New 2025 WHO Recommendations Antiretroviral treatment Advanced HIV disease

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c/o

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Background

2.5 million people with HIV in LA and 340M in the Caribbean

2 million in ART

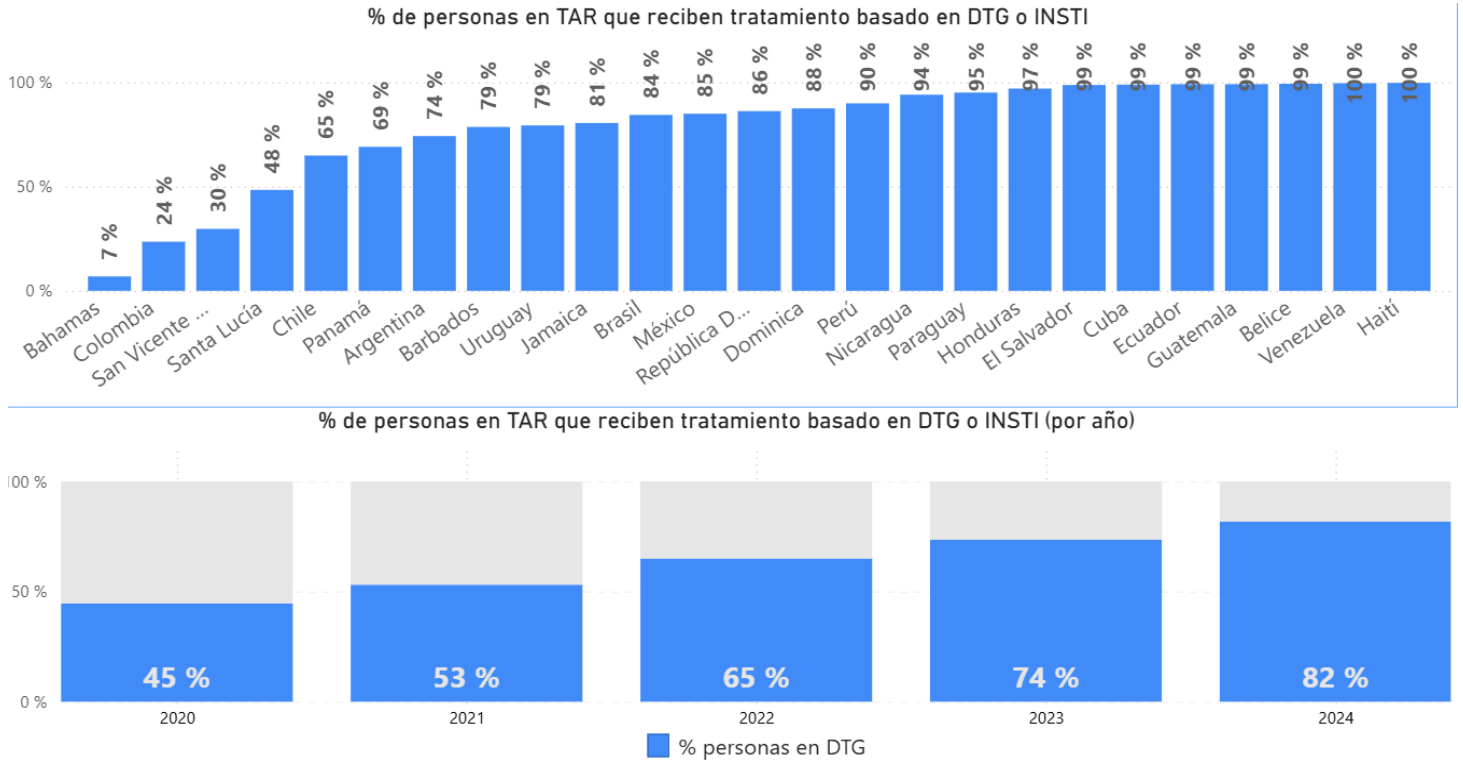
TLD is the most widely used scheme for both naïve and pre-treated patients

More data on efficacy of DTG, protease inhibitors, and TAF are available

Dual therapy data solidifies it as a safe and effective option

Long-acting injectables are beginning to be used in low- and middle-income countries

IM transmission continues to be a major problem



What did we already know and DIDN'T CHANGE?

Brief summary of the PAHO-WHO Consolidated HIV Treatment Guidelines 2021

WHEN TO START:

ART Quick Start: On the same day if the patient is ready, or at least within 7 days of confirmation of the diagnosis, regardless of viral load or CD4

- **TB/HIV co-infection: start within 2 weeks of starting TB treatment**
- **CNS infections (Neuro TB, cryptococcosis): wait 4-8 weeks from treatment of CNS infection**

WHAT TO START WITH:

- **TLD (fixed-dose) is the preferred regimen for initiating ART for all PLHIV**
- **Consider the use of ABC, TAF, EFV, or PIs in special circumstances**
- **DTG is the preferred choice for those who have not previously used DTG**

WHAT TO USE IN 2ND LINE:

PIs is the preferred choice for people who failed on DTG

OPTIMIZATION:

- **Simplify patients on EFV to TLDs regardless of viral load.**
- **Simplify patients on PIs to TLD if they never used DTG before**

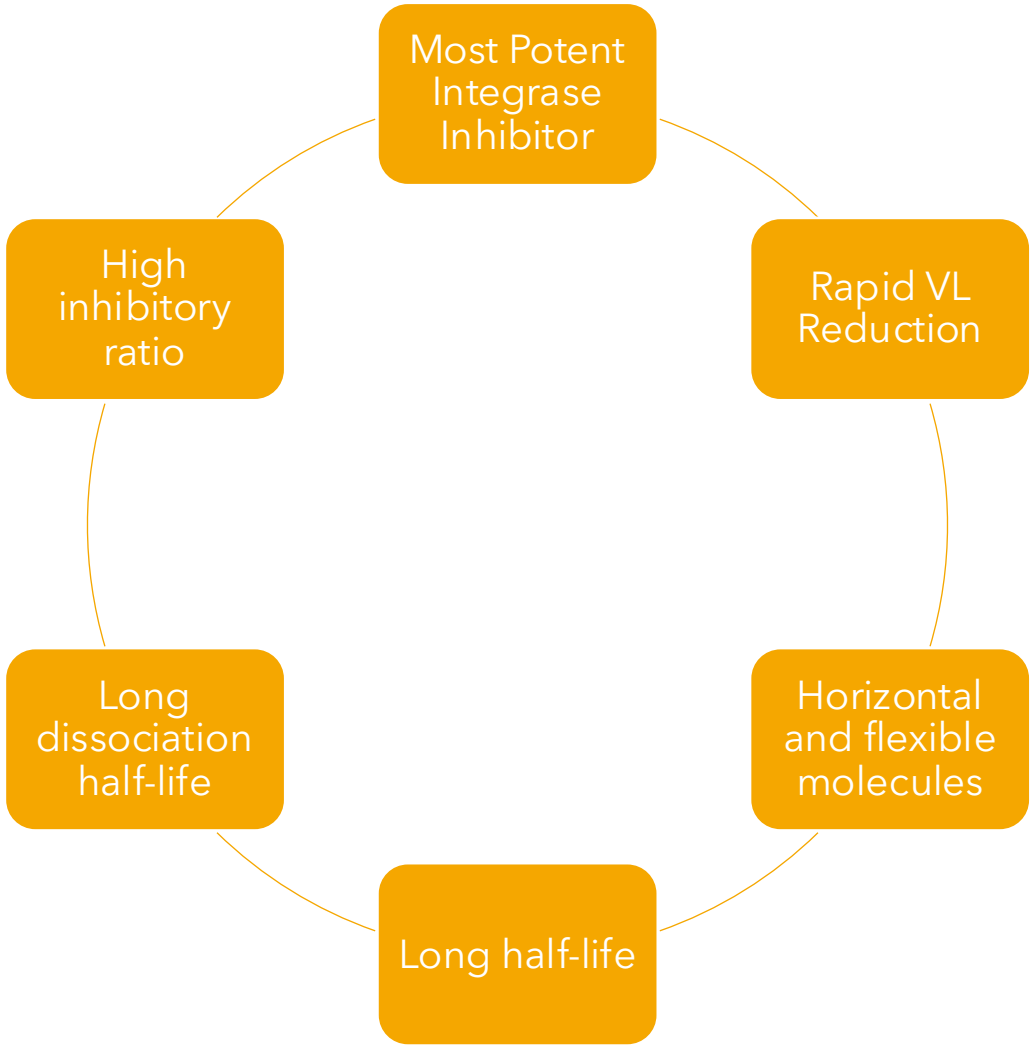
SPECIAL SITUATIONS:

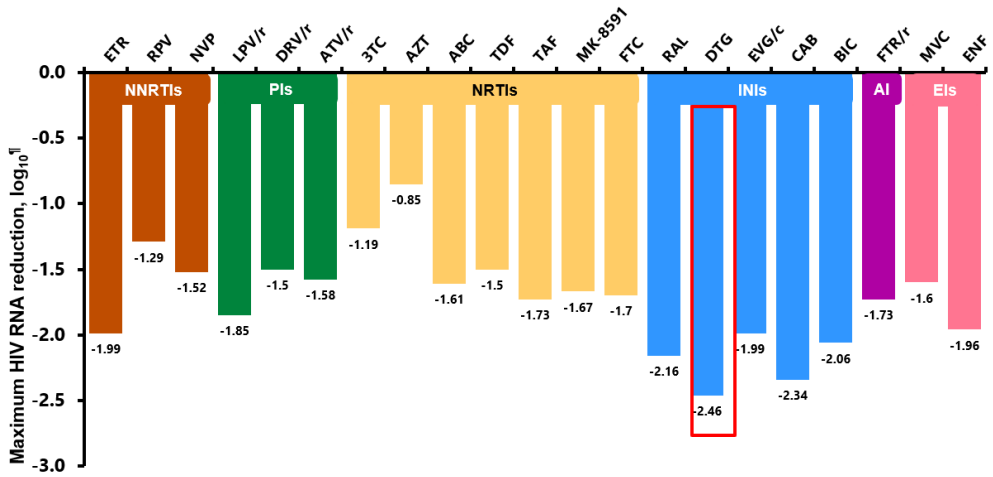
- **Double the dose of DTG in people using rifampicin, phenytoin, or carbamazepine or failure prior to INSTI**

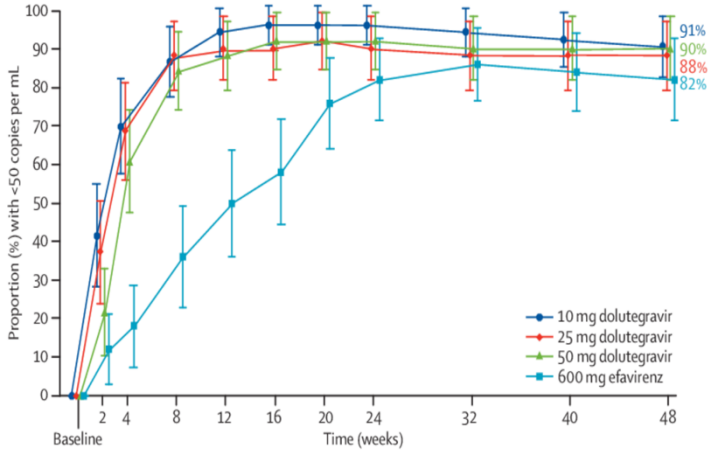
Core of New Guidelines

- Regimen simplification
- Injectables
- Pediatric treatment
- Breastfeeding
- Advanced HIV management
- TB prevention

Features of Dolutegravir (DTG)

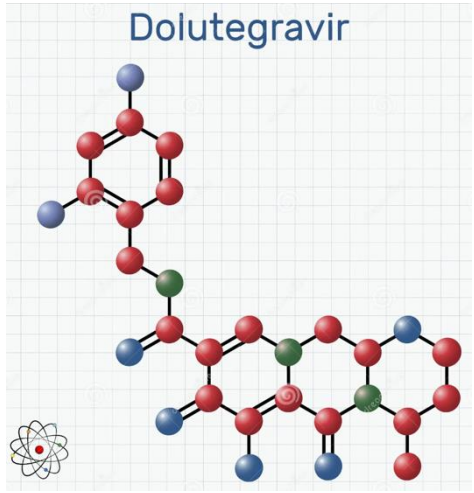






van Lunzen J, *et al.* Lancet Infect Dis 2011. la Porte C. Curr Opin HIV AIDS. 2008. Hare S. et al Mol Pharm 2011. Hightower et al. Antimicrob Agents Chemother 2011

What to accompany DTG with?



NAIVE	**NRTI backbone TDF-3TC-DTG**	**Bottles of 30- 90- 180 comp Price 0.1 USD-pill**
	NRTI backbone TAF-3TC-DTG	**Bottles of 30 tablets. Price 0.13 USD-pill**
	Alternative ABC-3TC + DTG	**Not FDC, price 0.3 USD per day (2 pills)**
UNDETECTABLE VIRAL LOAD	**Dual therapy 3TC-DTG**	**Bottles of 30 tablets Price 0.09 USD-pill**

AZT Use Limited

Over time, the indications for AZT have been eliminated

It is no longer recommended in children

No longer recommends sequencing NRTI in ART failure to use as alternate

Rapid initiation of TLD in pregnancy instead

Second line use with AZT + 3TC when TDF or ABC can't be used

- AZT less potent than TDF even when TDF resistance present
- NADIA Study
  - Failure with EFV-TDF-3TC, better to keep TDF-3TC than switch to AZT
  - AZT did not outperform TDF even with TDF resistance present

Paton. Lancet. 2022; Paton. CROI 2022. Abstr 137. Paton. NEJM. 2021;385:330. Sivile. AIDS 2024. Abstr OAB3806LB. Mulenga. CROI 2022. Abstr 135.

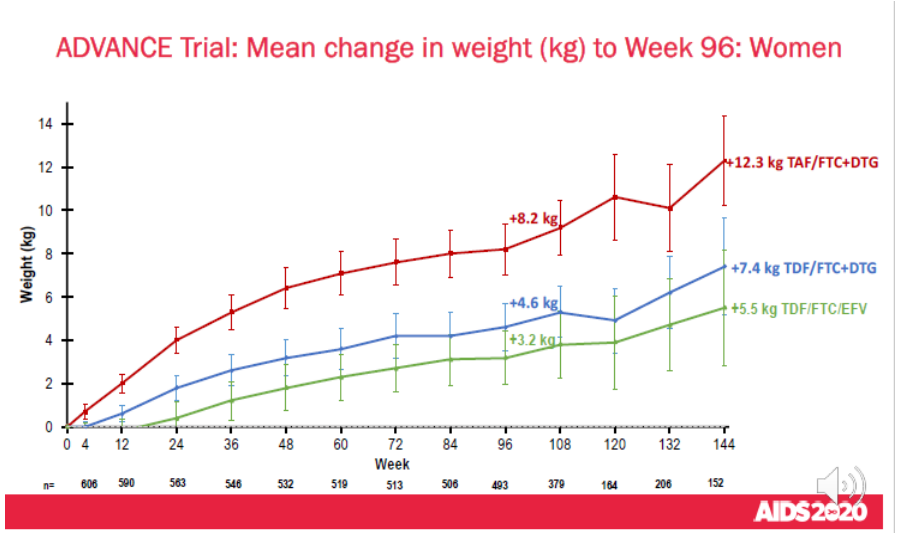
Tenofovir alafenamide fumarate vs Tenofovir disoproxil fumarate (TAF vs TDF)

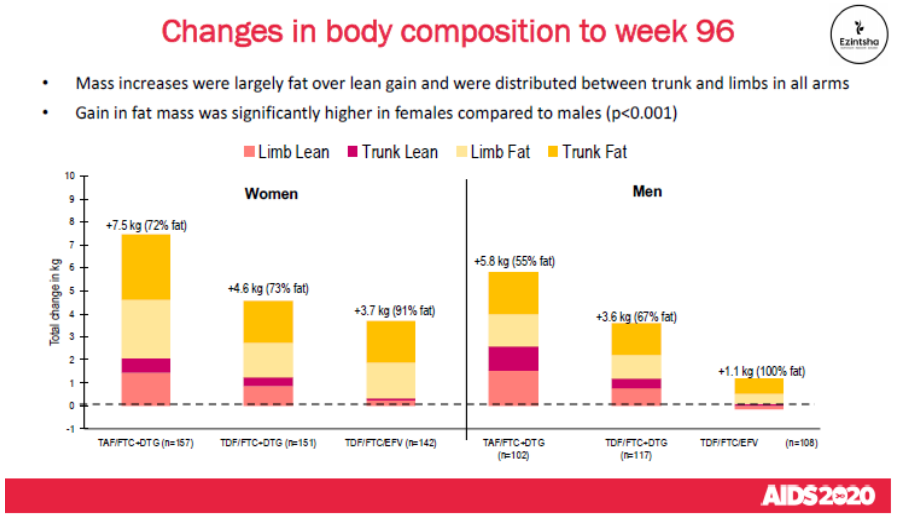
Clinical Benefit of TAF

- Less toxic to bone and kidneys but no difference in clinical outcomes (fx or kidney failure
- Preferred with osteoporosis and kidney failure
- Safe in pregnancy and HBV co-infection

Toxicity Profile and Interactions of TAF

- Greater weight gain with DTG vs TDF
- Greater frequency of dyslipidemia, HTN, NASH/NAFD
- Contraindicated with rifampin due to DDI



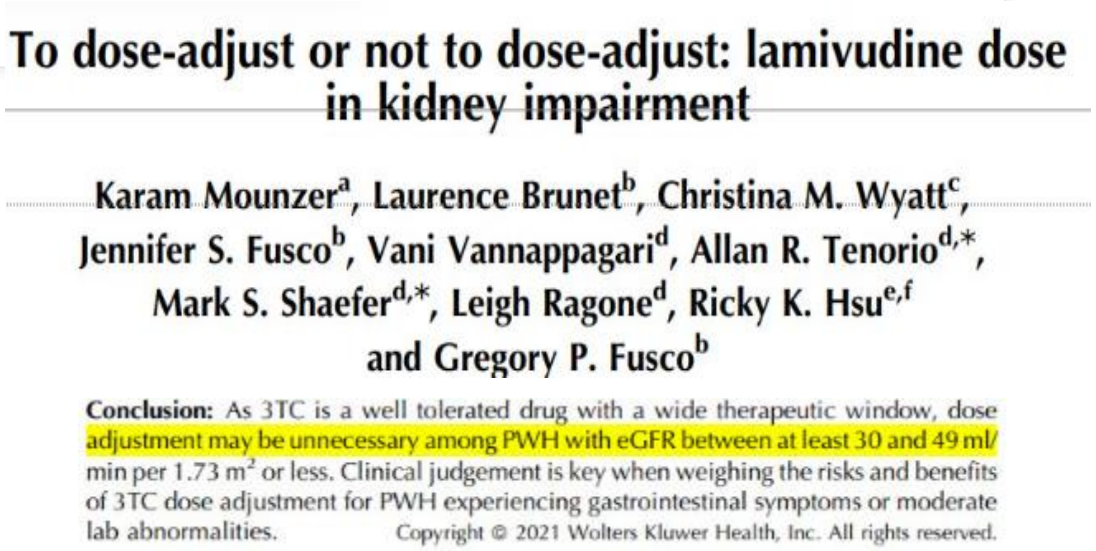


Pilkington, AIDS 2021, Tao IJID 2020, Esber JIAS 2022, Venter Lancet 2020

Fixed Dose Combination with CKD

Real-World Experience With Higher-Than-Recommended Doses of Lamivudine in Patients With Varying Degrees of Renal Impairment."
Published in Open Forum Infectious Diseases (OFID), 2018; 5(10): ofy225

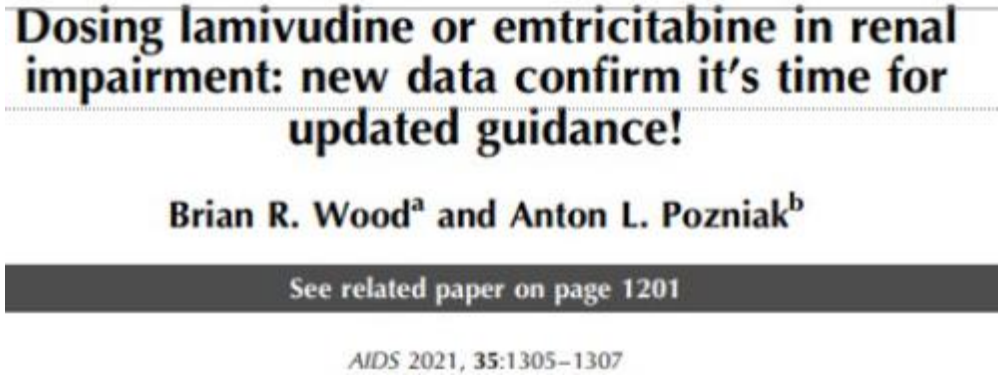
- This study showed that when CrCl was <30 mL/min, use 3TC 150 mg daily
  - Previously, it was suggested to adjust between 50-30 CrCl to 150mg of 3TC per day.
- Use FDC in anybody with CrCl >30mL
- This study shows that there was no accumulation or toxicity. Lactic acid did not increase. The dose was well tolerated
- Conclusion:
  - LAMIVUDINE SHOULD NOT BE ADJUSTED UNTIL GFR DROPS BELOW 30
  - Avoid syrups



To dose-adjust or not to dose-adjust: lamivudine dose in kidney impairment

Karam Mounzer[a], Laurence Brunet[b], Christina M. Wyatt[c], Jennifer S. Fusco[b], Vani Vannappagari[d], Allan R. Tenorio[d,*], Mark S. Shaefer[d,*], Leigh Ragone[d], Ricky K. Hsu[e,f] and Gregory P. Fusco[b]

Conclusion: As 3TC is a well tolerated drug with a wide therapeutic window, dose adjustment may be unnecessary among PWH with eGFR between at least 30 and 49 ml/min per 1.73 m^2 or less. Clinical judgement is key when weighing the risks and benefits of 3TC dose adjustment for PWH experiencing gastrointestinal symptoms or moderate lab abnormalities.



Dosing lamivudine or emtricitabine in renal impairment: new data confirm it's time for updated guidance!

Brian R. Wood[a] and Anton L. Pozniak[b]

See related paper on page 1201

AIDS 2021, **35**:1305–1307

DHHS 2026

Appendix B. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

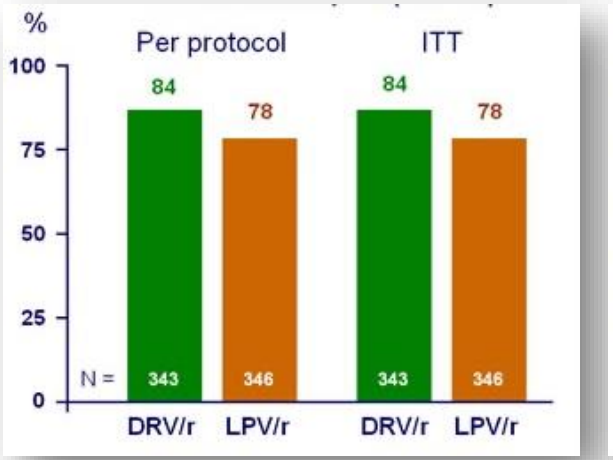
Generic Name (Abbreviation) *Trade Name*	**Usual Dose**[a]	**Dosing in Adults With Renal Insufficiency**	**Dosing in Adults With Hepatic Impairment**
Dolutegravir/ Lamivudine (DTG/3TC) *Dovato*	One tablet PO once daily	Not FDA recommended if CrCl <30 mL/min due to 3TC component **Note:** There is insufficient evidence to recommend for or against the use of full-dose 3TC in people with CrCl <30 mL/min. To allow people to remain on the FDC product, some Panel members use full-dose 3TC.[d]	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**

Protease inhibitors

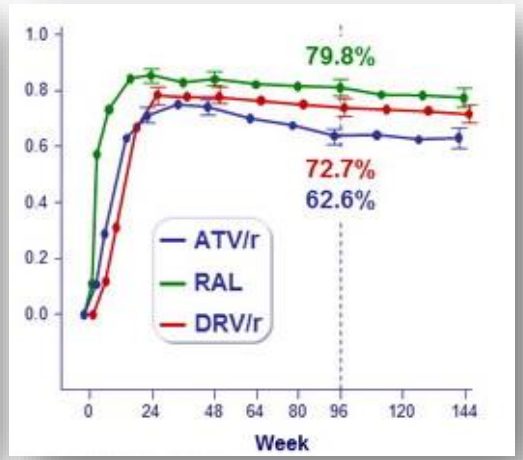
- They always require ritonavir
- Important interaction with rifampin
- (do not use with TB or LTBI treatment)
- Important interactions with other drugs: with **carbamazepine, phenobarbital, phenytoin, simvastatin, ergotamine, sildenafil**
- New WHO guidance recommends DRV-r as the preferred PI
- The indication is second line (after failing a DTG regimen)
  - Dose 800-100 once daily (generic available 400/50 x 60 pills 17 USD)
- For patients failing to other PI (atazanavir or lopinavir) or failing low dose of DRV/r a “high dose” should be used (DRV/r 600-100 BID)

Darunavir is the preferred protease inhibitor for people who cannot use DTG

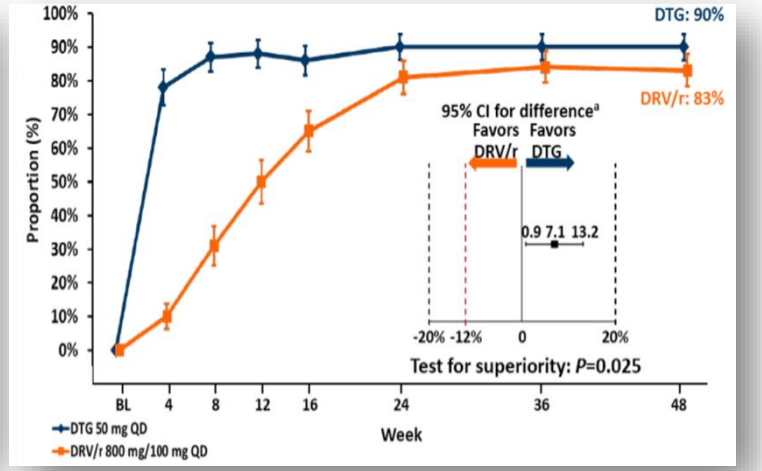
In ARTEMIS, DRV/r is better than LPV/r



In ACTGA5257 DRV/r is better than ATV/r



In Naïve (FLAMINGO study) DRV/r is worse than DTG, especially in high CV



- Better than LPV/r and ATV/r
- Worse than DTG in naïve patients, and similar to DTG in pretreated
- Available as generic prequalified co-formulated dose with ritonavir in doses 400/50mg
- Cannot be used with rifampin (use rifabutin or switch)
- The DRV dose 600/100 c/12hs for:
  - On the third line (failure of another IP)
  - Pregnant women

Clotet Lancet 2014, Orkin, HIV Med 2013, Lennox JL AIM 2014, Fienberg 2013

Comparison of ATV/r, LPV/r, DRV/cobi, DRV/r

Parameters	ATV/r	LPV/r	DRV/cobi	DRV/r
Consistency with pediatric regimens	From 3 months (a)	From 2 weeks	No	From 3 years old[b]
Number of pills per day (standard dose, CDF)	1	4	1	2 (400/50mg) [c]
Convenience (daily dose)	1	2	1	1[c]
Pregnancy Safety	Yes	Yes [d]	Not evaluated	Limited evidence with low doses[c]
Gastrointestinal intolerance	+	+++	+	+
Genetic barrier	Weak	Weak	Strong	Strong
Availability as generic CDF for adults	Yes	Yes	No	Yes
Availability as a pediatric generic co-formulated dose	No	Yes [f]	No	No [e]
Hyperbilirubinemia	++	No	No	No
Dyslipidemia	+	+++	++	++
Price (per month, in USD)	10.5	18.50	518 (in Mex)	17.50

Treatment Algorithm

First line

TDF/3TC/DTG
or
TAF/FTC/DTG

- Alternative
  ABC-3TC-DTG

Fail

Second line

TDF-FTC-DRV/r
800-100

- Alternative
  TDF or TAF/FTC/ ATV-r

Genotype might not be necessary

Fail

Third line

DRV/r 600-100 c/12
+ DTG 50 c/12 +/-
ETV 200/12hs

- Alternative: build a regimen with 2 active drugs (like doravirine, maraviroc or fostemsavir

Genotype is needed to define the residual activity of DTG, NRTI, DRV/r and susceptibility to Etravirine (or doravirine)

What do the guidelines say about dual therapy?

- Most efficacious dual combination:
  - 3TC-DTG (300-50mg) once daily
  - Pill price 0.08 USD

Advantages:

Less Drug

Less toxicity

Less cost

Easier monitoring

Best Candidate:

Undetectable people with no prior history of multiple treatment failures

Undetectable people who do not have chronic hepatitis B (HBsAg+)

Vaccinated for hepatitis B

If creatinine is <30ClCr, the separate pills must be used:
1 DTG+ 1 3TC of 150mg

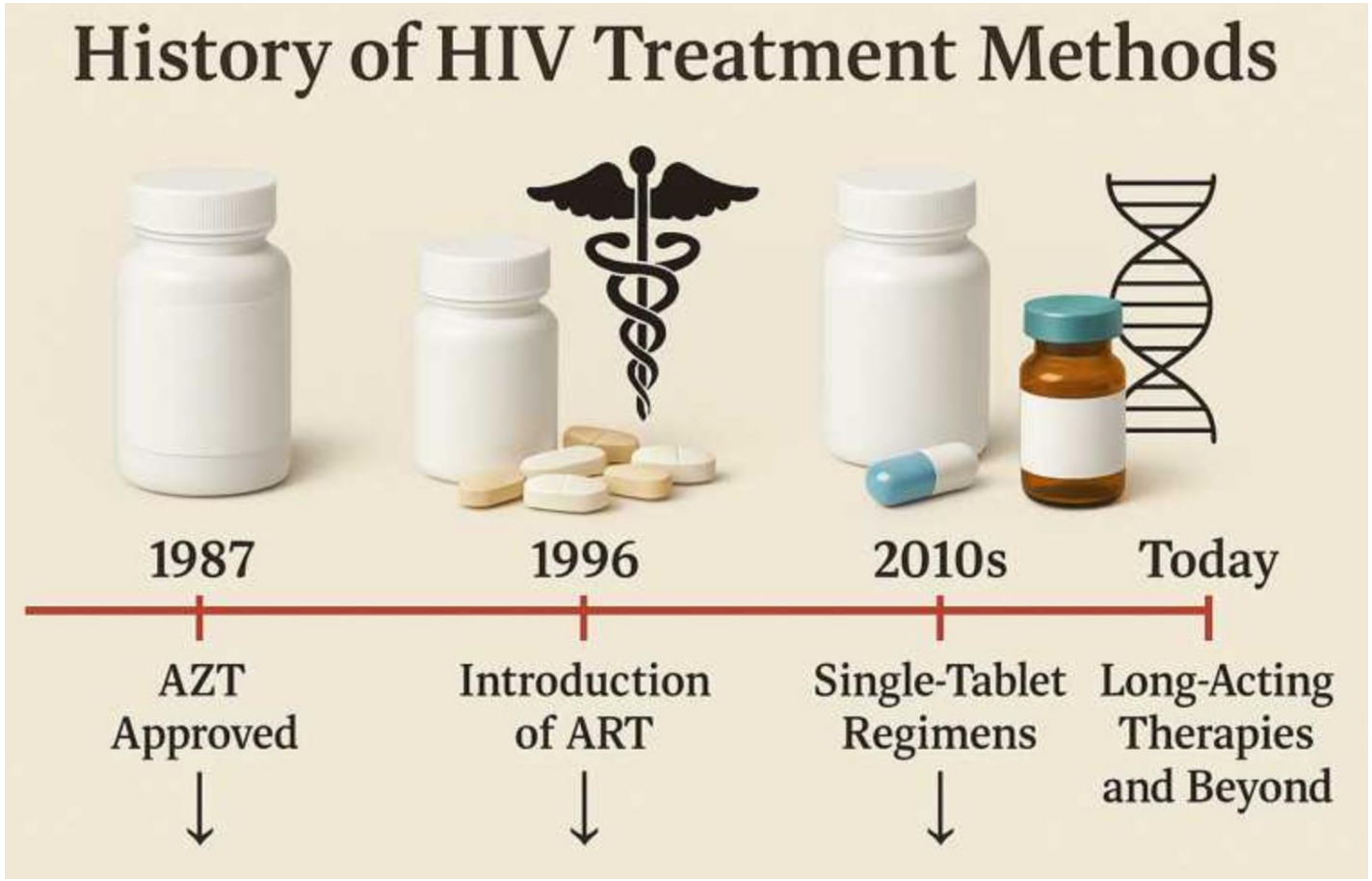
3TC + DTG (Dual Therapy)
DTG + 3TC is not inferior to DTG + FTC/TDF

Key Results	When It Can Be Used	Evidence is Limited/Use caution in	Studies Supporting this

• High viral suppression (~86-89%) at 96 weeks
• Similar outcomes compared to DTG + TDF/FTC
• No difference in:
  • Inflammatory markers
  • Proviral DNA
  • Viral "blips"
	• Strong evidence
	  • Treatment-naïve adults
	  • Patients without M184/V mutation
	  • CD4 > 200
		• Pregnancy
		• Children
		• Patients with M184/v mutation
			• Naïve
			  • PADDLE
			  • ACTG A5353
			  • **GEMINI 1&2**
			  • DOLCE (<200CD4)
			  • STAT (inicio rápido)
			• Stewardship
			  • TANGO
			  • SALSA
			  • DOLAMA
			  • PASO DOBLE
			• With 184V mutation
			  • SOLAR-3D
			  • ART-PRO

•Cahn, *Lancet*, 2019 (GEMINI-1 y GEMINI-2), van Wyk, *Lancet HIV*, 2020 (TANGO), Llibre, *Clin Infect Dis*, 2022 (SALSA), Gatell, *HIV Med*, 2023 (PASO DOBLE), Taiwo, *Clin Infect Dis*, 2018 (ACTG A5353), Orkin, *Lancet HIV*, 2021 (STAT), Cahn, *JAC*, 2024 (DOLCE)

Injectables



CAB-RPV LA in low-income countries

CARES study

- Sub-Saharan Africa
- Switch from oral to CAB showed good suppression and non-inferiority

Case Series of People With HIV on the Long-Acting Combination of Lenacapavir and Cabotegravir: Call for a Trial

Monica Gandhi,[1,©] Lucas Hill,[2] Janet Grochowski,[1] Alexander Nelson,[3] Catherine A. Koss,[1] Francis Mayorga-Munoz,[1] Jon Oskarsson,[1] Mary Shiels,[1] Ann Avery,[4] Laura Bamford,[2] Jillian Baron,[5,©] William R. Short,[5] and Corrilynn O. Hileman[4]

IMPALA study

- Sub-Saharan Africa
- Some patients who dropped out experienced VL rebound
  - All re-suppressed with TLD restart
  - Even with DTG
- WHO – consideration for LA CAB-RPV as simplification

Viral Suppression Rates at 48 Weeks in People With HIV Starting Long-Acting Cabotegravir/Rilpivirine With Initial Viremia

Matthew D. Hickey,[1,©] Nathanael Gistand,[1] Janet Grochowski,[1] Francis Mayorga-Munoz,[1] Elizabeth Imbert,[1,©] John D. Szumowski,[2,©] Jon Oskarsson,[1] Mary Shiels,[1] Samantha Dilworth,[1] Ayesha Appa,[1,©] Diane V. Havlir,[1] Monica Gandhi,[1,©] and Katerina Christopoulos[1,©]

Adult Recommendations 2025

Area	Before	New recommendation 2025	Rational
Protease Inhibitors	• ATV/r y LPV/r • DRV/r was only alternative	• DRV/r is preferred • ATV/r LPV/r **Alternatives**	Safer, more powerful, generic available. ARTEMIS, FLAMINGO
NRTI for Onset Treatment	• TDF preferred for adults • ABC the preferred for children • AZT or TAF as an alternative and for special situations	• **Children>30kg, adolescents and adults: TDF or TAF preferred option, both for initiation and follow-up** • **Children <30kg ABC is the preferred choice**	Better tolerated, safe in the long term, TAF available as CDF TAF-ED. ODDYSEY shows more efficacy than LPV or NVP
NRTI Sequencing	• Required NRTI sequencing in case of failure	• Do not sequence, keep the preferred ones in the second line	NADIA, VISCEND, DAWNING
NEW **Dual 3TC-DTG therapy**	• Not recommended	• Simplify to DTG+3TC adults and adolescents with CVND who do not have active hepatitis B	PADDLE, GEMINI, TANGO, SALSA, SOLAR
NEW **Long-lasting ARVs for Treatment**	• Not recommended	• CAB+RPV as an Alternative to Simplify Adults and Adolescents with CVND Who Do Not Have Active Hepatitis B	CARES e IMPALA studies in Africa that demonstrate feasibility

Conclusions of ART in adults

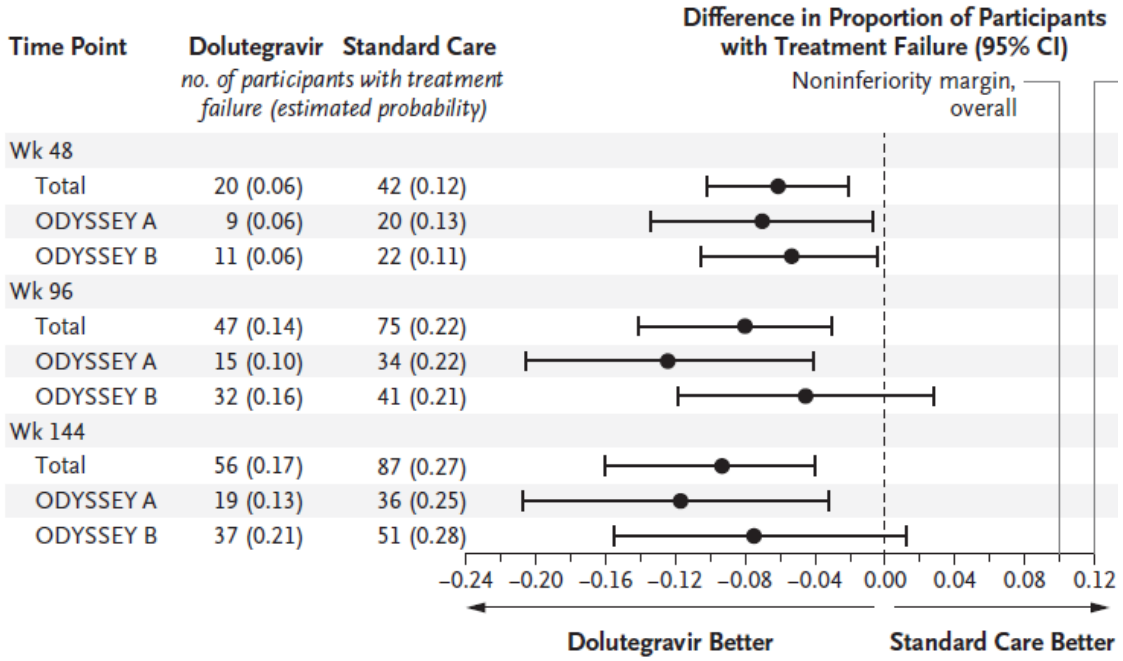
Eliminate	Use	Simplify
Limit use of AZT	FDCs in any patient with ClCr >30ml/m • >60 TLF • 60-30 TAF/FTC/DTG or ABC/3TC + DTG DRV/r as the preferred PI	Consider DTG-3TC (FDC) in stable patients

New recommendations in pediatric treatment

- Changes in low- and high-risk prophylaxis regimens
- Changes in treatment of HIV positive children
- Breastfeeding Options

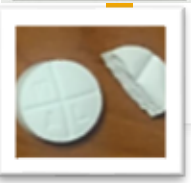
pDTG changed the perspective of pediatric ART

- Dolutegravir has revolutionized pediatric treatment
- 86% suppression at 2 years, with less toxicity and better tolerance
- Can be administered from birth (the first two weeks every 48 hours)
- Treatment with ABC-3TC-DTG is recommended for all children



Turkova, NEJM 2021, Cressey JAIDS 2025

Antiretroviral treatment of children



Neonates (birth to one month of age)

pDTG 10mg dispersible + ABC/3TC 120/60mg

Age	DTG 10 mg dispersable	ABC-3TC 120-60mg dispersable	Frequency
Birth to 2 weeks	**½ tablet**	**¼ tablet**	**Every 48 hours.**
2 to 4 weeks	**½ tablet**	**¼ tablet**	**Once a day**

* For children ≥37 weeks at delivery

Children from 4 weeks of age and +3 kg in weight

- pADL (ABC/DTG/3TC 60/30/5mg)

Weight	# tablets per day
3 a < 6kg	**1**
6 a <10kg	**3**
10 a <14kg	**4**
14 a <20kg	**5**
20 a <25kg	**6**

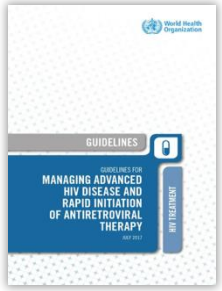
2025 Recommendations Pediatric HIV and PMTCT

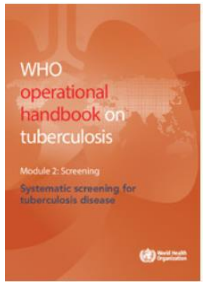
Area	Before	New recommendation 2025	Rational
NEW **DTG dosage**	• DTG only to those over one month of age	Using DTG from birth in full-term children • First 2 weeks give every 48hs • More than 2 weeks give daily	Petite study shows comparable PK.
NEW **High-risk prophylaxis**	• AZT-3TC-NVP, or • AZT-3TC-RAL	• ABC/3TC/DTG is the preferred choice. Duration 6 weeks • If breastfed, continue NVP (DTG or 3TC alternative) until breastfeeding is stopped (or until the mother achieves viral suppression)	Safer, less toxic and more effective drugs are used
NEW **Low-risk prophylaxis**	• AZT syrup VO 6 weeks	• 6 weeks of a single drug (preferably NVP, or alternatively DTG or 3TC	AZT is more toxic, every 12 hours, less effective than NVP, DTG or 3TC
NEW **Breastfeeding**	• Allow breastfeeding replacement if AFASS	• Where breastfeeding is replaced, mothers in ART with CVND should be offered and supported in the choice of breastfeeding • Interventions can be provided in health and community centers to support adherence and improve retention of the binomial, to optimize breastfeeding	It is important to inform the mother about the risks and benefits of breastfeeding, and to explore the social determinants that influence not being able to replace it

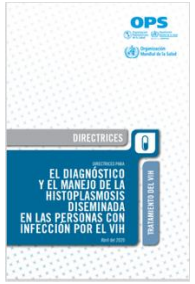
Recommendations on Advanced HIV

Recommendations are maintained on:

- 2017 Care Package
- TB Guides
- Cryptococcus Management
- Management of histoplasmosis
-







Added

- Evaluate for AHD on all people who start or restart care with CD4
- 3HP as preferred tuberculosis prophylaxis
- Post-discharge management
- Recommendation for treatment of Kaposi's Sarcoma

2025 Recommendations for Advanced Disease

Area	Before	New recommendation 2025	Rational
Revised AHD Detection	• Choice of CD4 or clinical stages	• CD4 is the preferred method, only using clinical staging if CD4 is not available	It is not easy to train in the clinical stage, and CD4 is more available
New Post-discharge care	• There was no recommendation	• Hospitalized people must have transitional services to avoid readmissions	19% of hospitalized people die in the year after discharge
New Sarcoma de Kaposi	• There was no recommendation	• The use of pegylated paclitaxel or liposomal doxorubicin and initiation of ARV treatment are suggested.	Systematic reviews show benefit
Revised TB prophylaxis	• 4 options were proposed at the same level	• Suggests the 3HP regimen as the preferred regimen for TPT in people with HIV initiating care	Lowered price ($10 per treatment), better completion rate, lower toxicity Combined availability

3HP is the preferred regimen for TPT

World Health Organization

Preferred Tuberculosis preventive Treatment (TPT) regimen for people living with HIV

Bock P[1], Vovc,E[2], Rangaraj A[2], Falzon D[2], Ford N[2,3], Cox H [4,5]

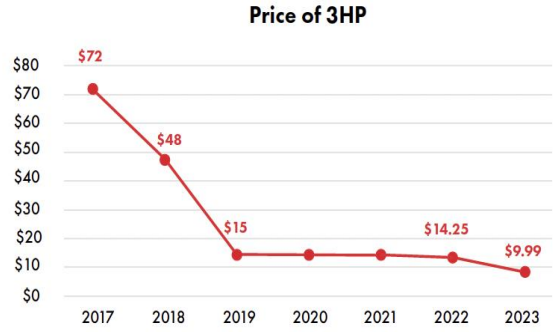
[1]Desmond Tutu TB Centre, Dept of Paed and Child Health, Stellenbosch University; [2]World Health Organization, Global HIV, TB, viral Hepatitis, STIs programme,; [3]University of Cape Town (UCT), Dept Public Health and Family Medicine; [4]Burnet Institute,Melbourne; [5]UCT, Dept of Med Microbiology.

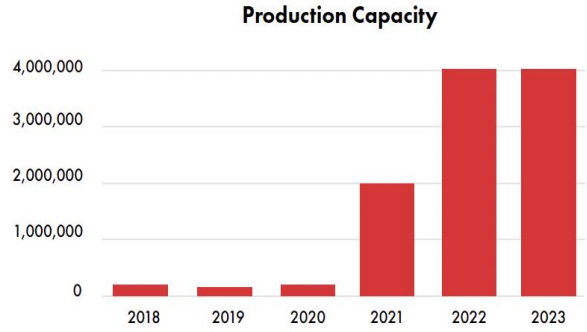
Failure to complete TPT and fear of toxicity are the biggest barriers to expanding TPT. These data support prioritizing iHP and 3HP in places with high TB and HIV prevalence.
3HP Associated with Better Completion Rates and Lower Toxicity.

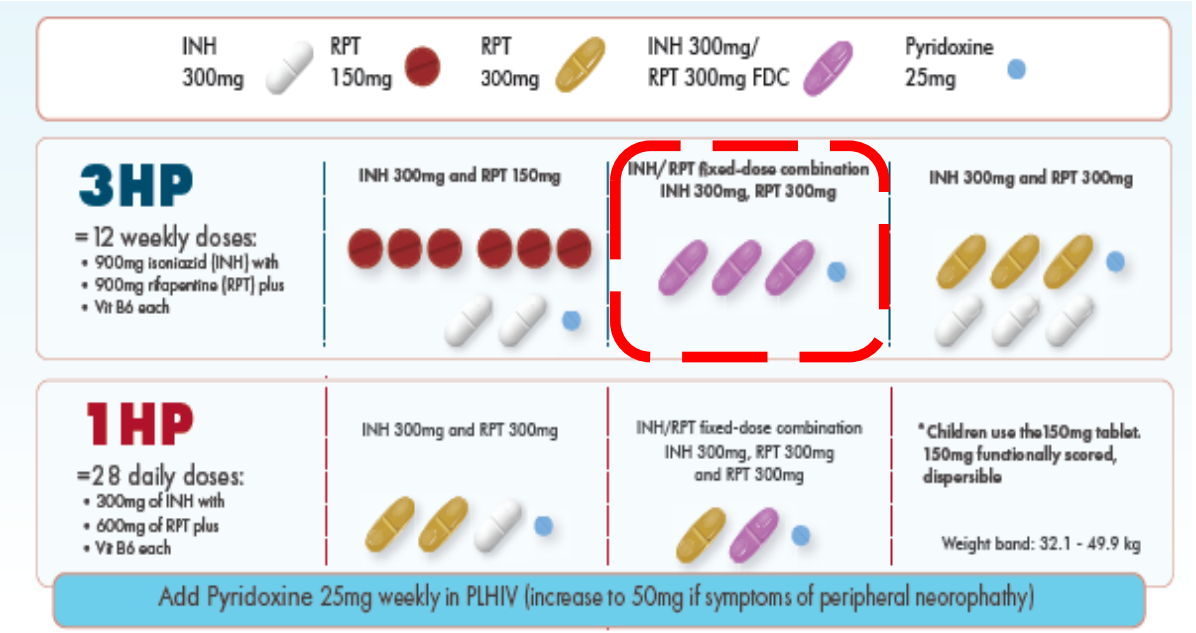
Abstract # EPLB014 late-breaker **IAS2025**
https://programme.ias2025.org/Abstract/Abstract/?abstractid=6944

TAG Treatment Action Group **Improvements to Affordability and Availability of Rifapentine**

Source: Adapted from IMPAACT4TB Project







Examples of Country Implementation of 3HP for TPT in People Living with HIV

Country	Organization	Description	Results
South Africa	IMPAACT4TB	National 3HP expansion with focus on PLHIV; supported by IMPAACT4TB.	≥80% completion of treatment; High acceptance from both patients and providers.
Uganda	CHAI, Unitaid	Integration of 3HP into routine HIV care; emphasis on the training of health workers and the provision of medicines.	~70% adhesion; better results using 3HP compared to 6H.
India	National TB Elimination Program (NTEP)	Pilot studies in high-load districts; Assessing feasibility, adherence and safety.	Pilot data show high adherence and minimal adverse effects.
Brasil	Ministry of Health	Inclusion of 3HP in national guidelines; Integration in primary care and provider training.	Wide acceptance: early implementation showed high tolerability.

Takeaways

Treatment:
- Simplify regimen for those w/out Hep B
-3TC-DTG
- PI - DRV

New Patient:
- Evaluate with CD4
- If CD4 <200, check Ag for Histoplasmosis, TB, and Cryptococcosis

WHO HIV 2025 Summary

Maternal Child Health
- Eliminate AZT and NVP
- Nutrition couseling for pregnancy

Preventative TB
- INH-Rifapentine weekly for 3 months

With Gratitude