



# POLICY BRIEF

## Simultaneous initiation of isoniazid and rifapentine-based TB preventive therapy and dolutegravir-based antiretroviral therapy in treatment-naïve people with HIV

### Synopsis

TB is a leading cause of death in South Africa. People living with HIV (PLHIV) are at far higher risk of progressing from TB infection to active, communicable TB disease than people without HIV. TB preventive treatment (TPT) using 3 months of once-weekly isoniazid and rifapentine (3HP) is already recommended by the World Health Organization (WHO) and recommended and in use by the South African National Department of Health. Results from the **DOLPHIN-TOO** Study show that simultaneous

initiation of 3HP and dolutegravir (DTG)-based antiretroviral therapy (ART) in ART-naïve PLHIV in high-burden settings is safe and effective. Given the high risk of TB disease and death in PLHIV and the public health importance of preventing disease progression and transmission, uptake of simultaneous 3HP and DTG-based ART initiation can support the 2023-2028 South African National Strategic Plan mission to eliminate HIV & TB as public health threats by 2030 [1].

### Context

TB and HIV are the sixth and seventh leading causes of death in South Africa, respectively [1]. In South Africa in 2022, 152,000 incident TB cases occurred in PLHIV, and TB claimed the lives of 31,000 PLHIV [2]. First-line therapy for HIV is dolutegravir plus two nucleoside reverse transcriptase inhibitors.

WHO recommends TPT for all PLHIV even if TB infection testing is not available; 3HP, a three-month oral treatment taken once weekly is a short, safe, and effective form of TPT recommended by WHO for children and adults aged 2 years and above, including for PLHIV [3].

South Africa also recommends use of 3HP for TPT among PLHIV, and the regimen is already in use in the country [4].

The recommendation for use of 3HP among PLHIV was based on the **DOLPHIN Study**, which found 3HP to be safe, effective, and have high potential to improve outcomes in virally suppressed individuals with HIV on first-line DTG-based ART (see textbox on page 2). However, at the time, 3HP had not yet been rigorously studied in ART-naïve individuals starting DTG-based ART. The **DOLPHIN-TOO** Study was conceived to address this gap.

## DOLPHIN Study: Investigating 3HP as TPT in virally suppressed PLHIV on first-line DTG-based ART [5]

- **Study Design:** Phase 1/2 single-arm trial of 61 virally suppressed PLHIV in South Africa
- **Study Findings:**
  - 3HP can be given as TPT to PLHIV taking DTG-based ART, without the need for dose adjustments
  - Rifapentine induces DTG clearance via inducing CYP-450 enzymes. Co-administered 3HP and DTG results in DTG trough lowering by 64% and 56% (at 2 and 5-6 days post 3HP dose)
  - Despite this, all participants remained virally suppressed

## DOLPHIN-TOO Study: Investigating initiation of 3HP in ART-naïve PLHIV newly starting DTG-based ART [6,7]

### Study Design

- **Design:**
  - Phase I/II comparative trial of 3HP versus 6 months isoniazid (6H) among ART-naïve adults with HIV initiating once-daily 3-drug DTG-based ART in South Africa
  - Participants sequentially enrolled from 31 August 2021 to 28 June 2022 and assigned to 6H (N=25) and 3HP (N=50)
- **Endpoints:**
  - Primary: Safety and DTG pharmacokinetics during coadministration of DTG and 3HP versus 6H
  - Secondary: HIV viral load

### Study Findings

The study found the **simultaneous start of 3HP and DTG-based ART was safe, well-tolerated**, and achieved rapid and maintained viral suppression.

**Pharmacokinetic results were also favourable**, with robust DTG troughs observed. A 72% induction effect of RPT on DTG clearance was observed, and DTG troughs were significantly lower in the 3HP group than the 6H group at weeks 3 and 8, but still sufficient to achieve and maintain HIV viral load <50 copies/mL.

## Implications for TB prevention policy

- PLHIV are at **greatly increased risk** for developing active TB disease
- Simultaneous start of DTG-based ART and 3HP in newly diagnosed people with HIV is **safe and effective**
- Offering 3HP at the same time as ART initiation is an **early opportunity to provide life-saving TB prevention** for PLHIV

### References

- [1] Department of Statistics, Republic of South Africa. [Mortality and causes of death in South Africa: Findings from death notification](#) (2020). 2024.
- [2] World Health Organization. [Tuberculosis profile: South Africa](#). 2023.
- [3] World Health Organization. [WHO consolidated guidelines on tuberculosis: module 1: prevention: tuberculosis preventive treatment](#). 2020.
- [4] Department of Health, Republic of South Africa. [National Guidelines on the Treatment of Tuberculosis Infection](#). 2023.
- [5] Dooley KE et al, Lancet HIV. 2020 Jun; 7(6):e401-e409. Mar 30, 2020.
- [6] Weld ED et al, The Union Meeting, Paris, Nov 16, 2023.
- [7] Weld ED et al, CROI Conference, Denver, CO, Mar 11, 2024