Adult ART guidelines update

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SAHCS Conference

University of the Witwatersrand
WITS RHI

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

Disclosures

- Speaker fees and honoraria from Gilead Sciences, AbbVie, Cipla, Mylan, Aspen, Sanofi, Pfizer and Janssen
- Conference sponsorship from BD, Gilead, Janssen, Merck, Cipla and Mylan
- Part of ART optimisation collaborations
- Funding from USAID, Unitaid, SAMRC and study drug donations from ViiV Healthcare and Gilead Sciences for ART optimisation studies

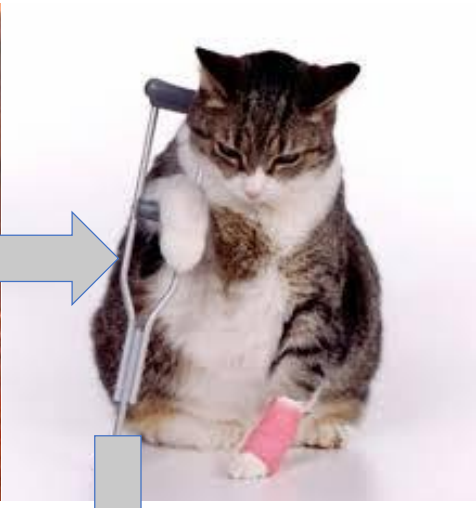
USAID FROM THE AMERICAN PEOPLE

PEPFAR

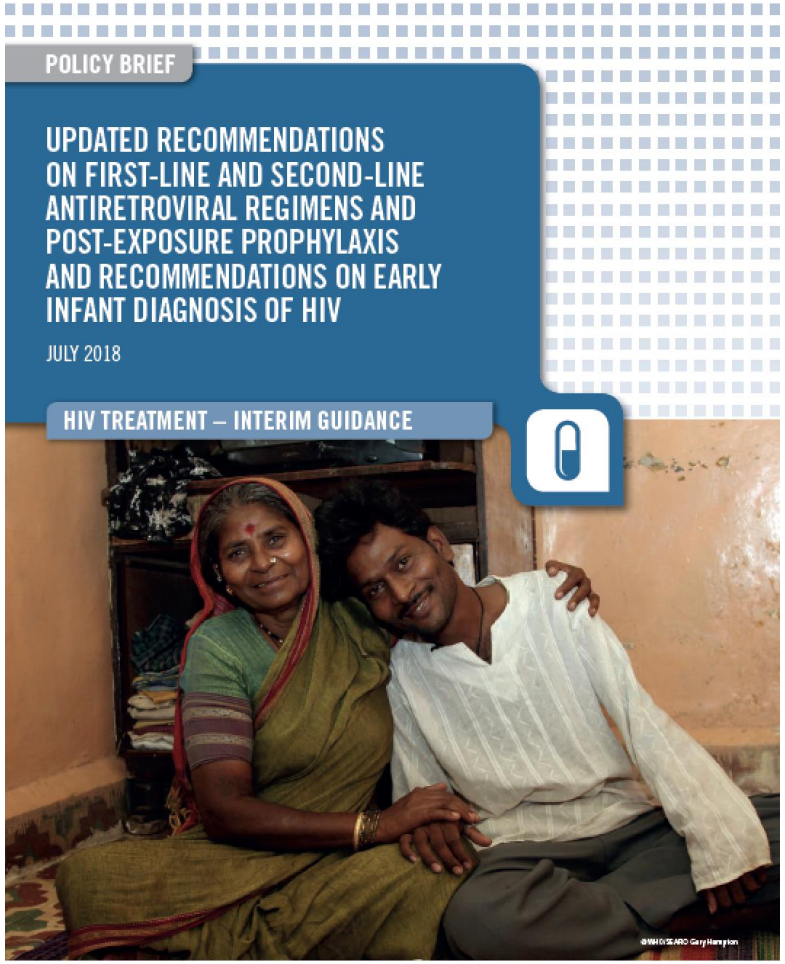
saMRC

Unitaid

Process for GL development



What prompts guideline updates?



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

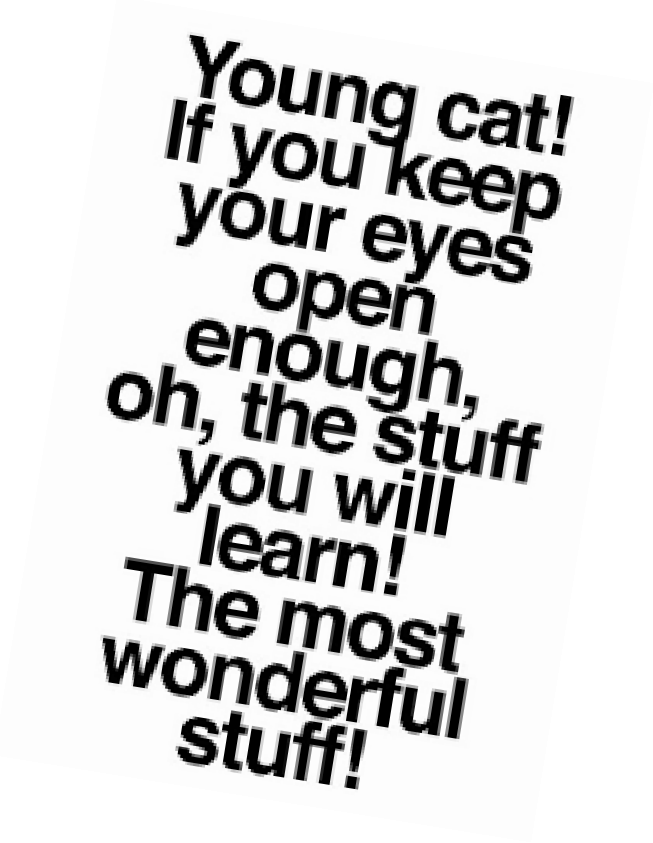
ESTABLISHED IN 1812 AUGUST 27, 2015 VOL. 373 NO. 9

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

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”



Meintjes, G et al. Adult antiretroviral therapy guidelines 2017. Southern African Journal of HIV Medicine, [S.l.], v. 18, n. 1, p. 24 pages, july 2017.

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

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

Meintjes, G et al. Adult antiretroviral therapy guidelines 2017. Southern African Journal of HIV Medicine, [S.l.], v. 18, n. 1, p. 24 pages, july 2017.

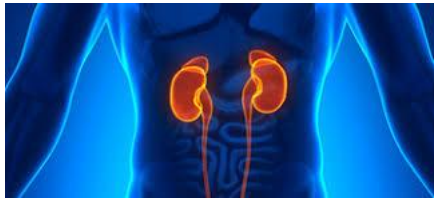
When to defer ART?

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

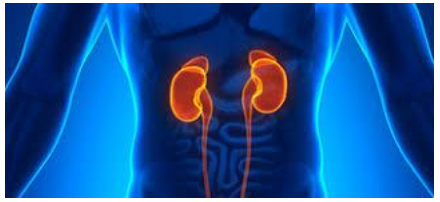
CM, cryptococcal meningitis; ART, antiretroviral therapy; TB, tuberculosis; ALT, alanine transaminase; DILI, drug-induced liver injury; LP, lumbar puncture.

Meintjes, G et al. Adult antiretroviral therapy guidelines 2017. Southern African Journal of HIV Medicine, [S.l.], v. 18, n. 1, p. 24 pages, july 2017.

First-line in 2015

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

First-line in 2017

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

Meintjes, G et al. Adult antiretroviral therapy guidelines 2017. Southern African Journal of HIV Medicine, [S.l.], v. 18, n. 1, p. 24 pages, july 2017.

What ART to start?

	SAHIVSOC	SA NDoH	WHO 2018
NRTIs **Recommended** Alternative	**TDF + FTC/3TC** ABC ZDV Short term d4T	**TDF + FTC/3TC** ABC	**TDF + FTC/3TC** ZDV ABC Short term d4T
Third drug **Recommended** Alternative	**EFV** DTG RPV	**EFV** NVP LPV/r	**DTG** EFV600 EFV400 PI/r

Meintjes, G et al. Adult antiretroviral therapy guidelines 2017. Southern African Journal of HIV Medicine, [S.l.], v. 18, n. 1, p. 24 pages, July 2017.

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

Meintjes, G et al. Adult antiretroviral therapy guidelines 2017. Southern African Journal of HIV Medicine, [S.l.], v. 18, n. 1, p. 24 pages, july 2017.

When to check VL

	SA Dept. Health	SA HIV Clin. Soc.	DHHS (USA)
At initiation	X	✓	✓
Before 6 months	X	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.

Meintjes, G et al. Adult antiretroviral therapy guidelines 2017. Southern African Journal of HIV Medicine, [S.l.], v. 18, n. 1, p. 24 pages, july 2017.

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

Meintjes, G et al. Adult antiretroviral therapy guidelines 2017. Southern African Journal of HIV Medicine, [S.l.], v. 18, n. 1, p. 24 pages, july 2017.

Other monitoring?

Test	When? Baseline	Ongoing	Comments
FBC	✓	M1, 2, 3, 6	On ZDV
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."

Meintjes, G et al. Adult antiretroviral therapy guidelines 2017. Southern African Journal of HIV Medicine, [S.l.], v. 18, n. 1, p. 24 pages, july 2017.

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**

Meintjes, G et al. Adult antiretroviral therapy guidelines 2017. Southern African Journal of HIV Medicine, [S.l.], v. 18, n. 1, p. 24 pages, july 2017.

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

Meintjes, G et al. Adult antiretroviral therapy guidelines 2017. Southern African Journal of HIV Medicine, [S.l.], v. 18, n. 1, p. 24 pages, july 2017.

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

DRV/r 800/100 mg once daily

Recently approved by MCC for the following indication:

- PREZISTA, in combination with low dose ritonavir (PREZISTA/rtv) and with other antiretroviral medicines, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral **treatment experienced** adult patients who are **protease-inhibitor-naïve** patients or after **exclusion of darunavir resistance** associated mutations (DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V).
- Genotypic or phenotypic testing should guide the use of PREZISTA/rtv.
- Ritonavir is used as a pharmacokinetic enhancer of darunavir.
- There is no information on the use of darunavir in combination with ritonavir in the paediatric population for the once daily dose.

SA HIV Clinicians Society Guidelines

- Currently recommends ATV/r 300/100 mg as preferred PI/r for second-line ART
- “When the appropriate dose tablet becomes available, the [DRV/r] 800/100 mg daily dose will be a feasible option in second-line ART, with fewer side effects than the twice-daily dosing”
- DRV/r 600/100 mg bid recommended in third-line ART

Using DRV/r 800/100 mg in second-line ART

- Patient failing failing first-line NNRTI- or InSTI-based regimen: switch to DRV/r 800/100 mg daily + 2NRTIs (sequence NRTIs as per guidelines)
- Patient on PI/r-based second-line regimen: check VL
- If VL LDL – can switch PI/r to DRV/r 800/100 mg daily. Retain same NRTI backbone
- If detectable VL, intensify adherence interventions and repeat VL in 2-3 months. If VL LDL, can switch PI/r to DRV/r 800/100 mg daily. If VL > 1000 copies/mL, resistance genotype is needed to determine if eligible for third-line ART

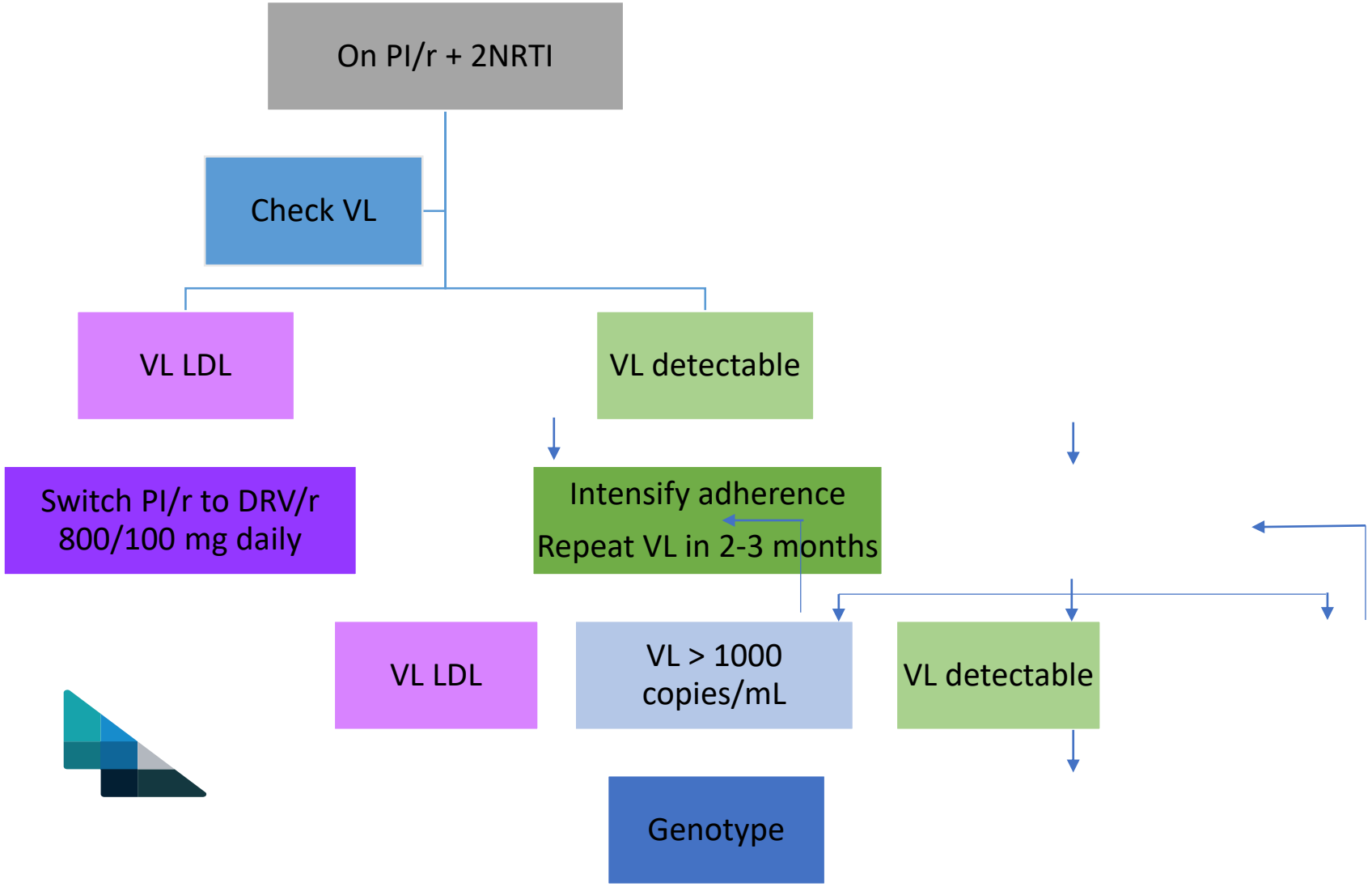
Failing NNRTI- or InSTI-based first-line ART

NNRTI/InSTI + 2NRTI

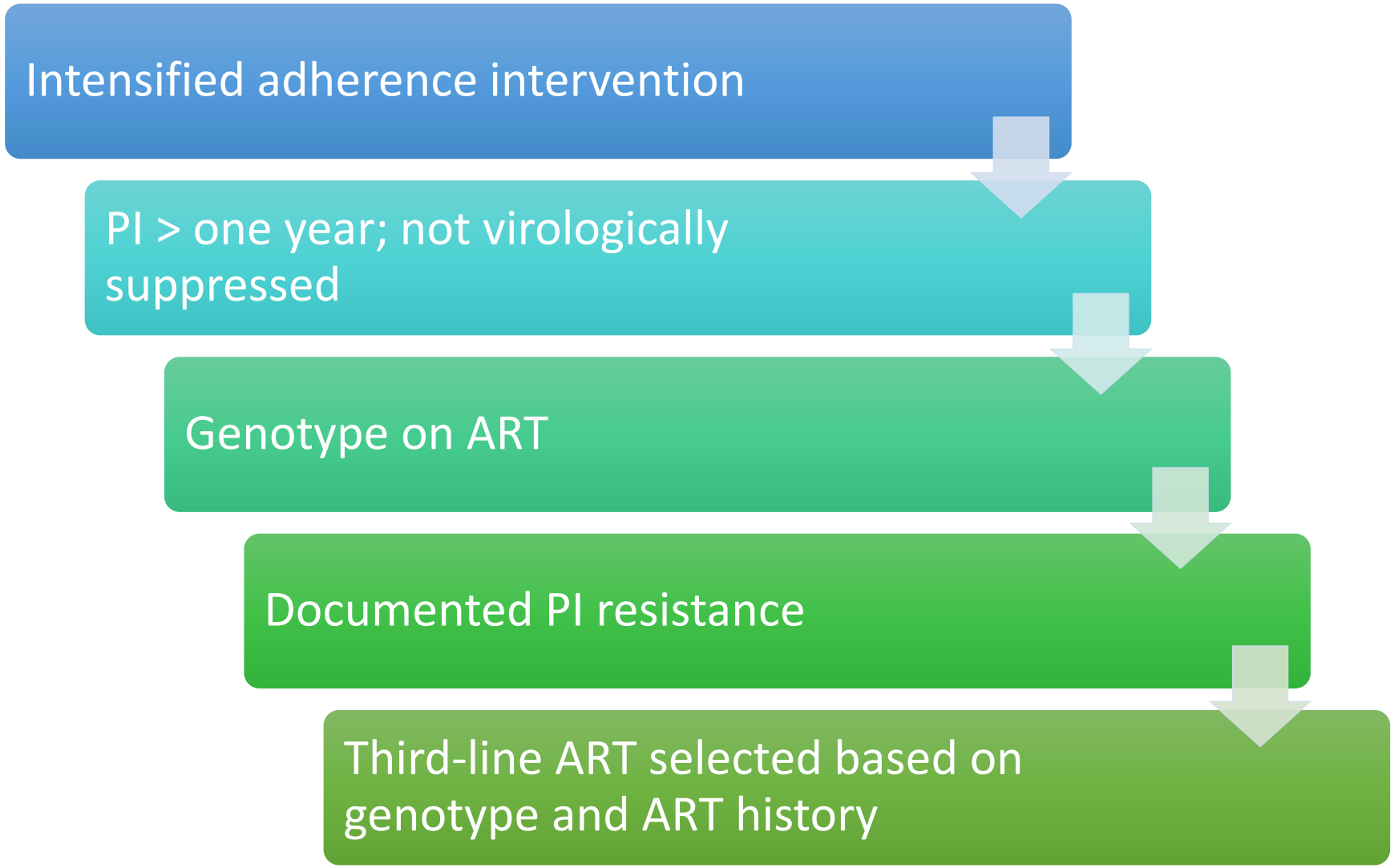
VL > 1000 copies/mL (confirmed)

DRV/r 800/100 mg daily + 2NRTI

On PI/r-based second-line ART



Patients failing on second-line ART



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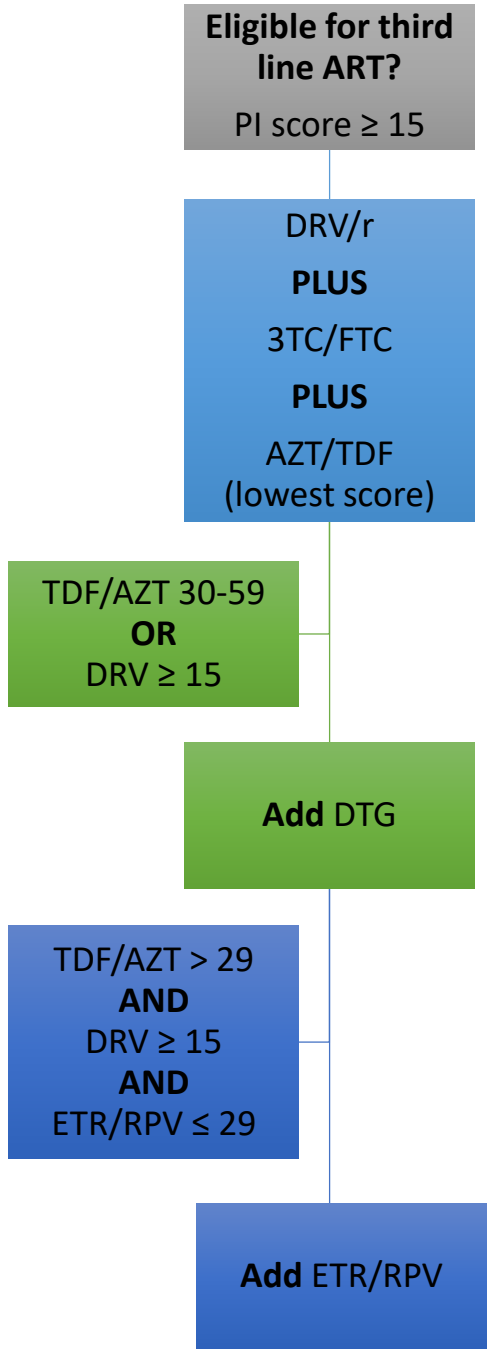

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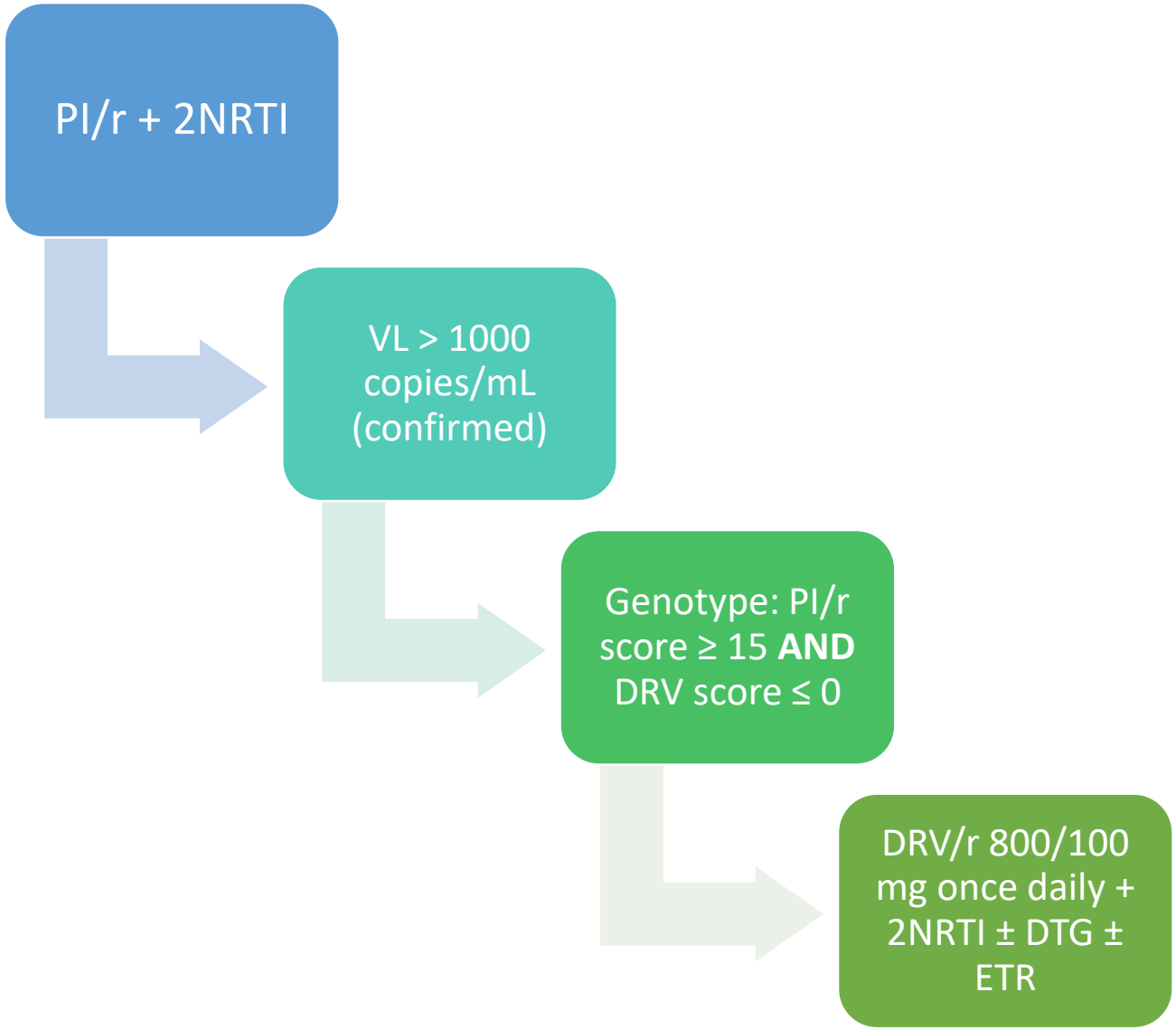
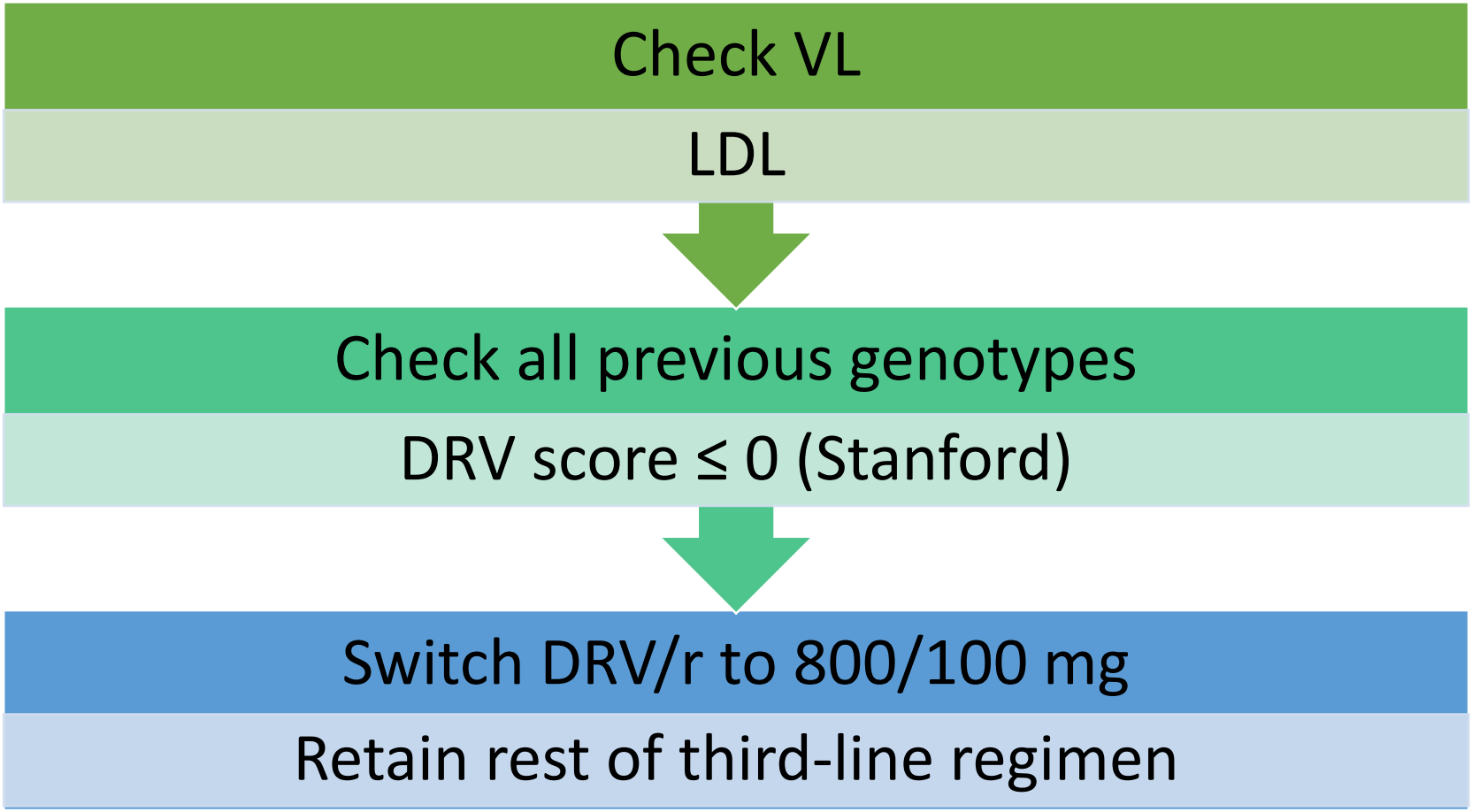
DRV 400 mg is now available in SA

- Currently patients on DRV in third-line receive DRV/r 600/100 mg bid
- A small proportion of third-line patients have no DRV RAMs, and in such patients it may be possible to use DRV/r 800/100 mg daily instead of DRV/r 600/100 mg bid to, reducing pill burden, dosing frequency and side effects
- Patients initiating third-line ART: if DRV score (Stanford) is zero on all genotypes, may initiate DRV 800/100 mg daily
- Switching patients already on third-line: the patient's VL must be LDL, AND the DRV score (Stanford) MUST be zero on all genotypes the patient has had done

Initiating third-line ART



On DRV/r based third-line ART (600/100 mg bid)



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.

Meintjes, G et al. Adult antiretroviral therapy guidelines 2017. Southern African Journal of HIV Medicine, [S.l.], v. 18, n. 1, p. 24 pages, july 2017.

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

Meintjes, G et al. Adult antiretroviral therapy guidelines 2017. Southern African Journal of HIV Medicine, [S.l.], v. 18, n. 1, p. 24 pages, july 2017.

Guidance for DTG in first-line ART

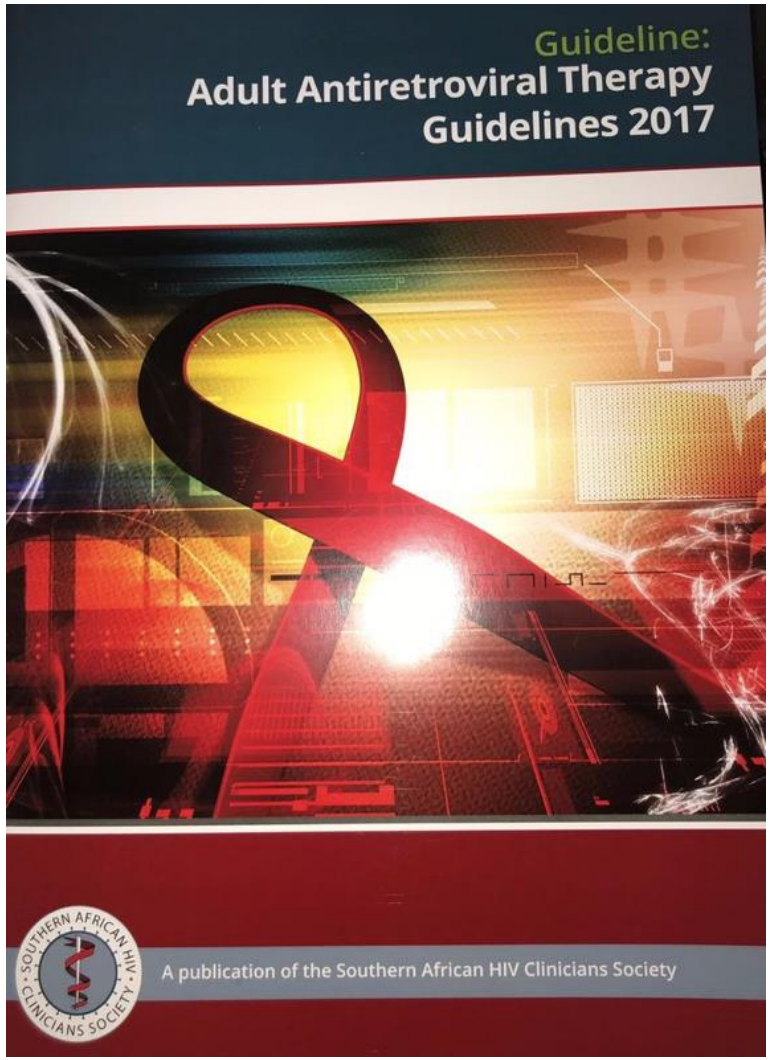
Population	Regimen
Women* on effective contraception or not of childbearing potential	DTG-based first-line ART is recommended
All pregnant (from eight weeks after conception) and breastfeeding women	
WOCP** who want to become pregnant or have no effective contraception	Counsel about risks and benefits of DTG- versus EFV-based ART. Offer choice of both treatments. Document discussion, preferably along with consent from those women opting for DTG-based ART
Confirmed pregnancy <8/40	

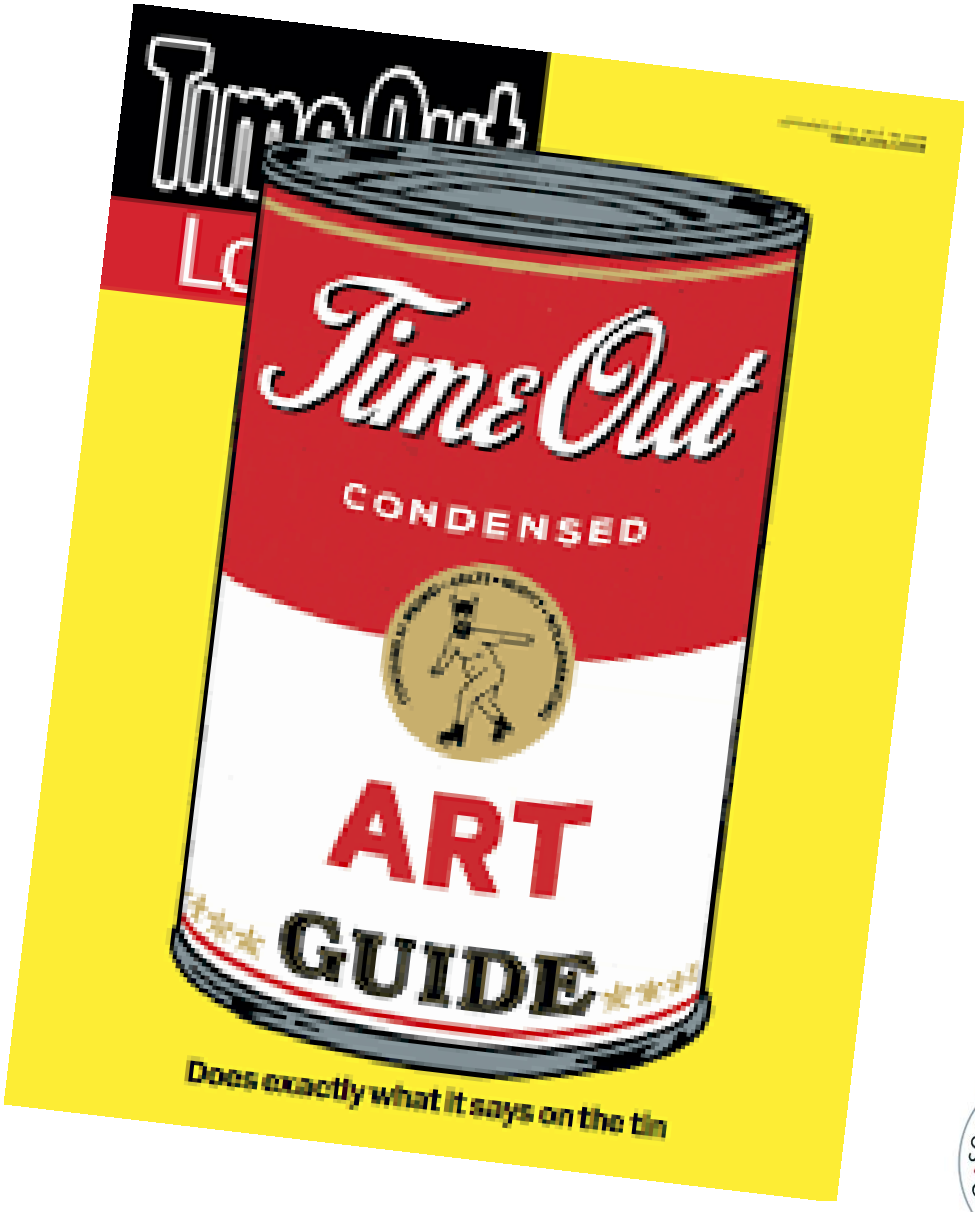
* Women includes adolescent girls
** Women of childbearing potential

"A woman-centred approach should be adopted: healthcare providers should give women information and options to allow for informed choices about using lifelong ART regimens."

Moorhouse, M A. et al. Southern African HIV Clinicians Society Guidance on the use of dolutegravir in first-line antiretroviral therapy. Southern African Journal of HIV Medicine, [S.l.], v. 19, n. 1, p. 2 pages, oct. 2018.

Final thoughts





Acknowledgements