electronic Excel database and includes additional initiation variables for the district managers to complete. The provincial DR-TB office sends the database to the district programme managers, who then distribute it to the sub-district and facility officials. These officials complete the patient linkage-to-care variables on the spreadsheet and send it back to the provincial DR-TB team weekly. The provincial DR-TB team and the NICD epidemiologist maintain the continuous database. Additional variables completed include:

- Age
- Sex
- Human Immunodeficiency Virus (HIV) status
- Antiretroviral Treatment (ART) initiation
- ART initiation date
- Patient treatment initiation date
- Reasons a patient was not initiated on treatment that include:
    - Death status
    - Date patient died
    - Refusal of treatment status
    - Patient moved out status
    - ILTFU status

The provincial database with positive RR-TB RFA patients and linkage to care information was utilised for this study.

Definitions

- 'Started treatment' was defined as an RR-TB patient initiated on either the six-months short regimen or the 18- to 20-months individualised long regimen. The composition of the long regimen depends on the drug resistance pattern, prior drug exposure, and toxicity for the patient.[6] Prior to the updated guidelines implemented in September 2023, patients received a 9–11-month regimen or the long regimen.[5,6]
- 'Initial loss to follow up (iLTFU)' was defined as an RR-TB patient not initiated on treatment for more than six months following TB diagnosis.
- 'Died before treatment initiation' was defined as a patient linked to a TB treatment facility and who died before treatment initiation could commence.
- 'Refused treatment' was defined as a patient who refused TB treatment when contacted by the health facility once the positive RR-TB results were available.
- 'Moved out' was defined as a patient who transferred out of a facility in Gauteng to a facility in another province or country to continue treatment when the TB NAAT results were available.
- 'Time to treatment initiation' was defined as the time between RR-TB results being reviewed at the facility and the date that TB treatment was initiated.

Data analysis

The continuous electronic Excel RR-TB RFA database was obtained, variable options were standardised, and duplicates were removed. The team performed a descriptive analysis to investigate the distribution of demographic characteristics of RR-TB patients using STATA version 17 (StataCorp LLC). Categorical variables such as age group, sex, district of treatment initiation, HIV status, ART initiation, time of ART initiation (before/after DR-TB treatment initiation), time between ART initiation and TB testing intervals, and time to treatment initiation intervals were analysed and presented as counts and percentages, and the chi-square test was utilised to test for differences between groups. Lastly, we analysed continuous data such as age in years using a median with an interquartile range and used the Wilcoxon Rank Sum test to test for differences between age and HIV status and ART initiation status.

Results

According to the RR-TB RFA consolidated data, Gauteng identified 867 and 895 RR-TB NAAT cases in 2022 and 2023, respectively, with Johannesburg Health District reporting the highest proportion of cases (2022: 302/867, 35% and 2023: 386/895, 43%) (Table 1). The majority of cases were male (2022: 487/867, 56%, and 2023: 498/895, 56%) and were in the 35–44-year-old age group across all districts except for Sedibeng District in 2023 (25–34-year-old age group; 29/76, 38%) (Table 1).

Table 1. Demographic characteristics of Rifampicin Resistant Tuberculosis (RR-TB) diagnosed patients by district in Gauteng province, South Africa, 2022 and 2023.

	2022						2023					
	JHB	**TSH**	**EKU**	**SED**	**WR**	**GP**	**JHB**	**TSH**	**EKU**	**SED**	**WR**	**GP**
	n(%)						n(%)					
Total diagnosed	302(100)	147(100)	259(100)	93(100)	66(100)	867(100)	386(100)	129(100)	227(100)	76(100)	77(100)	895(100)
Age groups (years)												
<5	1(0)	3(2)	1(0)	0(0)	0(0)	5(1)	3(1)	1(1)	0(0)	1(1)	0(0)	5(1)
5–14	0(0)	1(1)	3(1)	0(0)	0(0)	4(1)	3(1)	1(1)	0(0)	0(0)	1(1)	5(1)
15–24	32(11)	6(4)	16(6)	9(10)	6(9)	69(8)	26(7)	8(6)	15(7)	3(4)	3(4)	55(6)
25–34	67(22)	29(20)	65(25)	22(23)	15(23)	198(23)	80(20)	32(25)	61(27)	29(38)	20(26)	222(25)
35–44	83(27)	33(22)	87(34)	21(23)	23(35)	247(28)	105(27)	35(27)	71(31)	26(34)	27(35)	264(29)
45–54	48(16)	18(12)	36(14)	14(15)	13(20)	129(15)	57(15)	15(11)	45(20)	8(11)	10(13)	135(15)
55+	15(5)	15(10)	18(7)	11(12)	6(9)	65(8)	30(8)	26(20)	32(14)	7(9)	14(18)	109(12)
Unknown	56(19)	42(29)	33(13)	16(17)	3(4)	150(17)	82(21)	11(9)	3(1)	2(3)	2(3)	100(11)
P-value						0.122						0.151
Sex												
Female	107(36)	37(25)	87(34)	35(38)	23(35)	289(33)	122(32)	53(41)	85(37)	31(41)	23(30)	314(35)
Male	167(55)	76(52)	144(55)	57(61)	43(65)	487(56)	187(48)	71(55)	141(62)	45(59)	54(70)	498(56)
Unknown	28(9)	34(23)	28(11)	1(1)	0(0)	91(11)	77(20)	5(4)	1(1)	0(0)	0(0)	83(9)
P-value						<0.001						0.446

JHB = Johannesburg Health District, TSH = Tshwane Health District, EKU = Ekurhuleni Health District, SED = Sedibeng District, WR = West Rand District, GP = Gauteng province.

In 2022, the treatment initiation rate was 83% (721/867) and increased to 89% (798/895) in 2023 (Figure 1). For both years, all districts initiated more than 50% of their cases on treatment within one week after diagnosis, except for Sedibeng District (30/76; 44%) and West Rand District (34/77; 49%), both in 2023 (Table 2). For the years combined, the median time to treatment was six days (IQR: 1-12), and 14 patients (14/1 763; 1%) were initiated on treatment more than two months after positive RR-TB results were received (Table 2).

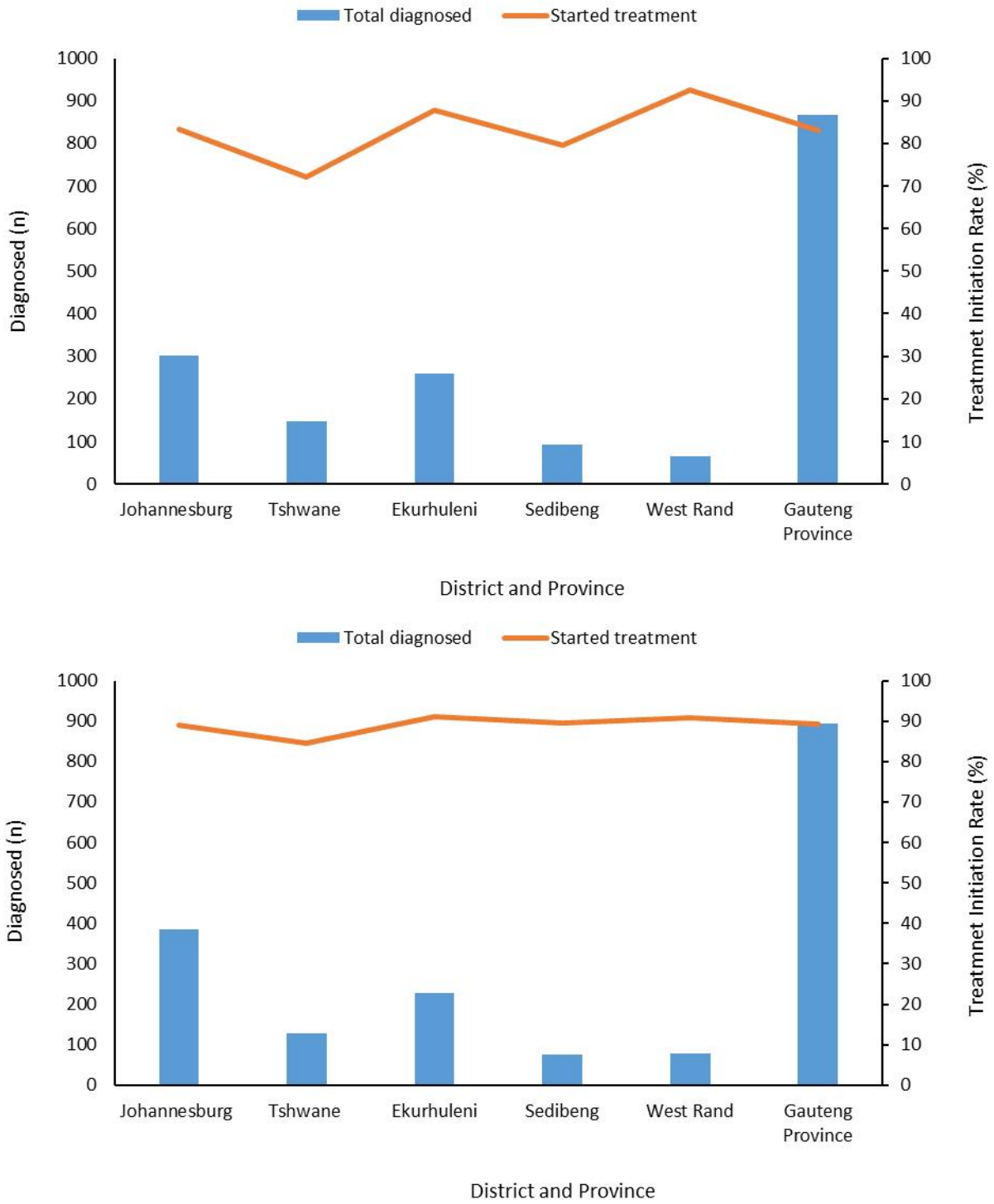

Figure 1. Treatment initiation of RR-TB diagnosed patients by district, Gauteng province, South Africa, in (a) 2022 and (b) 2023.

In 2022, 63/867 (26%) RR-TB patients died before treatment initiation, while 56/895 (6%) were iLTFU (Table 2). In the same year, the highest proportion of deaths among RR-TB patients was noted in Sedibeng District (11/93; 12%), followed by Tshwane Health District (14/147; 10%) (Table 2). A similar pattern was noted in 2023, with Tshwane Health District (10/129; 8%) and Sedibeng District (5/76; 7%) reporting the highest proportion of deaths prior to DR-TB treatment initiation (Table 2).

The RR-TB patients iLTFU were highest in Johannesburg Health District in 2022 (31/302; 10%) and in Tshwane Health District in 2023 (9/129; 7%) (Table 2). The age group with the highest proportion of patients with iLFFU was 25–34 years (2022: 7/56, 13% and 2023: 9/38, 24%), despite the highest case numbers being reported in the 35–44-year-old age group.

Table 2. Linkage-to-care indicators in RR-TB-diagnosed patients by district in Gauteng province, South Africa, 2022 and 2023.

	2022						2023					
	JHB	**TSH**	**EKU**	**SED**	**WR**	**GP**	**JHB**	**TSH**	**EKU**	**SED**	**WR**	**GP**
	n(%)						n(%)					
Total diagnosed	302(100)	147(100)	259(100)	93(100)	66(100)	867(100)	386(100)	129(100)	227(100)	76(100)	77(100)	895(100)
Died before treatment	15(5)	14(10)	20(8)	11(12)	3(5)	63(7)	21(5)	10(8)	14(6)	5(7)	5(6)	55(6)
Refused treatment	1(0)	5(3)	3(1)	1(1)	0(0)	10(1)	2(1)	1(1)	0(0)	1(1)	0(0)	4(1)
Moved out	3(1)	11(7)	0(0)	3(3)	0(0)	17(2)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
iLTFU	31(10)	11(8)	8(3)	4(4)	2(3)	56(6)	19(5)	9(7)	6(3)	2(3)	2(3)	38(4)
Time to treatment initiation (days)												
0–7	150(60)	56(53)	156(68)	38(51)	35(57)	435(60)	223(65)	72(66)	123(59)	30(44)	34(49)	482(60)
8–14	57(23)	28(26)	46(20)	18(24)	20(33)	169(23)	52(15)	19(17)	57(28)	19(28)	21(30)	168(21)
15–30	36(14)	15(14)	17(8)	12(16)	3(5)	83(12)	48(14)	16(15)	20(10)	14(21)	14(20)	112(14)
31–60	8(3)	6(6)	6(3)	4(6)	3(5)	27(4)	16(5)	2(2)	5(2)	5(7)	1(1)	29(4)
> 61	1(0)	1(1)	3(1)	2(3)	0(0)	7(1)	5(1)	0(0)	2(1)	0(0)	0(0)	7(1)
P-value						0.080						0.002

JHB = Johannesburg Health District, TSH = Tshwane Health District, EKU = Ekurhuleni Health District, SED = Sedibeng District, WR = West Rand District, GP = Gauteng province. iLTFU = initial loss to follow-up.

More than 60% (2022: 564/867, 65%, and 2023: 613/895, 69%) of patients diagnosed with RR-TB were people living with HIV. West Rand District had the highest proportion of RR-TB and HIV co-infected patients (2022; 57/66, 86% and 2023; 56/77, 73%). However, in 2023, West Rand District had the lowest proportion of RR-TB and HIV co-infected patients initiated on ART (2023: 36/56, 64%) compared to the other districts in Gauteng (Figure 2). In both years, the majority of RR-TB and HIV co-infected patients were initiated on ART before starting TB treatment (2022: 221/301, 73% and 2023: 337/480, 70%) (Table 3). Lastly, over 20% (21% in 2022 and 23% in 2023) of HIV-positive, ART-initiated prior to TB diagnosis, RR-TB patients on RR-TB treatment were found positive for RR-TB within six months after ART initiation, and over 60% (69% in 2022 and 65% in 2023) a year or more after ART initiation (Figure 3). Time to TB treatment initiation did not significantly differ between HIV-positive and negative patients ($p>0.05$).

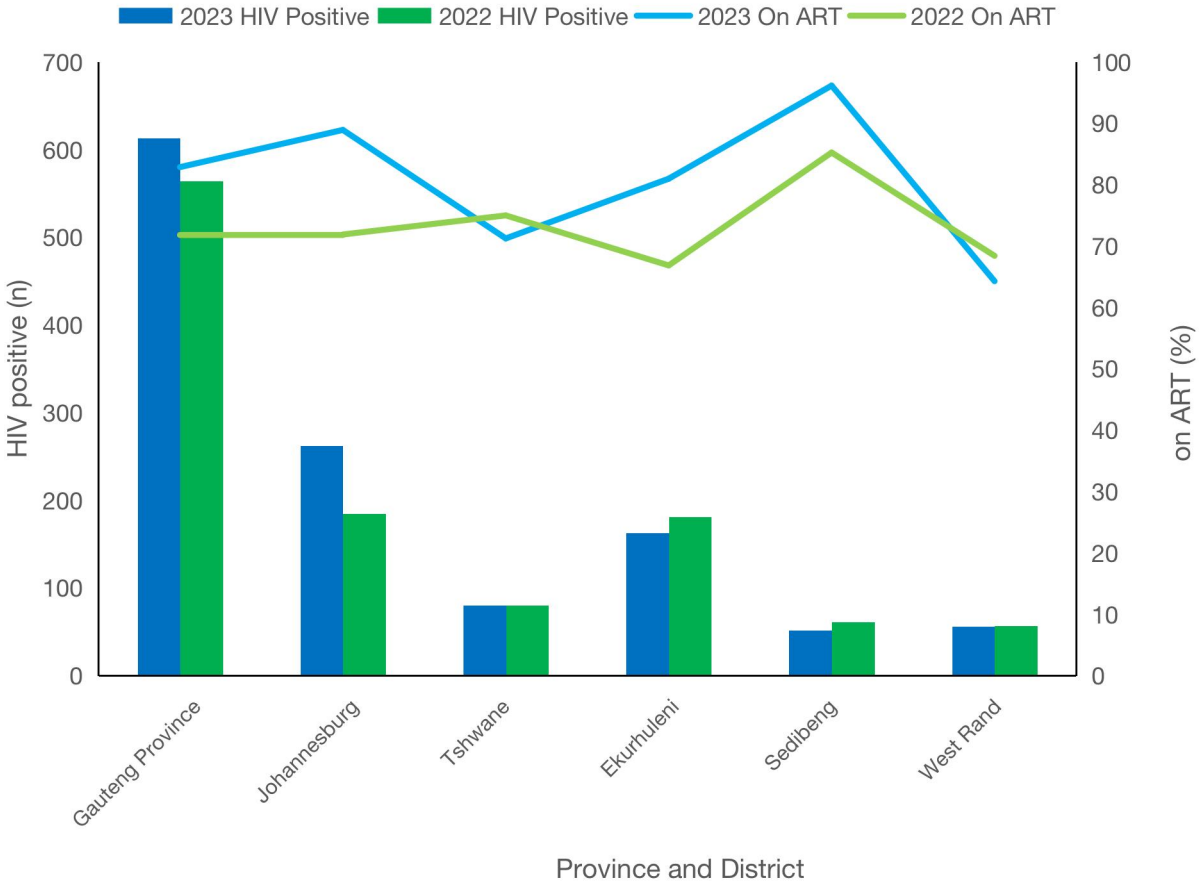

Figure 2. ART initiation in all HIV-positive RR-TB-diagnosed patients by district in the Gauteng province, South Africa, 2022 and 2023.

Table 3. ART initiation before or after RR-TB treatment initiation in HIV-positive RR-TB-diagnosed patients initiated on treatment by district, Gauteng province, South Africa, 2022 and 2023.

	2022						2023					
	JHB	**TSH**	**EKU**	**SED**	**WR**	**GP**	**JHB**	**TSH**	**EKU**	**SED**	**WR**	**GP**
	n(%)						n(%)					
HIV positive, ART, and RR-TB treatment initiated	114	41	106	14	26	301	219	55	126	47	33	480
ART initiation before TB treatment initiation	69(61)	33(80)	86(61)	10(71)	23(88)	221(73)	142(65)	42(76)	91(72)	35(74)	27(82)	337(70)
ART initiation after TB treatment initiation	45(39)	8(20)	20(39)	4(29)	3(12)	80(27)	77(35)	13(24)	35(28)	12(26)	6(18)	143(30)
P-value						0.002						0.293

JHB = Johannesburg Health District, TSH = Tshwane Health District, EKU = Ekurhuleni Health District, SED = Sedibeng District, WR = West Rand District, GP = Gauteng province.

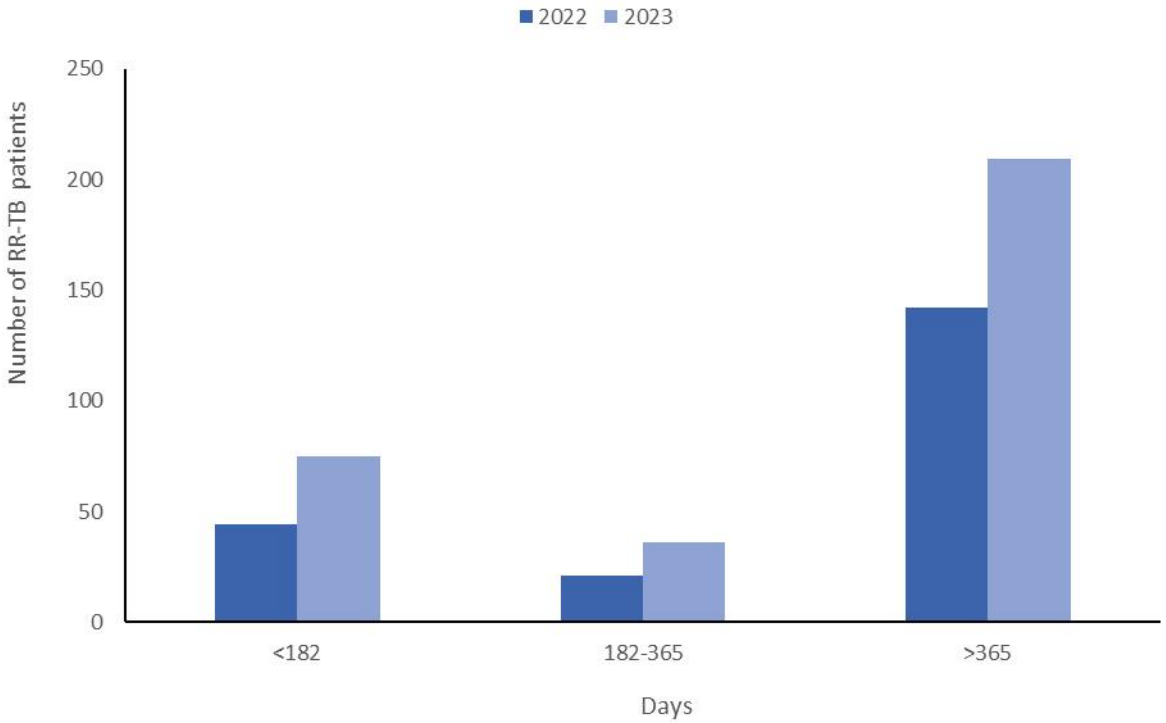

Figure 3. Number of days between ART initiation and RR-TB test date in all HIV-positive, RR-TB-diagnosed patients initiated on DR-TB treatment with ART initiated prior to RR-TB testing in Gauteng province, South Africa, 2022 and 2023.

Discussion

Gauteng reported improved RR-TB treatment initiation rates from 83% to 89% over two years. The initiation rate in 2023 is above the national target of 85% set for 2022 in the TB recovery plan.[12] However, it is below the 95% target stipulated in the NSP.[11] The improved linkage to care is possibly due to the considerable efforts of the TB programme to improve the TB referral system by strengthening the use of electronic TB information systems in conjunction with laboratory information systems.[20,21] Other possible advances include training healthcare workers to improve pre- and post-TB testing counselling, improving supply chain management including TB treatment stock at facilities, and new shorter TB regimens.[6,22,23]

The median time to treatment initiation in Gauteng for both years combined was six days (IQR: 1-12). This time is shorter than the median of 39 days reported through a systematic review of 53 studies but longer than the three days (IQR 1-8) reported by a low-income country in Central Asia.[24,25] In the current study, less than 1% of patients were initiated on treatment two or more months after receiving RR-TB results. According to the clinical RR-TB guidelines, a patient should be initiated on treatment immediately or within seven days.[6] Delays in treatment initiation are likely due to failures in tracing the patient, as incorrect addresses are sometimes provided, and patients hesitate to seek care due to insufficient information given by healthcare workers.[26–28]

Another factor that influences DR-TB time to treatment initiation is referral of patients from a non DR-TB site to a DR-TB site for treatment initiation.[29] Similarly, within DR-TB facilities, delays from the time of diagnosis in casualty or a non-TB ward to the transfer of a patient to a TB ward for treatment initiation may delay initiation. Late treatment initiation is strongly associated with an increased risk for mortality once a patient is initiated on treatment.[30]

Five per cent of TB patients were iLTFU in Gauteng, which is lower than other studies that have reported proportions of 20% to 25%.[14,31] Although most RR-TB cases were diagnosed in the 35–44 year age group, the majority of patients who were iLTFU were in the 25–34 year age group. Similarly, studies from the Western Cape in South Africa and from Uganda reported that patients of the same age group were the most affected amongst the iLTFU.[31,32] In contrast, a study from Zimbabwe found that the greatest risk for iLTFU was in the 65 years and older age group.[33] Research indicates that the economically active age groups would rather go to work than seek healthcare for TB, increasing the risk for iLTFU.[34] Another factor that contributes towards TB iLTFU is the diagnosis and discharge of patients prior to treatment initiation, which may result in failure to trace those patients again.[35]

The greatest proportion of people who died prior to treatment initiation was from Sedibeng District in 2022, the second smallest district by population size in Gauteng,[36] and, in 2023, it was Tshwane Health District. TB is preventable and curable; therefore, a death prior to initiation is likely due to late presentation and failed tracing activities.[28] There is still a need to improve case tracing by recording patient details clearly, following up on patients, and improving healthcare workers' interaction with patients.[37]

In South Africa, studies have reported the prevalence of DR-TB and HIV coinfection to be greater than 60%.[38] In the current study, 65% of RR-TB patients in 2022 and 69% of RR-TB patients in 2023 were co-infected with HIV. The greatest proportion of HIV-positive, RR-TB patients were already on ART prior to TB testing and treatment

initiation. This indicates that these patients were already linked to care at some point in the past, and therefore the risk of losing them to care once diagnosed with TB should be lower.[39] This highlights an opportunity to reduce iLTFU through patients having positive, supportive experiences within the health system prior to TB diagnosis, such as reduced waiting times at clinics to access healthcare services.[26,27]

Less than 1% of the DR-TB cases in the current study were in children. Under-reporting of child and adolescent TB has been identified in both low- and middle-income countries globally.[40] Malnourished children are at higher risk for TB and DR-TB, and South Africa is one of the top 20 countries contributing towards two-thirds of severe child food poverty worldwide.[41,42] This highlights the vital need to strengthen case identification in children in Gauteng.

Limitations of this study include missing data, with more than 15% of the data for ART initiation and age variables not completed in 2022. Therefore, it is possible that childhood cases of RR-TB have been underestimated.

This study's strengths include the use of one dataset based on reports of laboratory-confirmed RR-TB, with key indicators imputed by district officials. Due to data fragmentation and a lack of unique identifiers in the health system,[12] correct treatment initiation rates may be difficult to obtain, as different data sources are utilised for the numerator and denominator without cases being matched. Using a single database, as highlighted in this study, enables accurate calculation of patient initiation and iLTFU, underscoring the need for an integrated data system for TB.

Conclusion

The DR-TB programme in Gauteng showed improvement in the treatment initiation rates for RR-TB patients between 2022 and 2023, with reductions in iLTFU and deaths prior to treatment initiation. The opportunity to improve linkage to care still exists, although significant improvements have already been made.

Recommendations

- Healthcare workers should strengthen TB pre-testing and post-testing counselling to encourage patients to return to TB facilities to get their TB results and be linked to care.
- Healthcare workers should ensure positive patient experiences to build patient trust in order to attain correct patient contact details for follow-up.
- The National Department of Health and other stakeholders should establish an integrated information system for the entire TB cascade, including testing, linkage to care, and monitoring of patients until treatment completion.

Acknowledgements

We acknowledge the district, sub-district, and facility DR-TB managers for completing the weekly line list. In addition, we acknowledge Lehlohonolo Kumalo for reviewing the manuscript.

Funding

No funding or grant was used in the development of this publication.

Ethical considerations

The Human Research Ethics Committee (Medical), University of Witwatersrand, granted ethics approval (clearance number M210752) for this research.

Conflict of interest

The authors declare no conflicts of interest regarding the publication of this article.

References

1. Kaufmann SHE, Schaible UE. 100th anniversary of Robert Koch's Nobel Prize for the discovery of the tubercle bacillus. *Trends Microbiol*. 2005;13(10):469–75. doi: 10.1016/j.tim.2005.08.003.

2. World Health Organization. Global Tuberculosis report 2023. Geneva 2024. Available from: https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/tb-reports/global-tuberculosis-report-2023

3. World Health Organization. Tuberculosis Profile: South Africa. Geneva 2024. Available from: https://worldhealthorg.shinyapps.io/tb_profiles/

4. MacLean E, Kohli M, Weber SF, et al. Advances in molecular diagnosis of tuberculosis. *J Clin Microbiol*. 2020;58(10): e01582-19. doi: 10.1128/jcm.01582-19.

5. National Department of Health South Africa. National Tuberculosis Management Guidelines 2014. Pretoria 2014. Available from: https://knowledgehub.health.gov.za/elibrary/national-tuberculosis-management-guidelines

6. National Department of Health South Africa. Clinical management of rifampicin-resistant tuberculosis. Pretoria 2023. Available from: https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf

7. National Institute for Communicable Diseases. Microbiologically confirmed tuberculosis 2004–2015, South Africa. Johannesburg 2017. Available from: https://www.nicd.ac.za/wp-content/uploads/2017/04/K-12750-NICD-National-Survey-Report_Con_V3b.pdf

8. Statistics South Africa. Mortality and causes of death in South Africa: Findings from death notification. Statistical release. Pretoria 2020. Available from: https://www.statssa.gov.za/publications/P03093/P030932020.pdf

9. Zürcher K, Reichmuth ML, Ballif M, et al. Mortality from drug-resistant tuberculosis in high-burden countries comparing routine drug susceptibility testing with whole-genome sequencing: a multicentre cohort study. *The Lancet Microbe*. 2021;2(7):e320–e330. doi: 10.1016/S2666-5247(21)00044-6.

10. Tiemersma EW, van der Werf MJ, Borgdorff MW, et al. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. *PLoS One*. 2011;6(4): e17601. doi: 10.1371/journal.pone.0017601.

11. National Department of Health. National Strategic Plan for HIV, TB and STIs 2023–2028. Pretoria 2023. Available from: https://knowledgehub.health.gov.za/elibrary/national-strategic-plan-hiv-tb-and-stis-2023-2028

12. Department of Health South Africa. TB Recovery Plan 3.0. Pretoria 2024. Available from: https://knowledgehub.health.gov.za/webinar/update-tb-recovery-plan-30

13. Ndhlovu N. Unpublished Report. Account summary of rifampicin-resistant tuberculosis cases in 2021. Johannesburg 2021.

14. Naidoo P, Theron G, Rangaka MX, et al. The South African tuberculosis care cascade: estimated losses and methodological challenges. *J Infect Dis*. 2017;216(suppl_7):S702–S713. doi: 10.1093/infdis/jix335.

15. National Department of Health South Africa. Management of Rifampicin-Resistant Tuberculosis. Pretoria 2019. Available from: https://www.health.gov.za/wp-content/uploads/2020/11/management-of-rifampicin-resistant-tb-booklet-0220-v11.pdf

16. Cox H, Dickson-Hall L, Ndjeka N, et al. Delays and loss to follow-up before treatment of drug-resistant tuberculosis following implementation of Xpert MTB/RIF in South Africa: A retrospective cohort study. *PLoS Med*. 2017;14(2): e1002238. doi: 10.1371/journal.pmed.1002238.

17. National Health Laboratory Services. MEMO update on implementation of additional TB-NAAT assays. Johannesburg 2024.

18. National Institute for Communicable Diseases. NICD Laboratory Handbook. Johannesburg 2020. Available from: https://www.nicd.ac.za/wp-content/uploads/2020/11/NICD-Laboratory-Handbook_V18.pdf

19. World Health Organization. The END TB strategy. Geneva 2015. Available from: https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/the-end-tb-strategy

20. Ridho A, Alfian SD, van Boven JFM, et al. Digital health technologies to improve medication adherence and treatment outcomes in patients with tuberculosis: Systematic review of randomized controlled trials. *J Med Internet Res*. 2022;24(2): e33062. doi: 10.2196/33062.

21. Osman M, Karat AS, Khan M, et al. Health system determinants of tuberculosis mortality in South Africa: a causal loop model. *BMC Health Serv Res*. 2021;21(1):388. doi: 10.1186/s12913-021-06398-0.

22. Salomon A, Law S, Johnson C, et al. Interventions to improve linkage along the HIV-tuberculosis care cascades in low- and middle-income countries: A systematic review and meta-analysis. *PLoS One*. 2022;17(5): e0267511. doi: 10.1371/journal.pone.0267511.

23. Hwang B, Shroufi A, Gils T, et al. Stock-outs of antiretroviral and tuberculosis medicines in South Africa: A national cross-sectional survey. *PLoS One*. 2019;14(3): e0212405. doi: 10.1371/journal.pone.0212405.

24. Boyd R, Ford N, Padgen P, Cox H. Time to treatment for rifampicin-resistant tuberculosis: systematic review and meta-analysis. *Int J Tuberc Lung Dis.* 2017;21(11):1173–1180. doi: 10.5588/ijtld.17.0230.

25. Khushvakhtov S, Davtyan H, Alaverdyan S, et al. Scale-up and impact of digital and molecular diagnostic technologies on TB diagnosis and timely linkage to care in Tajikistan. *J Infect Dev Ctries*. 2021;15(9):58S-65S. doi: 10.3855/jidc.13758.

26. Skinner D, Claassens M. It's complicated: why do tuberculosis patients not initiate or stay adherent to treatment? A qualitative study from South Africa. *BMC Infect Dis.* 2016;16(1):712. doi: 10.1186/s12879-016-2054-5.

27. Vanqa N, Hoddinott G, Mbenyana B, et al. Linkage to TB care: A qualitative study to understand linkage from the patients' perspective in the Western Cape Province, South Africa. *PLoS One*. 2021;16(11): e0260200. doi: 10.1371/journal.pone.0260200.

28. Mwansa-Kambafwile JRM, Jewett S, Chasela C, et al. Initial loss to follow up of tuberculosis patients in South Africa: perspectives of program managers. *BMC Public Health*. 2020;20(1):622. doi: 10.1186/s12889-020-08739-w.

29. Iruedo JO, Pather MK. Time-to-treatment initiation in a decentralised community-care model of drug-resistant tuberculosis management in the OR Tambo District Municipality of South Africa. *Int J Environ Res Public Health*. 2023;20(14):6423. doi: 10.3390/ijerph20146423.

30. Ngabonziza JCS, Habimana YM, Decroo T, et al. Reduction of diagnostic and treatment delays reduces rifampicin-resistant tuberculosis mortality in Rwanda. *Int J Tuberc lung Dis.* 2020;24(3):329–39. doi: 10.5588/ijtld.19.0298.

31. Osman M, Meehan SA, von Delft A, et al. Early mortality in tuberculosis patients initially lost to follow up following diagnosis in provincial hospitals and primary health care facilities in Western Cape, South Africa. *PLoS One*. 2024;19(3): e0300768. doi: 10.1371/journal.pone.0300768.

32. Zawedde-Muyanja S, Musaazi J, Manabe YC, et al. Estimating the effect of pre-treatment loss to follow up on TB-associated mortality at public health facilities in Uganda. *PLoS One*. 2020;15(11): e0241611. doi: 10.1371/journal.pone.0241611

33. Mugauri H, Shewade HD, Dlodlo RA, et al. Bacteriologically confirmed pulmonary tuberculosis patients: Loss to follow-up, death and delay before treatment initiation in Bulawayo, Zimbabwe, from 2012–2016. *Int J Infect.* 2018; 76:6–13. doi: 10.1016/j.ijid.2018.07.012.

34. Mandal A, Basu M, Das P, et al. Magnitude and reasons of initial default among new sputum positive cases of pulmonary tuberculosis under RNTCP in a district of West Bengal, India. *South East Asia J Public Heal.* 2015;4(1):41-47. doi:10.3329/seajph. v4i1.21839.

35. Dudley L, Mukinda F, Dyers R, et al. Mind the gap! Risk factors for poor continuity of care of TB patients discharged from a hospital in the Western Cape, South Africa. *PLoS One*. 2018;13(1): e0190258. doi: 10.1371/journal.pone.0190258.

36. Statistics South Africa. Mid-year population estimates 2024. Pretoria 2024. Available from: www.statssa.gov.za

37. Khaitan A, Rai SK, Krishnan A, et al. "Better to die than take these medicines": a community-based qualitative study on the determinants of treatment loss-to-follow-up in tuberculosis patients in District Faridabad, Haryana, India. *Cureus*. 2022;14(5):e25030. doi: 10.7759/cureus.25030.

38. Van de Water B, Abuelezam N, Hotchkiss J, et al. The effect of HIV and antiretroviral therapy on drug-resistant tuberculosis treatment outcomes in Eastern Cape, South Africa: A cohort study. *Viruses*. 2023;15(11):2242. doi. 10.3390/v15112242.

39. Abubakar I, Lipman M. Reducing loss to follow-up during treatment for drug-resistant tuberculosis. *Eur Respir J*. 2019;53(1):1802268. doi: 10.1183/13993003.02268-2018.

40. Linn AR, Dubois MM, Steenhoff AP. Under-reporting of tuberculosis disease among children and adolescents in low and middle-income countries: a systematic review. *Trop Med Infect Dis*. 2023; 8(6):300. doi: 10.3390/tropicalmed8060300.

41. Vonasek BJ, Radtke KK, Vaz P, et al. Tuberculosis in children with severe acute malnutrition. *Expert Rev Respir Med*. 2022;16(3):273–284. doi: 10.1080/17476348.2022.2043747.

42. United Nations Children's Fund. Child food poverty. Nutrition deprivation in early childhood, child nutrition report. New York 2024. Available from: https://data.unicef.org/resources/child-food-poverty-report-2024/