Introduction to the 2017 SA HIV Clinicians Society ART guidelines

Francois Venter

March 2018

First-line ART Strategies Roadshow

University of the Witwatersrand

WITS RHI

Thanks all at SAHCS, Michelle Moorhouse

Disclosures

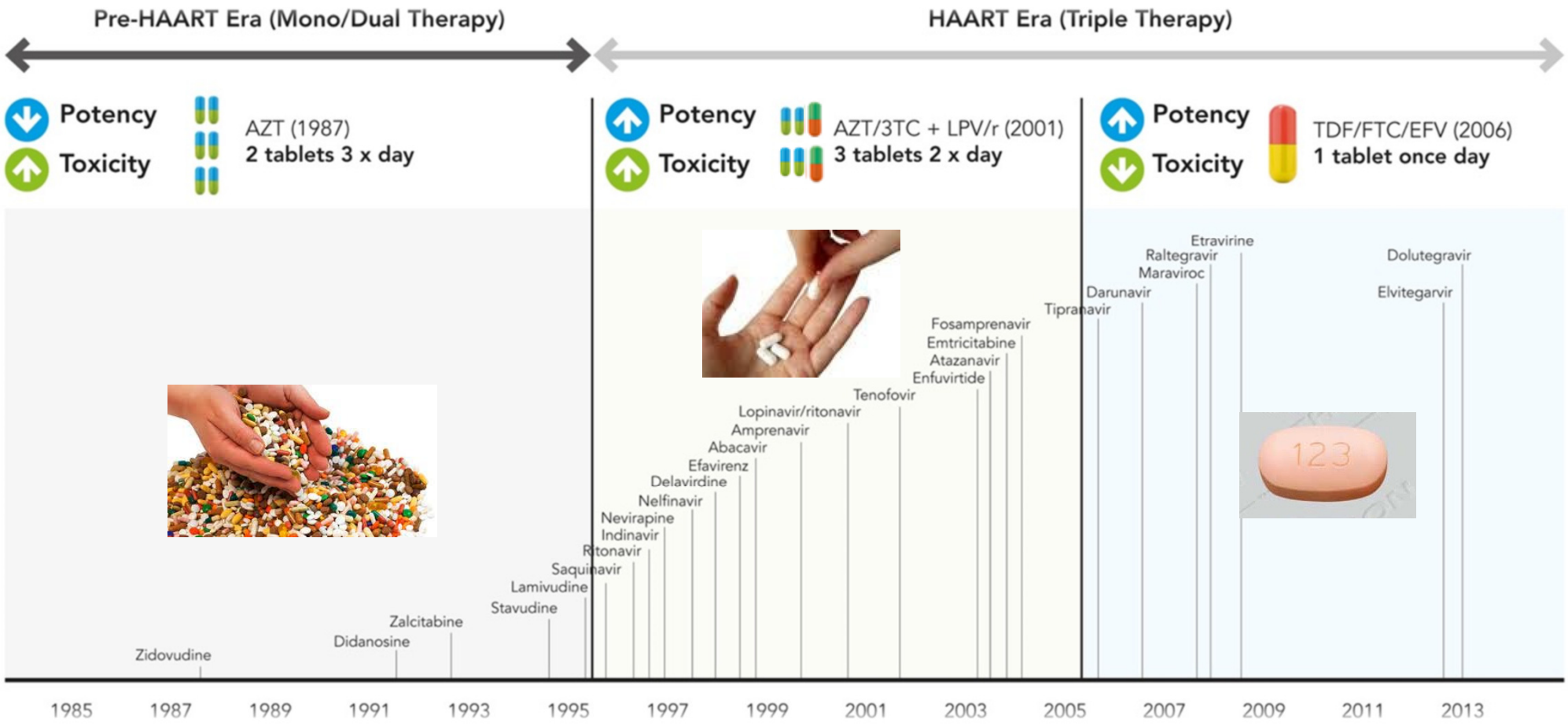
- Speaker fees and honoraria from Gilead Sciences, AbbVie, Cipla, Mylan, Janssen, Gilead, Merck, Cipla, Mylan.
- Part of ART optimisation collaborations
- Funding from USAID, Unitaid and study drug donations from ViiV Healthcare and Gilead Sciences

WHO guideline evolution

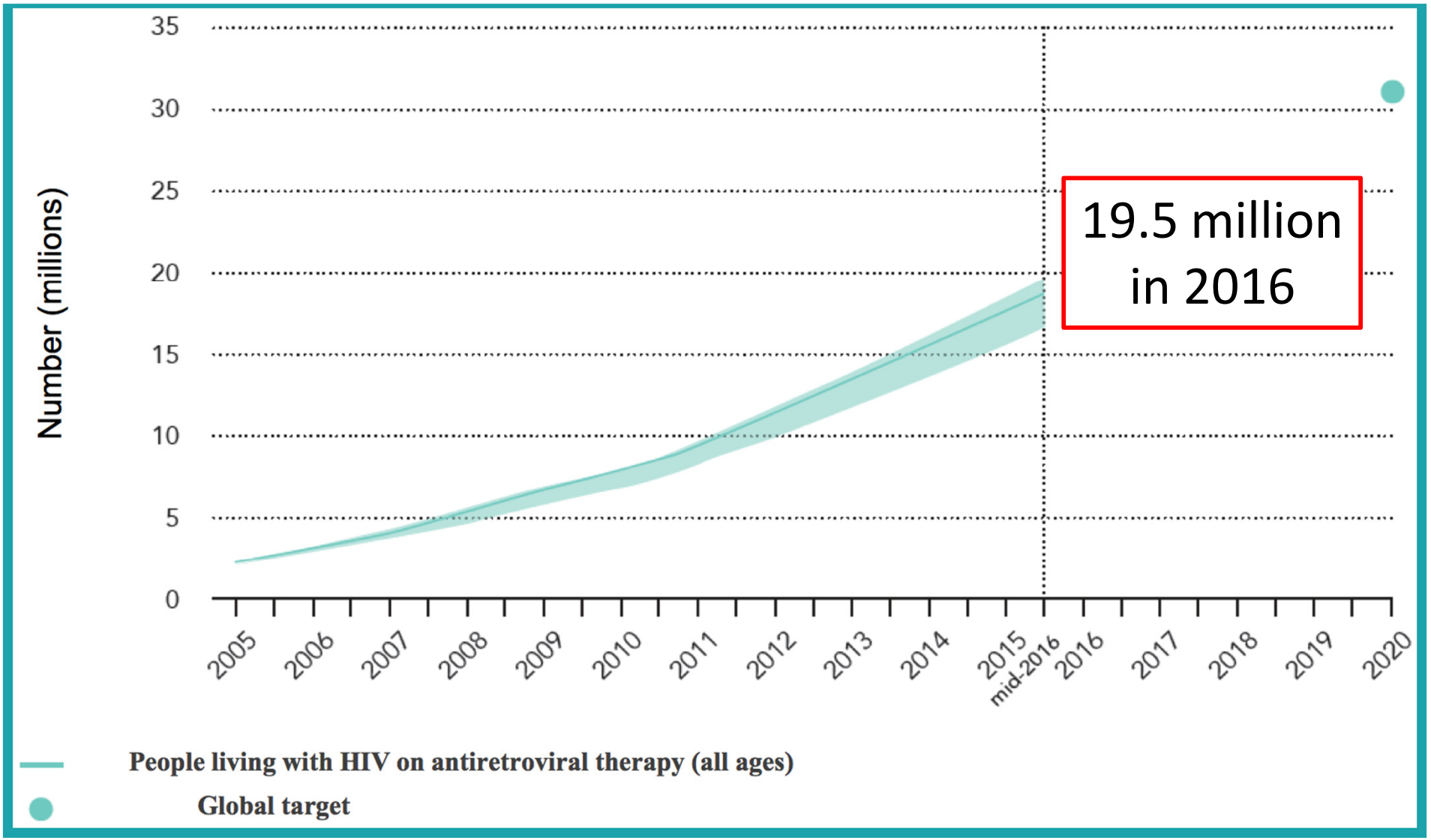
Topic	2002	2003	2006	2010	2013	2015
When to start	CD4 ≤200	CD4 ≤200	CD4 ≤200 – Consider 350 – CD4 ≤350 for tuberculosis (TB)	CD4 ≤350 – Regardless CD4 for TB and hepatitis B virus (HBV)	CD4 ≤500 – Regardless CD4 for TB, HBV PW and SDC – CD4 ≤350 as priority	**Toward Treat All adolescents age band**
Earlier initiation						
First-line ART	8 options – AZT preferred	4 options – AZT preferred	8 options – AZT or TDF preferred – d4T dose reduction	6 options and FDCs – AZT or TDF preferred – d4T phase out	1 preferred option and FDCs – TDF and EFV preferred across all populations	**Continue with FDC and harmonisation across age bands**
Simpler treatment						
Second-line ART	Boosted and non-boosted PIs	Boosted PIs – IDV/r LPV/r, SQV/r	Boosted PI – ATV/r, DRV/r, FPV/r LPV/r, SQV/r	Boosted PI – Heat stable FDC: ATV/r, LPV/r	Boosted PIs – Heat stable FDC: ATV/r, LPV/r	**Greater number of options**
Less toxic, more robust regimens						
Third-line ART	None	None	None	DRV/r, RAL, ETR	DRV/r, RAL, ETR	**Encourage HIV DR to guide**
Viral load (VL) testing	No	No (desirable)	Yes (tertiary centers)	Yes (phase-in approach)	Yes (preferred for monitoring, use of PoC, DBS)	**Support for scale up of VL using all technologies**

Drug optimisation

Science evolved: smarter and better HIV treatment options are now available

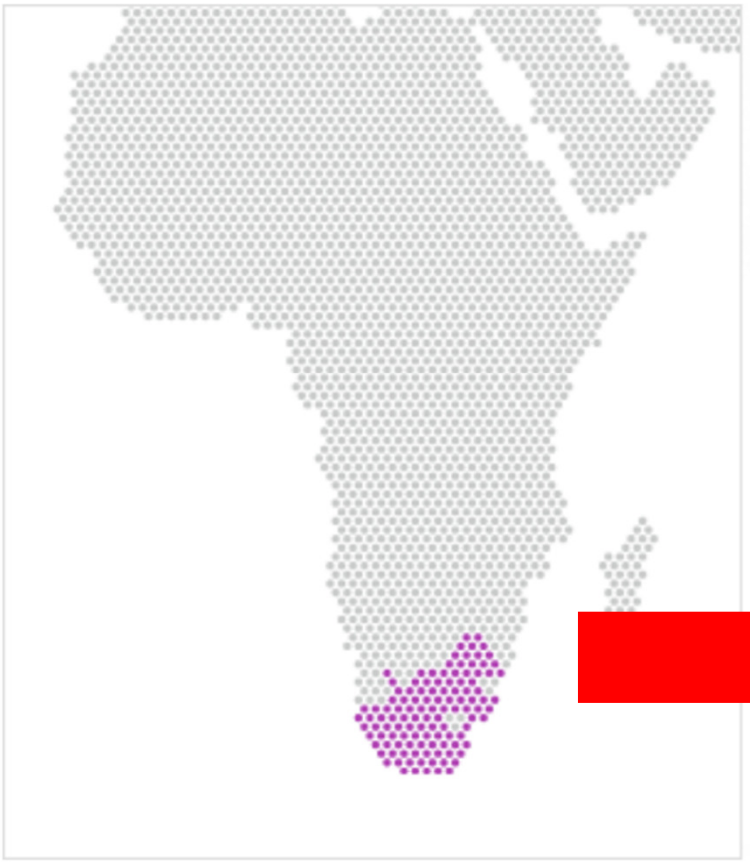


PLWH on ART globally 2005-2015



UNAIDS. Global AIDS Update 2016

HIV in South Africa, 2016



South Africa (2016)

7.1 million people living with HIV

18.9% adult HIV prevalence

270,000 new HIV infections

110,000 AIDS-related deaths

56% adults on antiretroviral treatment

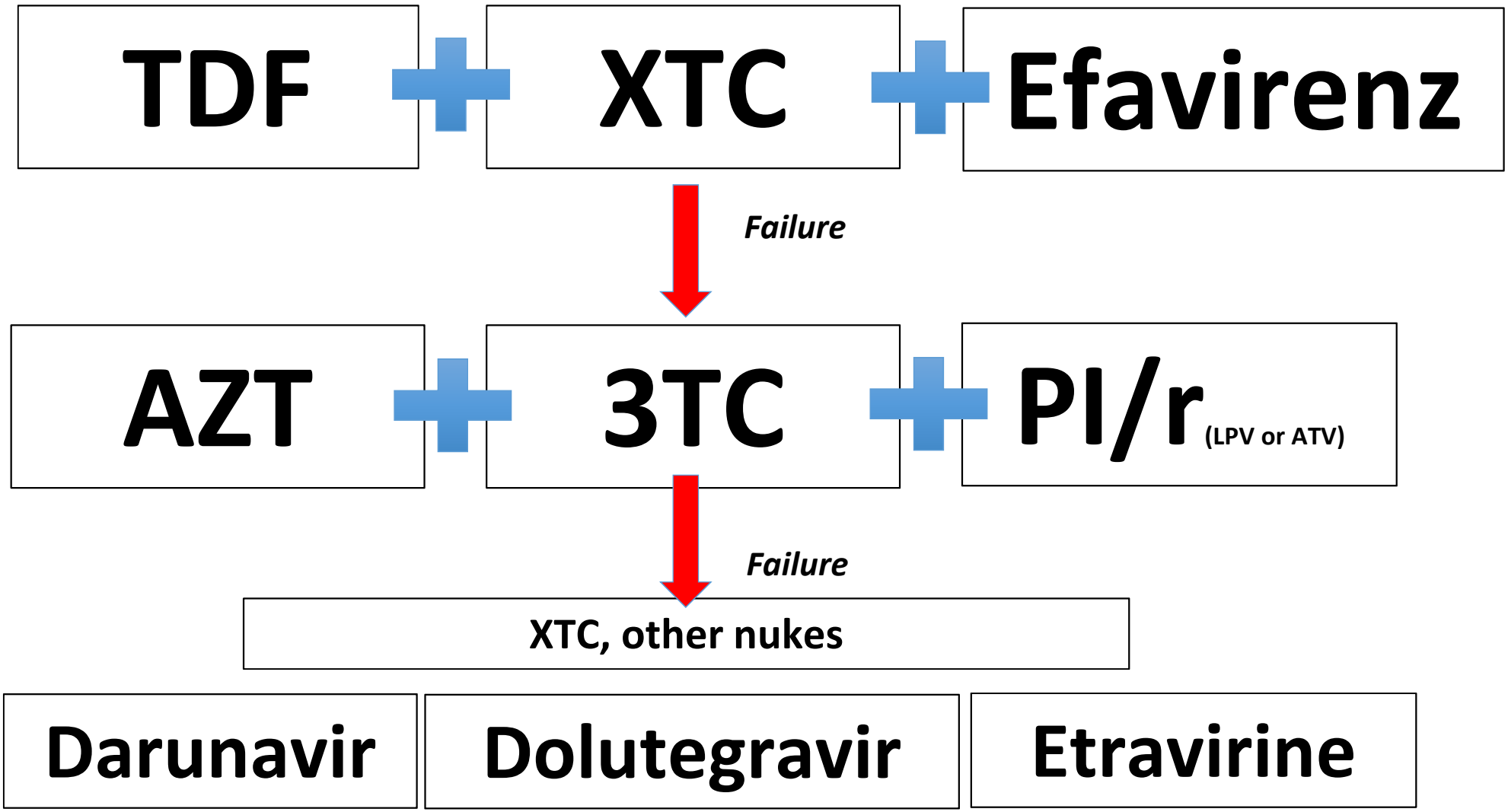
55% children on antiretroviral treatment

Source: UNAIDS Data 2017

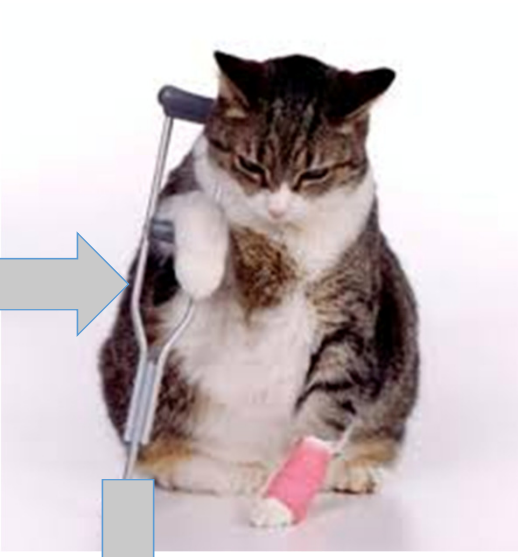
> 4 million on ART

UNAIDS data 2017

The drugs rock



Process for guideline development



Updated GL: underlying philosophy

- Affordability considered
- Only treatment and diagnostic options available in Southern Africa were considered
- Bridge gap between public and private sectors
- Intended to reflect “best practice”

When to start ART: 2015

We recommend initiation of lifelong ART for all patients diagnosed with HIV infection. The CD4 count and clinical stage of the patient should no longer be a consideration in the decision to start ART.

For patients who are asymptomatic with CD4 > 350 cells/µL, additional time (weeks to a few months) can be spent counselling and preparing the patient for lifelong ART with good adherence before starting. In those with CD4 < 350 cells/µL (and especially < 200 cells/µL), or with clinical indication for starting, there should not be undue delay.

Within ART programmes, it is important to factor in that the absolute benefit of ART is much greater at lower CD4 counts (there is a mortality benefit at CD4 < 350 cells/µL.[10†] Therefore, planners and clinicians should prioritise and fast-track those with low CD4 counts (especially < 200 cells/µL); this is particularly relevant where there are ART shortages or anticipated stock-outs.

S Afr J HIV Med. 2015;16(1), 4 pages

Evidence: TEMPRANO and START

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

The TEMPRANO ANRS 12136 Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 27, 2015 VOL. 373 NO. 9

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

Urgency to start ART

- CD4 count < 200 cells/uL
  - Within one week of adherence counselling (NB: exceptions)
- Same day as diagnosis or receiving CD4 count?
  - Less LTFU
  - Careful selection
- PCP and other OIs
  - Within 2 weeks

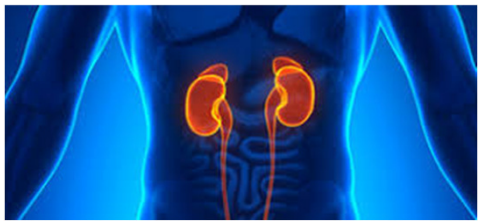
- TB if CD4 count < 50 cells/uL
  - Within 2 weeks
- TB if CD4 count > 50 cells/uL
  - Start 2-8 weeks
- CM
  - Defer 4-6 weeks
- TBM
  - Defer 4-8 weeks

When to defer ART?

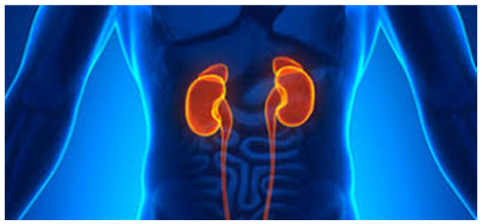
Reason	Action
Diagnosis of CM	Defer ART for 4–6 weeks after start of antifungal treatment
Serum or plasma cryptococcal antigen positive	Defer ART for 2 weeks after start of antifungal treatment (if meningitis is excluded on LP then ART does not need to be deferred)
Diagnosis of TB meningitis or tuberculoma	Defer ART until 4–8 weeks after start of TB treatment
Diagnosis of TB at non-neurological site	Defer ART up to 2 weeks after start of TB treatment if $CD4^+ \leq 50$ cells/μL and up to 8 weeks if $CD4^+ > 50$ cells/μL
Headache	Investigate for meningitis before starting ART
TB symptoms (cough, night sweats, fever, recent weight loss)	Investigate for TB before starting ART
Significantly abnormal liver function tests (ALT > 200 or jaundice)	Investigate and address the cause before starting ART, including other drugs causing DILI

CM, cryptococcal meningitis; ART, antiretroviral therapy; TB, tuberculosis; ALT, alanine transaminase; DILI, drug-induced liver injury; LP, lumbar puncture.

First-line in 2015

TDF	**XTC**	**EFV**
ABC		RPV*
AZT		NVP
d4T		RAL**

First-line in 2017

TDF	**XTC**	**EFV**
ABC		DTG
AZT		RPV*
d4T		

What ART to start?

	SAHIVSOC	SA NDoH	WHO
NRTIs Recommended Alternative	**TDF + FTC/3TC** ABC AZT Short term d4T	**TDF + FTC/3TC** ABC	**TDF + FTC/3TC** AZT ABC Short term d4T
Third drug Recommended Alternative	**EFV** **DTG** RPV	**EFV** NVP LPV/r	**EFV** EFV400 DTG

When to do a baseline resistance test

Baseline resistance test to guide first-line regimen choice only in the following situations:

- Pre-exposure prophylaxis (PrEP) received in the previous 6 months
- History of sexual exposure to a person with known drug resistant HIV or known to have failed an ART regimen

When to check VL

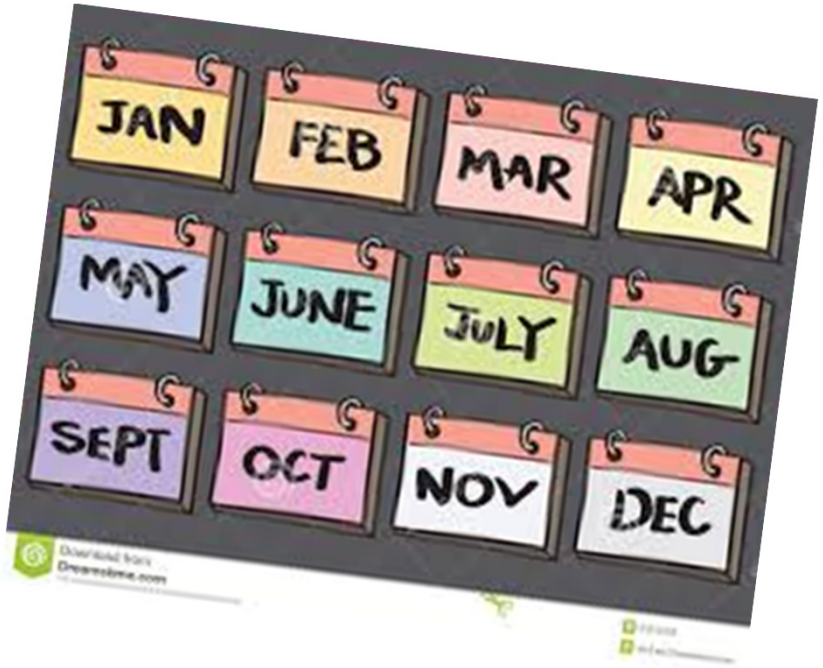
	SA Dept. Health	SA HIV Clin. Soc.	DHHS (USA)
At initiation	✗	✓	✓
Before 6 months	✗	3 months	At 2-8 weeks, then every 4-8 weeks until suppressed
6 months	✓	✓	✓
12 months	✓	✓	✓
Thereafter	Every 12 months	Every 6 (-12) months	Every 3-6 months

Why check viral loads before 6 months?

- Enables early detection of virological failure (usually due to poor adherence), before resistance develops, or worsens.
- At 3 months, most patients will be virally suppressed, but a small group of people who started with a very high viral load may still have detectable viraemia… although they'll still show at least a 2 $\log_{10}$ drop from their initiation viral loads.

When to check CD4 count

- At baseline
  - Identify patients at risk of OIs to start appropriate OI prophylaxis
- Every 6 months until CD4 > 200 cells/uL
  - Can stop checking if CD4 > 200 cells/uL if VL suppressed (and remains suppressed)
- Virological or clinical failure
- If otherwise clinically indicated



Other monitoring?

Test	When? Baseline	Ongoing	Comments
FBC	✓	M1, 2, 3, 6	On AZT
ALT	✓	W 2, 4, 8 and 12	Only if on NVP
Creat Cl	✓	M3, 6 and 6-monthly	Also M1 and 2: high risk
TC and TG	Not routine	M3	On PI/r. Only reassess if other CV risk factors

"This recommended routine monitoring ensures a standard level of care is given to patients on ART. However, it does not replace clinical judgement. These tests should also be carried out when clinically indicated, based on the discretion of the clinician."

When to switch?

- Two VL > 1000 copies/mL
- 2-3 months apart
- At least 4 weeks **adherence intervention** in between

Low level viraemia (200 – 1000 copies/mL)

- Prolonged (> 1 year)

OR

- With persistently low CD4 counts (< 100 cells/mm^3)

Despite **adherence interventions**

Switch to which?

NRTI combinations	
First line NRTI	Switch to
AZT d4T	TDF
TDF ABC	AZT

EARNEST trial suggested that NRTIs have important role in second-line with PI/r even when there is NRTI resistance present

Third drug options

Preferred PI/r
ATV/r LPV/r DRV/r*
* When 800/100mg daily available

Safety issues with PIs

LPV/r

- GI upset
- Lipids
- Hepatitis
- Dysglycaemia

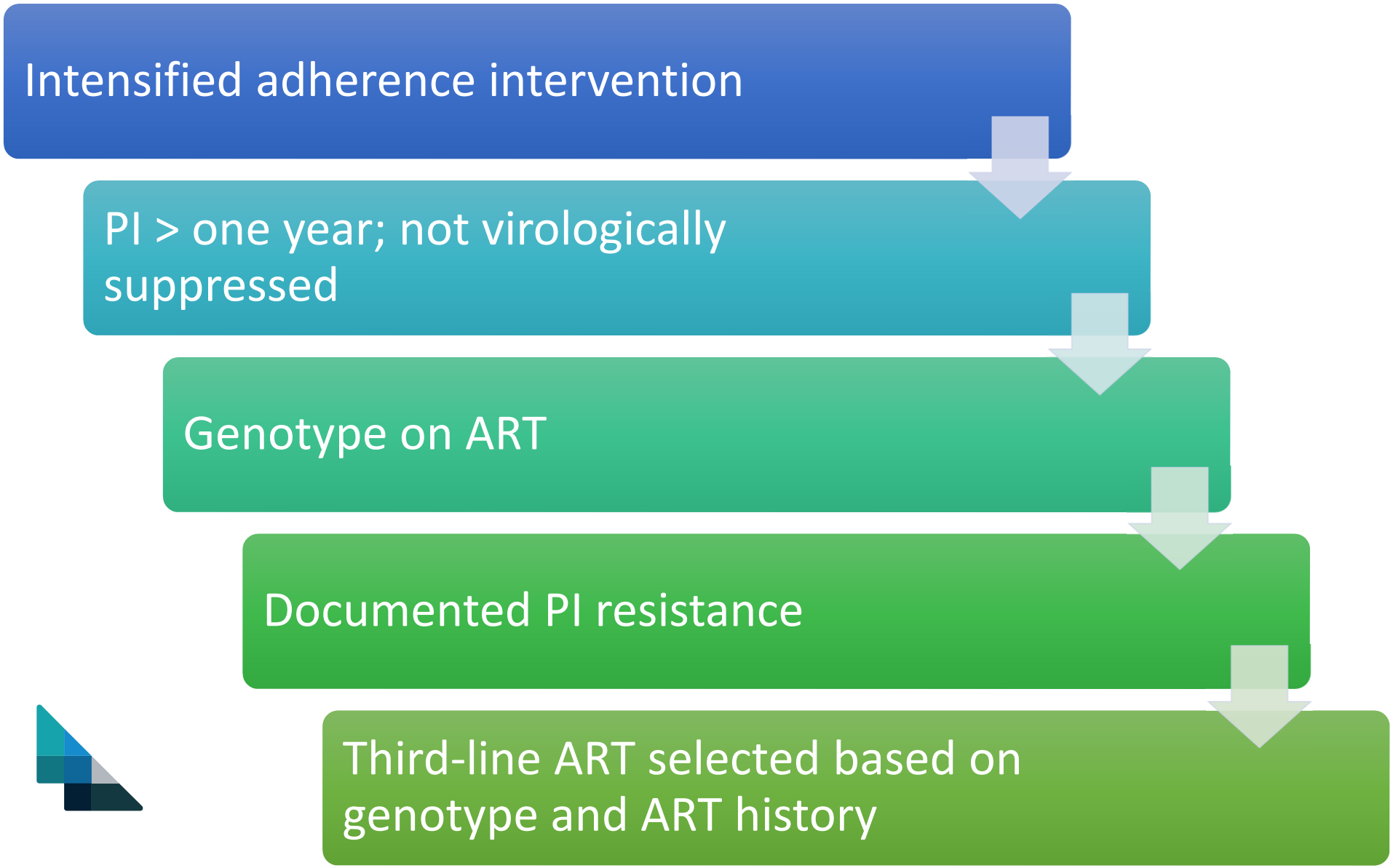
ATV/r

- Jaundice
- Lipids (low potential)
- Renal stones
- Hepatitis

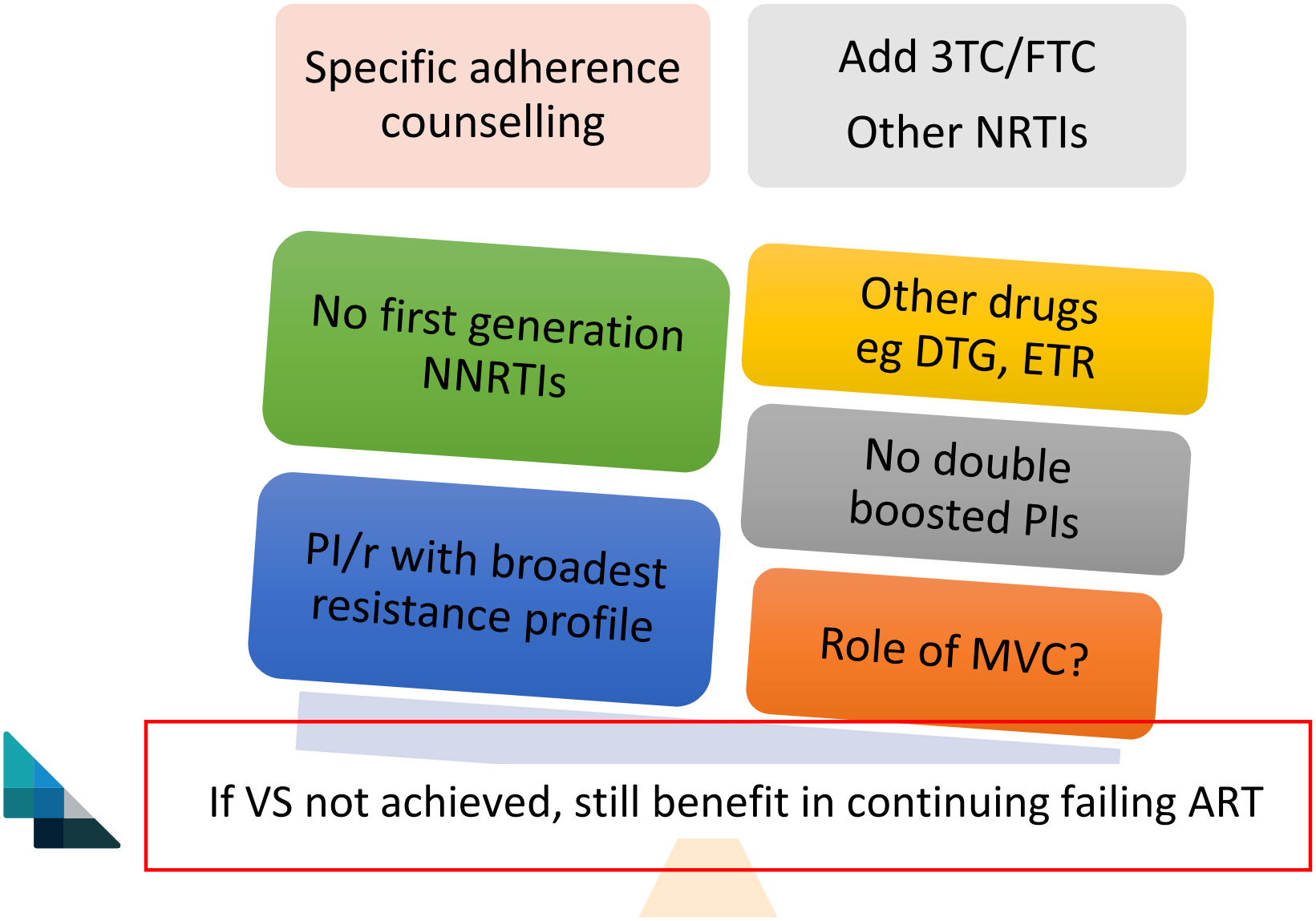
DRV/r

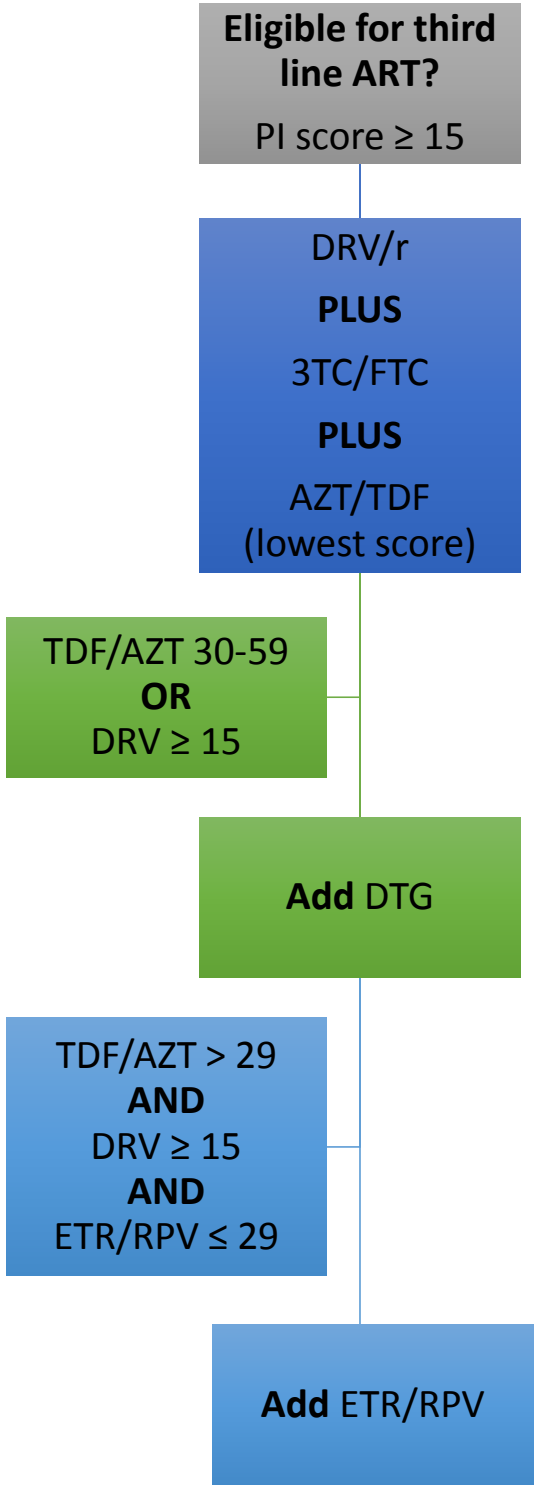
- Rash
- GI upset
- Hepatitis

Patients failing on second-line ART



Third-line regimen: principles




Eligible for third line ART?
PI score ≥ 15
DRV/r
PLUS
3TC/FTC
PLUS
AZT/TDF
(lowest score)
TDF/AZT 30-59
OR
DRV ≥ 15
Add DTG
TDF/AZT > 29
AND
DRV ≥ 15
AND
ETR/RPV ≤ 29
Add ETR/RPV

What about TB? Drug interactions

Class	ART drug	Interaction	Dose of ART drug with rifampicin
NRTI	All in class	No significant pharmacokinetic interactions	No dose adjustment required.
NNRTI	EFV	Mild reduction in EFV concentrations. In some patients on TB treatment, EFV concentrations may increase	No dose adjustment required (600 mg *nocte*).
	NVP	Moderate reduction in NVP concentrations with increased risk of virological failure compared with EFV	Use standard dosing, but omit the lead-in dose phase and start 200 mg NVP 12-hourly.
	ETR and RPV	Marked reduction in concentrations	Do not prescribe concomitantly with rifampicin.
PI	LPV/r	LPV plasma concentrations significantly decreased	The preferable strategy is to double the dose of LPV/r to 800/200 mg 12-hourly. Alternatively, add 300 mg RTV 12-hourly to standard dose of two tablets of LPV/r 12-hourly. There is an increased risk of hepatotoxicity with these strategies. These dose adjustments can be made gradually over 1–2 weeks†.
	All other PIs	Marked reduction in PI concentrations	Do not prescribe concomitantly.
InSTI	RAL	Reduction in concentrations, but a clinical trial showed that standard dosing results in adequate virological suppression[51]	No dose adjustment required (i.e. RAL 400 mg 12-hourly).
	DTG	Significant reduction in concentrations	Dosing frequency increased to 50 mg 12-hourly.

What about IPT?

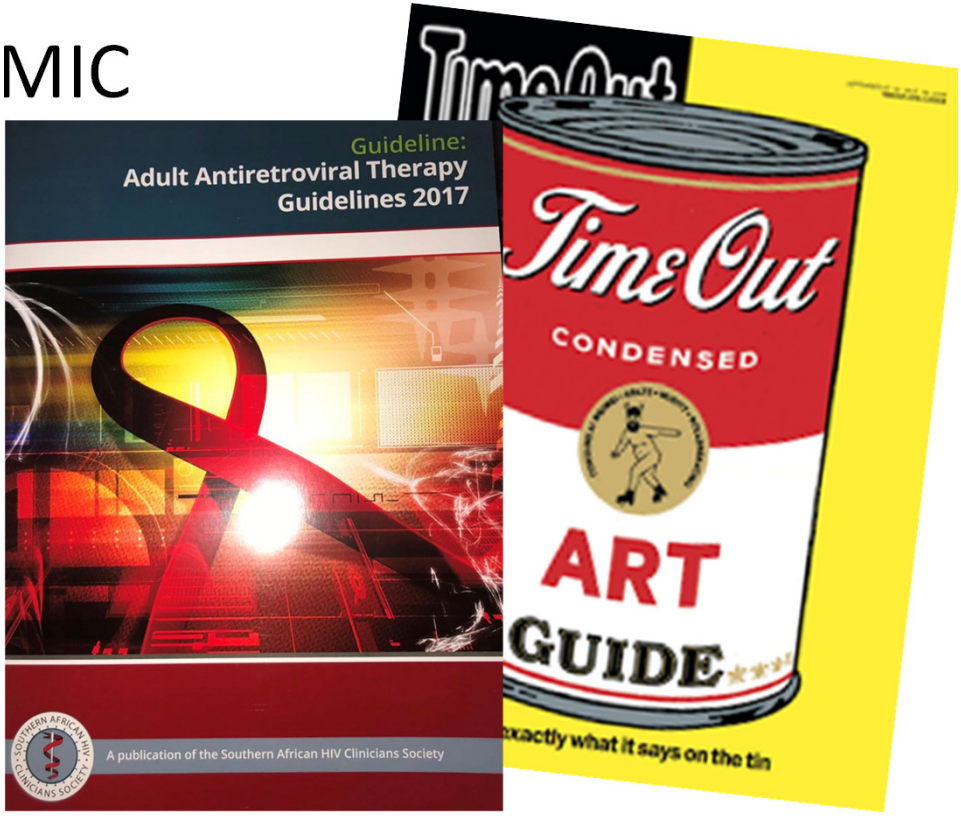
TST	Pre-ART	On ART
Not done	6 months	12 months
Negative	Not indicated	12 months
Positive	At least 36 months	At least 36 months

- TEMPRANO: separate randomisation to 6 months of IPT
  - addition of IPT to ART - provided added protection against active TB disease
  - Benefit to patients with relatively high CD4 counts
- Khayelitsha study: placebo controlled
  - 12 months of IPT to patients on ART
  - reduced TB incidence by 37%

NEJM 2015

Conclusion

- CD4 count no longer a barrier to ART initiation
- Earlier ART benefits all HIV-infected individuals
  - Reduces risk of disease progression
  - Prevents onward transmission
- Benefits of early ART in RLS/LMIC
  - Reduced rates of incident TB
- IPT for all patients on ART



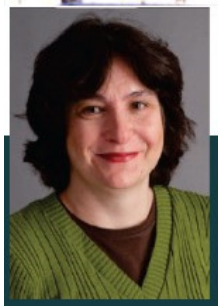
Save the Date

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY **CONFERENCE 2018**

JOHANNESBURG, SOUTH AFRICA | **24 - 27 OCTOBER 2018**

- ❑ **Current and thought-provoking academic presentations**
- ❑ **Fascinating ethics sessions**
- ❑ **Practical sessions including case studies and skills-building workshops**
- ❑ **CPD accredited**

JOIN US IN **2018** FOR THE SOUTHERN AFRICAN HIV CLINICIANS SOCIETY **4TH BIENNIAL CONFERENCE!**



www.sahivsoc2018.co.za