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Healthcare Professional Newsletter

August 2025 – Issue 57

Shortening the tuberculosis treatment duration in children and adolescents living with HIV who have non-severe pulmonary tuberculosis

Tuberculosis (TB) remains a major cause of morbidity and mortality in children and adolescents living with HIV (CALHIV). Suppressive antiretroviral therapy (ART) is key to prevention of TB. Every 10% increase in suppressive ART translates to a 2.33% reduction in incident TB. However, despite access to ART rates of TB remain high. Most at risk are CALHIV younger than 5 years and those with severe immune suppression. CALHIV with severe immune suppression are at a 5 [95% CI 4.0–6.0] times higher risk of developing TB when compared to those with insignificant immunosuppression.¹

The September 2024 South African guidelines for management of TB in children and adolescents younger than 16 years has some important changes for children with rifampicin susceptible pulmonary TB, including the care of CALHIV.²

The guideline recommends that all children receive ethambutol in the intensive phase of therapy. This is not a new recommendation for CALHIV, children older than 8 years, and younger children with severe pulmonary TB. However, these guidelines were often not followed. This change was adopted in South Africa because the rate of isoniazid mono-resistance ranges from 13.8% - 21.1%. In addition, the World Health Organization (WHO) recommends the use of ethambutol in the intensive phase where the seroprevalence of HIV is $\geq 1\%$ among adult pregnant women or $\geq 5\%$ among people with TB.^{2,3,4} Implementation of this recommendation will simplify decision making for all children and aligns with adult recommendations.

The guideline also recommends treatment shortening to 16 weeks for selected children with non-severe pulmonary TB. This shorter regimen is 8 weeks of intensive phase followed by 8 weeks of continuation phase, reducing therapy from 24 to 16 weeks.² The SHINE study was a non-inferiority trial. 1204 children with protocol defined non-severe TB were randomised to 24 or 16 weeks of TB therapy in a 1:1 ratio.⁵ The primary efficacy outcome was unfavourable status by 72 weeks. Unfavourable status included TB treatment failure, TB treatment extension beyond the replacement of missed doses, antituberculosis treatment drug change or restart, loss to follow-up during treatment and death from any cause. The study included 127 CALHIV balanced between the arms. There was no difference between the number of children with unfavourable status by 72 between the 16 and 24 week arms. A modified intention-to treat analysis showed that, for CALHIV the outcomes were consistent with the primary result, suggesting that treatment shortening can also be used for CALHIV. However, we should note that the majority of participants in the study were young, with a median age of 3.6 years (IQR 1.5-7 years).⁵ Older children and adolescents are more likely to have severe pulmonary TB. In addition, the study was not powered to detect a difference in the subgroup of CALHIV. In a secondary analysis of these data the authors compared the 127 CALHIV to those without HIV. Death occurred in 13 of 127 (10.2%) of CALHIV compared to 18 of 1077 (1.7%) other participants. CALHIV had significantly lower weight for age z-scores (WAZ) with a median of -2.3 (IQR -3.3;-0.8) compared to children without HIV who had a median WAZ of -1.0 (IQR -1.8;-0.2) $p < 0.01$. CALHIV also had significantly lower haemoglobin, median 9.5g/dl (IQR 8.7;10.0) vs median 11.5g/dL (10.4;12.2) $p < 0.1$.⁶

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The South African guidelines do allow for treatment shortening in CALHIV with pulmonary TB provided the following conditions are met²:

1. It is the first episode of TB AND
2. They are older than 3 months AND
3. They should be on ART for at least three months with a viral load result of < 1000 copies/mL at diagnosis or within 3 months prior to the diagnosis AND
4. The CXR should be that of uncomplicated pulmonary tuberculosis
 - Uncomplicated intrathoracic lymph node TB without airway obstruction/compression OR
 - Simple TB pleural effusion OR
 - Consolidation/opacification that is less than one lobe of the lungs, without any cavities, and without a miliary pattern.

Where CALHIV meet these criteria treatment shortening can be considered provided they adhere to therapy and show clinical improvement. Weight banded dosing is recommended with dose adjustment with weight gain. The addition of vitamin B6 is also recommended regardless of nutrition status.²

Treatment shortening in CALHIV who qualify will reduce pill burden and hopefully improve quality of life and treatment completion. However, prevention of TB with timely initiation of suppressive ART and TB preventive therapy where appropriate is essential.

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3HP for TB prevention in people living with HIV

Historically, TB preventive therapy (TPT) recommendations in South Africa for adults with HIV have been with isoniazid monotherapy of durations between 6 and 36 months. The South African National Department of Health guidelines have recently been updated to include combining a rifamycin with isoniazid, which allows the duration of TPT to be shortened with similar protection against active TB disease in clinical trials – the “3HP” regimen is one recommended option.

The 3HP regimen is 3 months of isoniazid and rifapentine, both administered weekly at a dose of 900mg, (i.e. total of 12 doses) in adults. Until recently, rifapentine (which is in the same rifamycin drug class as rifampicin) was largely unavailable outside the USA, but that is changing and it is now becoming available in many countries including South Africa.

3HP was evaluated in the PREVENT TB trial,¹ which was an open-label, randomised noninferiority trial comparing 3 months of directly observed once-weekly therapy with 3HP versus 9 months of self-administered daily isoniazid (300 mg) in individuals at high risk for TB. The minority of participants (~3%) had HIV infection in the trial. TB developed in 7 of 3986 participants in the 3HP group (cumulative rate, 0.19%) and in 15 of 3745 participants in the INH-only group (cumulative rate, 0.43%). It was concluded that 3HP was as effective as 9 months of INH in preventing active TB disease. Treatment completion was higher among 3HP participants and permanent drug discontinuation due to an adverse event and investigator-assessed liver toxicity were less frequent with 3HP. A subgroup analysis of participants with HIV, although this group was small, showed similar results to the overall study population.²

3HP can be used in patients on dolutegravir or efavirenz-based regimens. As is the case with rifampicin, there is a drug-drug interaction between rifapentine and dolutegravir, resulting in reduced dolutegravir exposure. However, when rifapentine is dosed weekly the amount of induction is modest and studies have shown that there is no need to increase the dolutegravir dose (i.e. dolutegravir can be dosed at 50mg daily when given with 3HP).^{3,4} 3HP cannot be co-administered with boosted protease inhibitors or rilpivirine.

Given this evidence and the fact that rifapentine is now available in South Africa, AfA supports 3HP as an option in patients with HIV who are eligible to receive TPT.

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Antiretroviral Resistance Testing (Genotyping)

This test may be funded by medical schemes if treatment failure is suspected, provided certain criteria are met:

- The test must be preapproved (contact AfA toll-free on 0800 227 700). If preapproval is not obtained, the patient will be liable for the cost of the test.
- The patient must be adherent to therapy and on the failing regimen at the time of doing the test in order for resistance mutations to be demonstrated, unless the presence of primary resistance is strongly suspected.

The interpretation of the results and the construction of new/salvage regimens is often complex. Please submit the results to AfA for analysis and advice on further management.

AfA study finds courier delivery of ART a viable alternative to retail dispensing

This study,¹ led by the leDEA-SA research team, investigated differences in viral suppression rates between beneficiaries of the Aid for Aids (AfA) programme receiving antiretroviral therapy (ART) by courier delivery and those receiving ART through traditional retail dispensing.

The research team analysed 442,619 viral load measurements from 68,720 beneficiaries between 2011 and 2022. Viral load suppression was detected in 398,901 (90.1%) tests, and 185,701 (42.0%) of the tests were taken while the beneficiary was receiving ART by courier delivery.

Courier delivery of ART was associated with improved viral suppression (defined as a viral load <400 copies/mL) from 2011 to 2016. This effect was not sustained, however, and there was no significant difference between courier delivery and retail dispensing on viral suppression from 2017 to 2022, which was the end of the study period. The table below shows the adjusted odds ratios for viral suppression comparing the two ART distribution methods, by calendar period and overall.

The reasons for the waning effect of courier delivery on viral suppression by calendar period are unclear – one hypothesis is that early adopters of courier delivery may have been more motivated and had better adherence. A randomised controlled trial in Tanzania of people who were stable on ART reported that community delivery of ART did not result in higher viral suppression than facility-based care in a public sector program, which was consistent with the findings of the AfA study.²

The authors concluded that courier delivery of ART is a viable alternative to traditional retail dispensing in the private sector, as it was associated with higher viral suppression until 2016 and similar suppression rates in recent years. Further research is needed to investigate the potential benefits and drawbacks of courier delivery of ART such as convenience and privacy for beneficiaries. Programmatic and economic factors associated with courier services also warrant further exploration.

	Calendar period				Overall
	2011-2013	2014-2016	2017-2019	2020-2022	
Retail dispensing	1	1	1	1	1
Courier delivery	1.37 (1.27, 1.48)	1.06 (1.00, 1.13)	0.95 (0.91, 0.99)	1.02 (0.97, 1.07))	1.05 (1.02, 1.08)

Table 1. Adjusted odds ratios for viral suppression comparing beneficiaries with courier ART delivery to those on retail ART dispensing. 95% confidence intervals are given in parentheses. Odds ratios were adjusted for sex, age, medical aid scheme, and history of mental illness – in the overall analysis calendar period was adjusted for.

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