
Update on Protease inhibitors 2019



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Thanks to Michelle Moorhouse

Disclosures...

- Part of optimisation collaborations – grants to improve testing, new drug regimens, linkage to care



O P T I M I Z E



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



Quick SA numbers update...

- **7.9 million with HIV/52 million**
- **Over 5 million people on ARVs in SA; 150 000 on second line, about 3000 third line**
- **Life expectancy up a decade**

Three lines of treatment in most LMICs

TDF + XTC + EFV

Failure

ZDV + 3TC + PI/r
(LPV/r or ATV/r)

Failure: genotype

XTC, other nukes

Darunavir Dolutegravir Etravirine

*

Uganda/ US/ UK – ‘higher life expectancy that matched populations

Life Expectancy of Persons Receiving Combination Antiretroviral Therapy in Low-Income Countries: A Cohort Analysis From Uganda

Edward J. Mills, PhD, MSc, LL.M.; Celestin Bakanda, MSc; Josephine Birungi, MBChB; Keith Chan, MSc; Nathan Ford, PhD, MPH; Curtis L. Cooper, MD, MSc; Jean B. Nachega, MD, PhD; Mark Dybul, MD; and Robert S. Hogg, PhD, MA

1. Expect a normal life expectancy:

May et al. AIDS 2014

- UK CHIC: 21 388 people started ART 2000-2010

Life Expectancy in Africa: Back to the Future?

From 1950 to 1990, life expectancy in sub-Saharan Africa... challenged global trade rules and regulations, ulti...

If 35 year old man started ART:

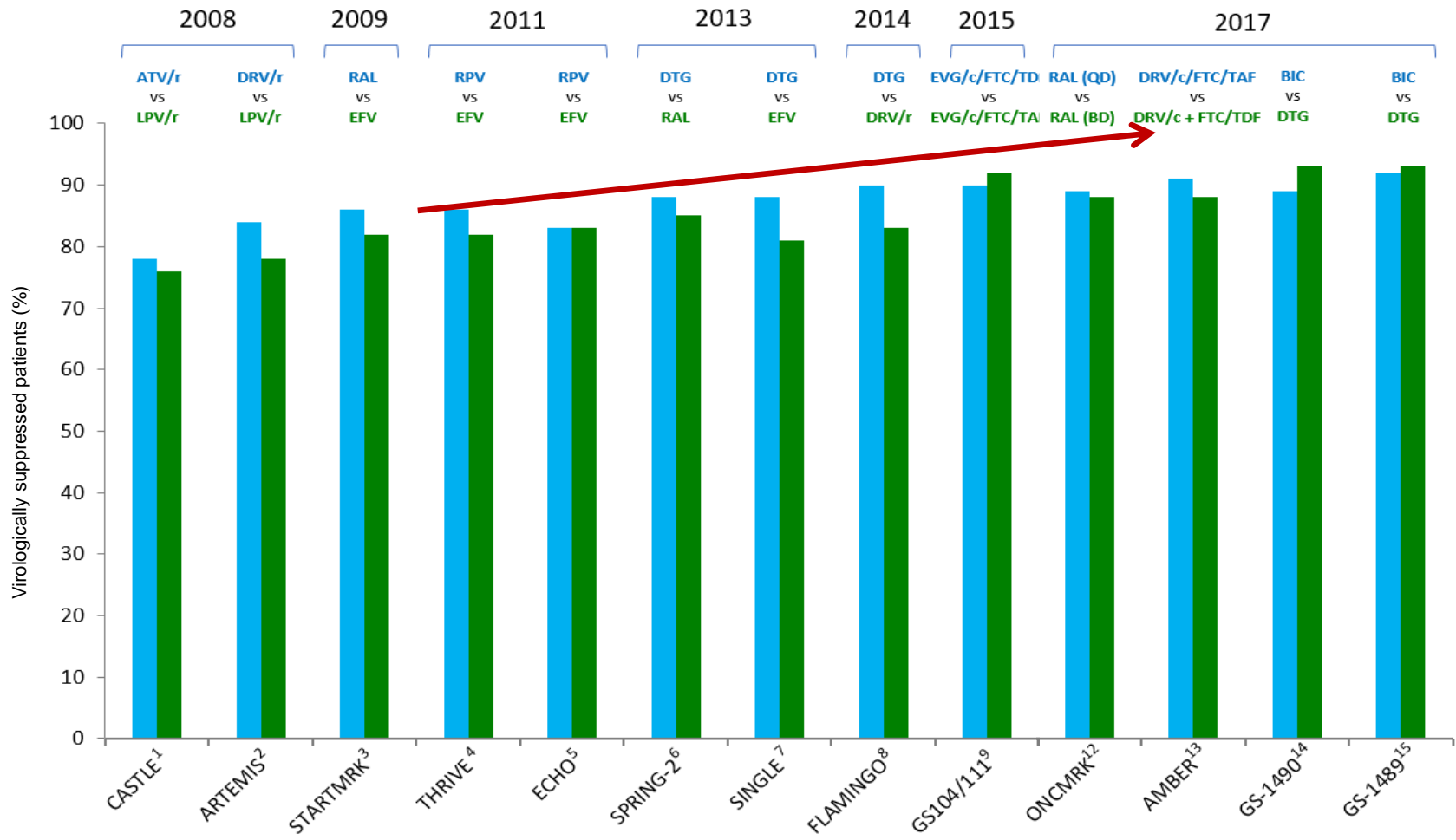
	life expectancy		
	Baseline	1 year ART	5 years ART
CD4 <200	71		& VL>50 54
200-349	78	78	
>350	77	81	& VL<50 80
General population	78		

Conclusion: If diagnosed, in care and on effective ART: life expectancy is normal

Great information to give to people newly diagnosed and encourage good adherence

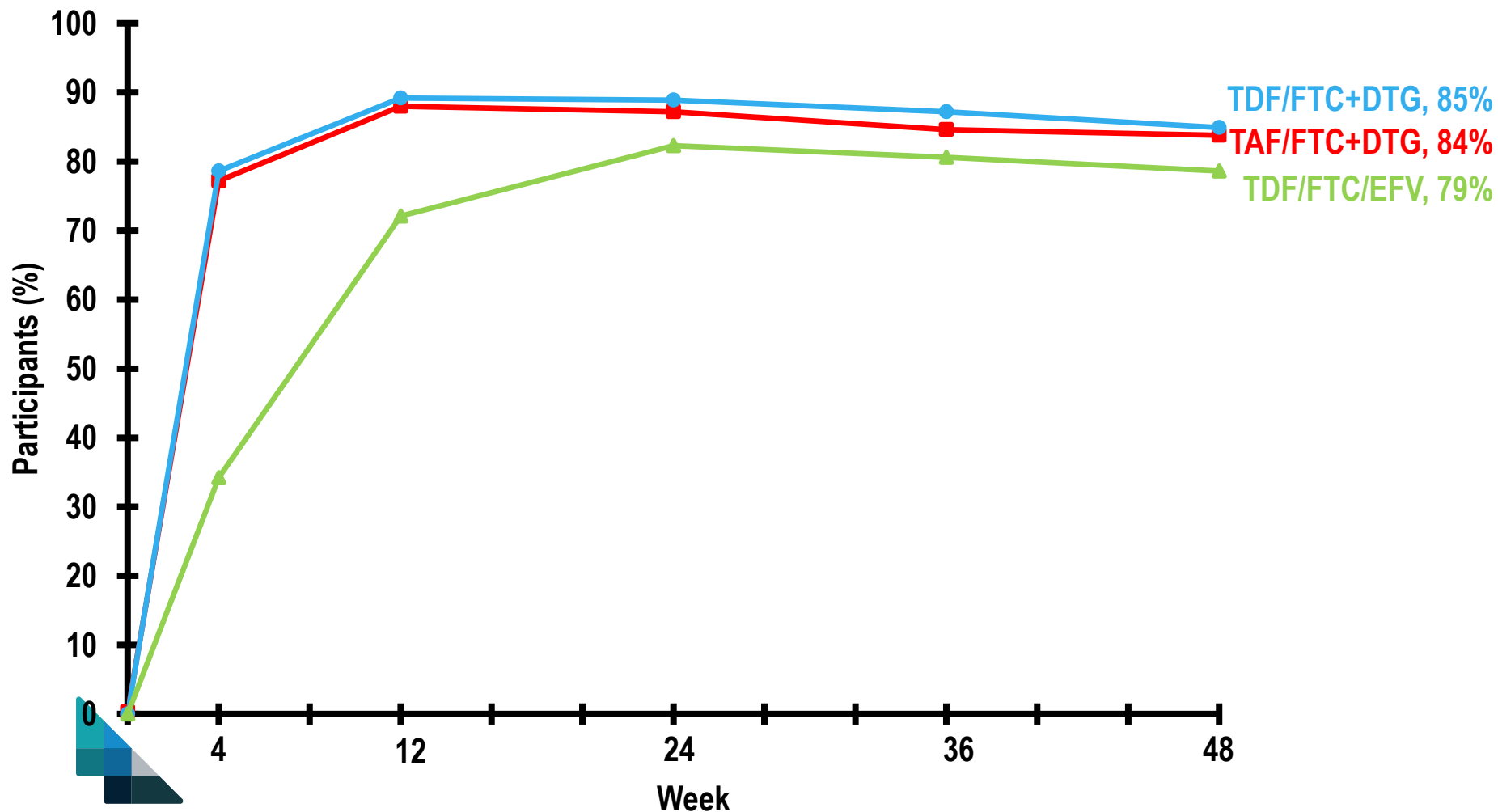
Thanks: Julie Fox, Guys

Overall efficacy outcomes at Week 48

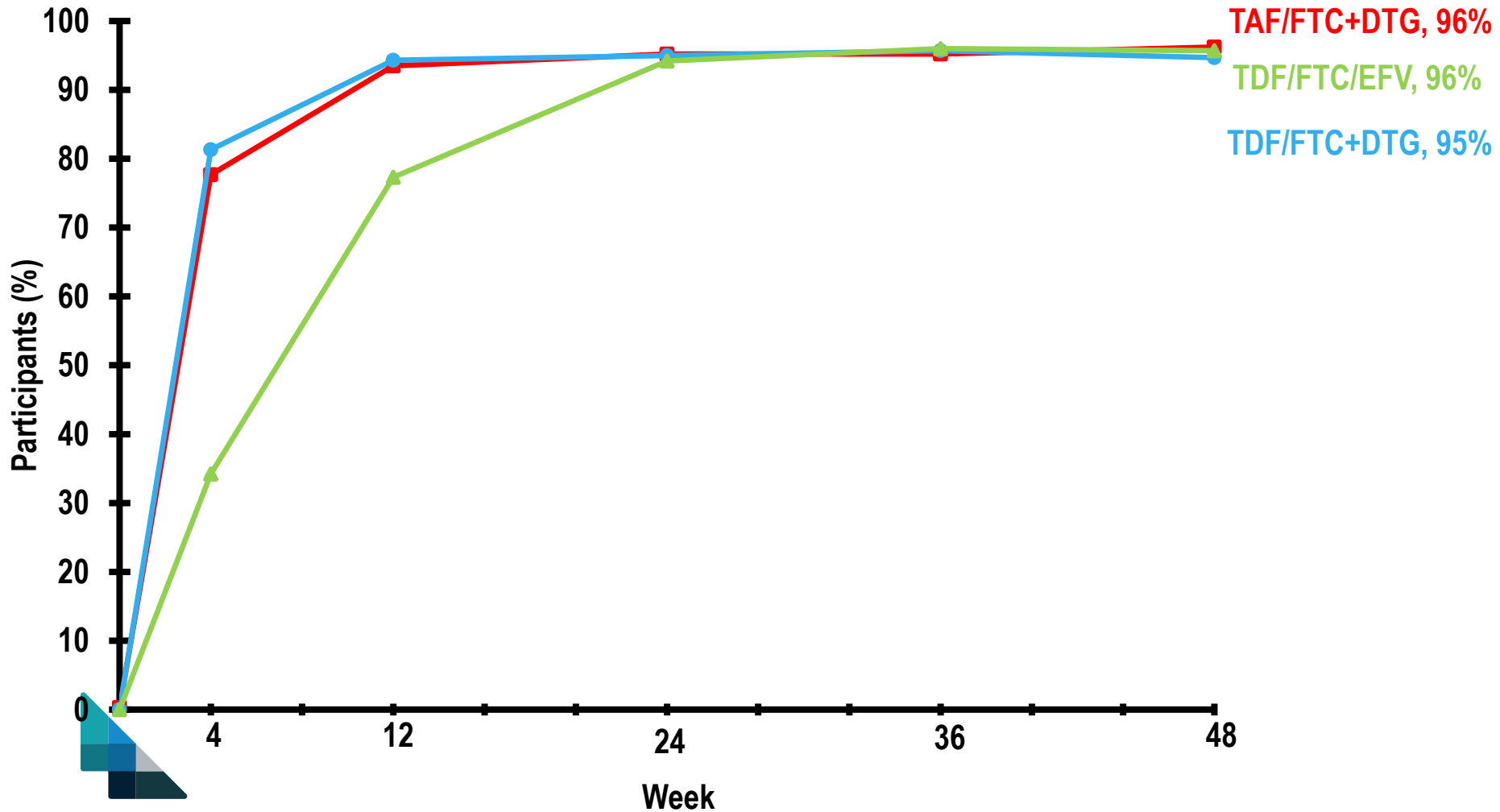


1. Molina JM, et al. *Lancet* 2008;372:646–55; 2. Ortiz R, et al. *AIDS* 2008;22:1389–97; 3. Lennox JL, et al. *Lancet* 2009;374:796–806; 4. Cohen CJ, et al. *Lancet* 2011;378:229–37; 5. Molina JM, et al. *Lancet* 2011;378:238–46; 6. Raffi F, et al. *Lancet* 2013;381:735–43; 7. Walmsley SL, et al. *N Engl J Med* 2013;369:1807–18; 8. Clotet B, et al. *Lancet* 2014;383:2222–31; 9. Sax PE, et al. *Lancet* 2015;385:2606–15; 10. Squires K, et al. *Lancet HIV* 2016;3:e410–20; 11. Orrell C, et al. *Lancet HIV* 2017;4:e536–46; 12. Cahn P, et al. *Lancet HIV* 2017;4:e486–94; 13. Eron J, et al. EACS 2017, Milan, Italy; Abstract #PS8/2; 14. Sax PE, et al. *Lancet* 2017;390:2073–82; 15. Gallant J, et al. *Lancet* 2017;390:2063–72

Proportion of participants with HIV-1 RNA level <50 copies/mL by time point (ITT)



Proportion of participants with HIV-1 RNA level <50 copies/mL by time point (per-protocol)

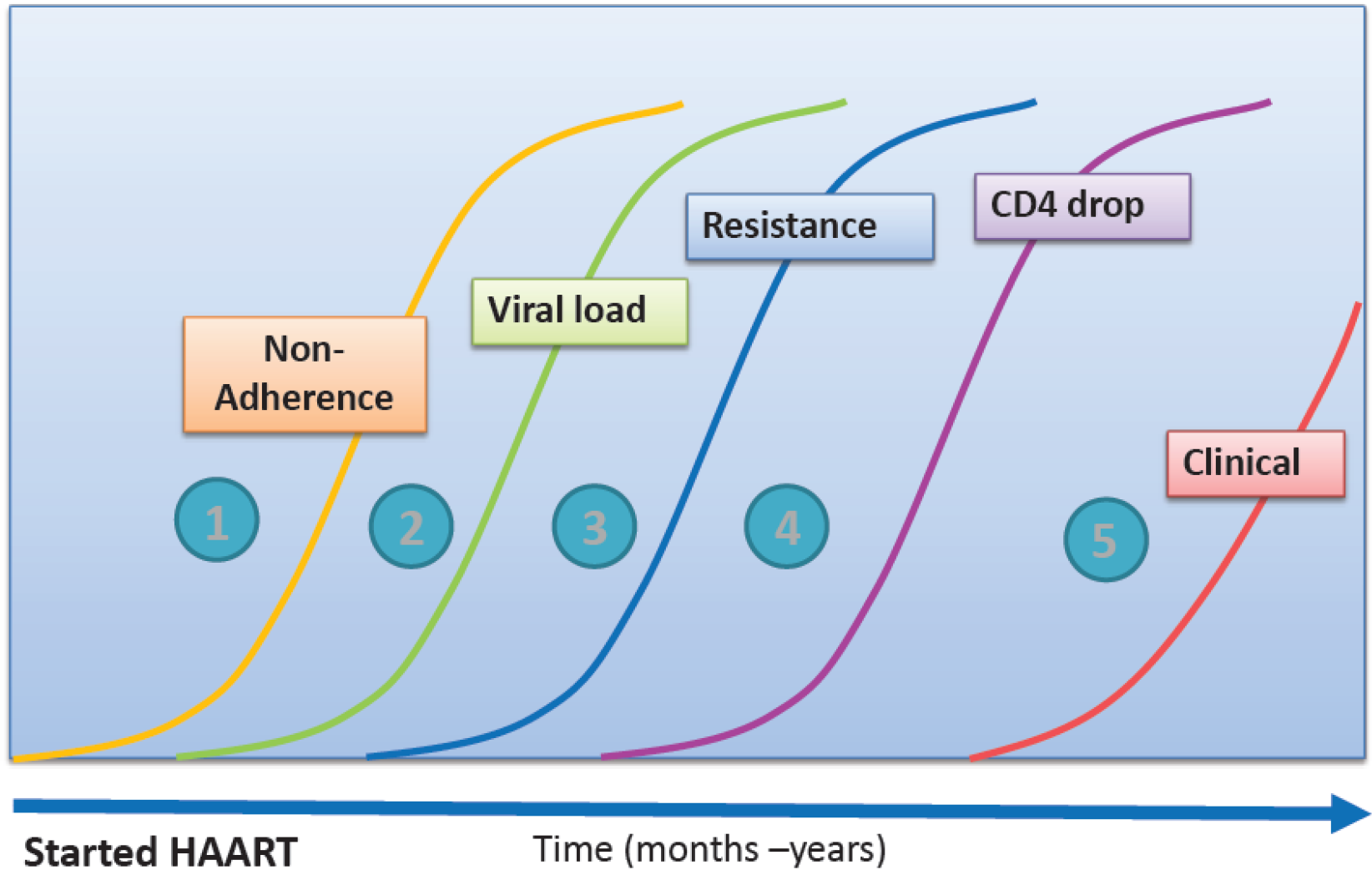


What is treatment failure?

- Clinical failure
 - New OIs (excluding IRIS) and/or other clinical evidence of HIV disease progression during therapy.
- Immunological failure
 - Suboptimal CD4+ response or a CD4+ decline while on ART
- Virological failure
 - VL of > 1000 copies/mL on 2 measurements taken 2–3 months apart

Failure	Definition
Clinical failure	Adults and adolescents New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) ^a after 6 months of effective treatment
	Children New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment
Immunological failure	Adults and adolescents CD4 count falls to the baseline (or below) or Persistent CD4 levels below 100 cells/mm ³
	Children Younger than 5 years Persistent CD4 levels below 200 cells/mm ³ or <10% Older than 5 years Persistent CD4 levels below 100 cells/mm ³
Virological failure	Plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support

How are they related?



Why not use immunological or clinical criteria? Surely cheaper?

Plasma Viral Load and CD4⁺ Lymphocytes as Prognostic Markers of HIV-1 Infection

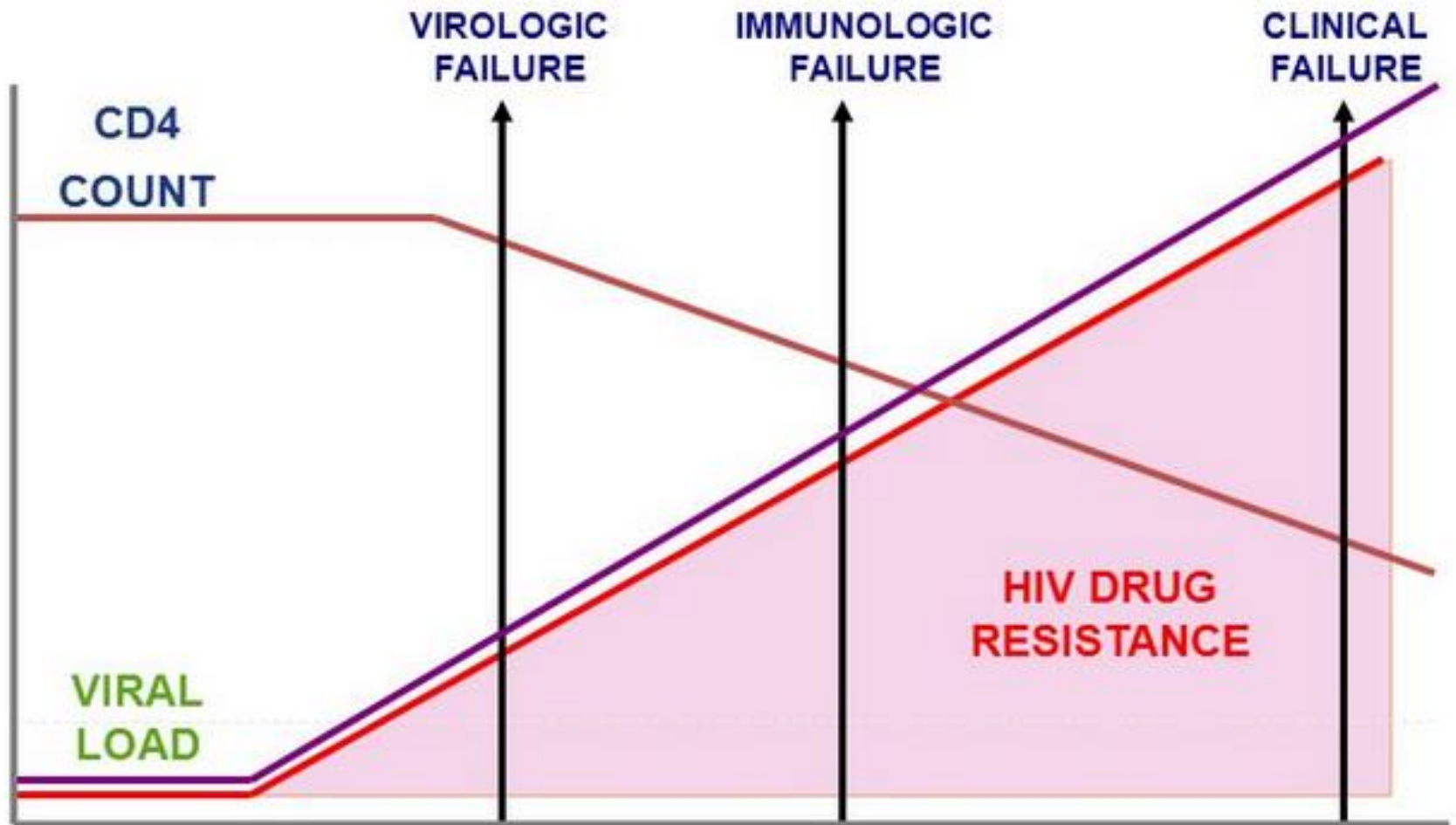
John W. Mellors, MD; Alvaro Muñoz, PhD; Janis V. Giorgi, PhD; Joseph B. Margolick, MD, PhD; Charles J. Tassoni, PhD; Phalguni Gupta, PhD; Lawrence A. Kingsley, DrPH; John A. Todd, PhD; Alfred J. Saah, MD; Roger Detels, MD; John P. Phair, MD; and Charles R. Rinaldo Jr., PhD

Ann Intern Med. 1997;126:946-954.

Results: Plasma viral load was the single best predictor of progression to AIDS and death, followed (in order of predictive strength) by CD4⁺ lymphocyte count and serum neopterin levels, serum β_2 -microglobulin levels, and thrush or fever. Plasma viral load discriminated risk at all levels of CD4⁺ lymphocyte counts and predicted their subsequent rate of decline.

VL criteria identified failure significantly earlier than CD4+ criteria
CD4+ sensitivity 58%; specificity 75%

Significant resistance by time of clinical failure



Managing a high viral load

Identify cause

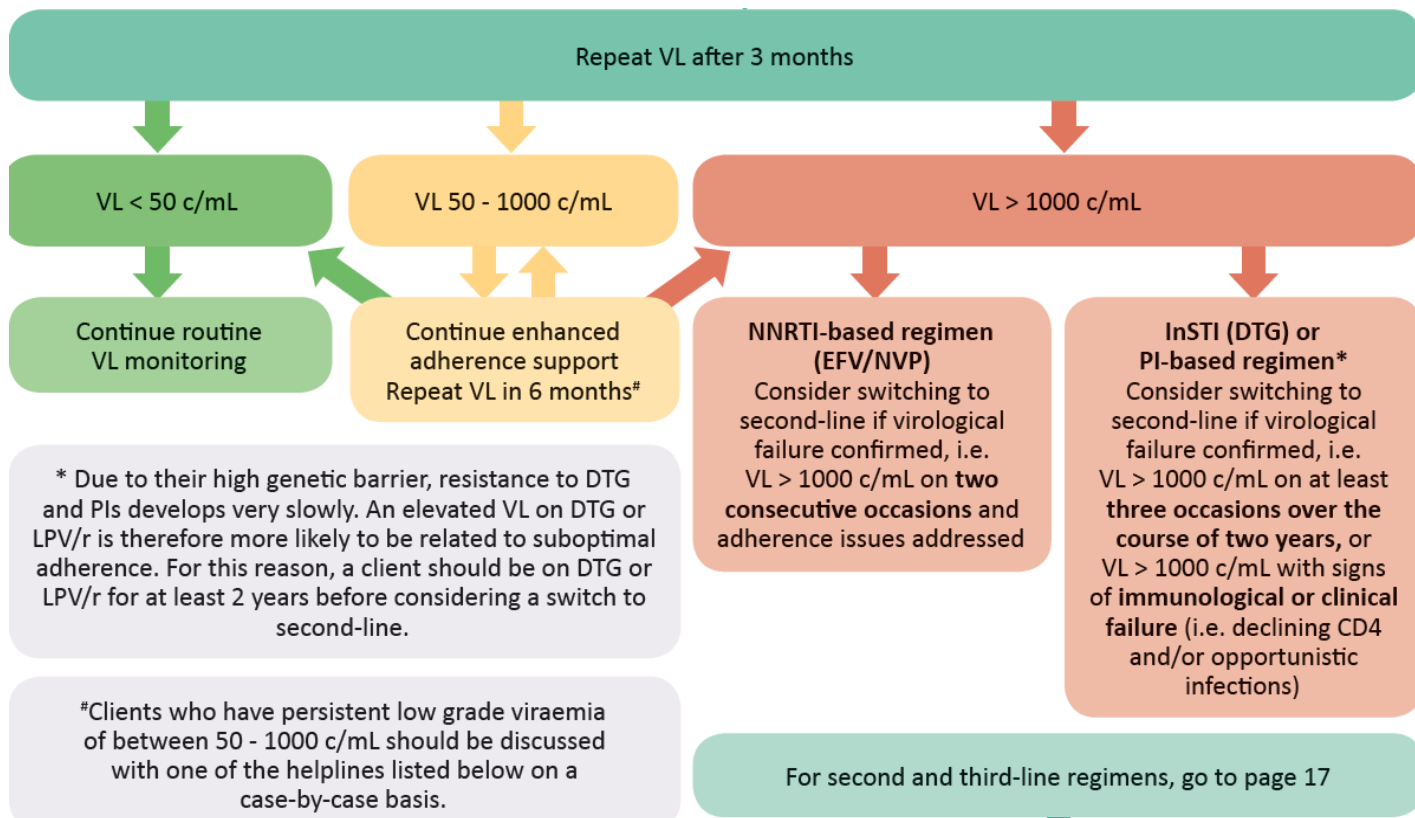
Address the problem

Repeat VL in 2-3 months

Second-line if appropriate



VL monitoring: Interpreting the results of the VL repeated after 3 months



* Due to their high genetic barrier, resistance to DTG and PIs develops very slowly. An elevated VL on DTG or LPV/r is therefore more likely to be related to suboptimal adherence. For this reason, a client should be on DTG or LPV/r for at least 2 years before considering a switch to second-line.

#Clients who have persistent low grade viraemia of between 50 - 1000 c/mL should be discussed with one of the helplines listed below on a case-by-case basis.

Switching for virological failure will now depend on

- **Current regimen** (NNRTI vs InSTI/PI)
- **Duration**

Barriers to adherence

Individual

- No autonomy
- Age > 15 years
- Conform with peers

Psychosocial

- Stigma
- Disclosure
- Forget
- Reminds of HIV
- Mental health
- Substance abuse
- Self image

Disease-related

- Pill burden/ fatigue
- Side effects
- HIV diagnosis
- Advanced disease

Contextual

- Orphanhood
- Poverty
- Changing/ absent guardianship
- Leaving school
- Poor social support
- Access

A detectable viral load should be acted on promptly



Adult antiretroviral therapy guidelines 2017

Virological criteria for treatment success

Treatment success is defined by a decline in VL to < 50 copies/mL within six months of commencing ART, and sustained thereafter.

Virological criteria for treatment failure

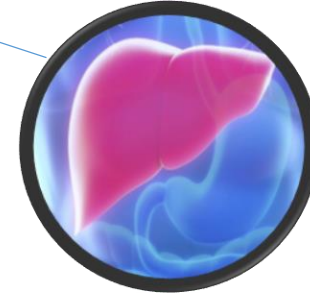
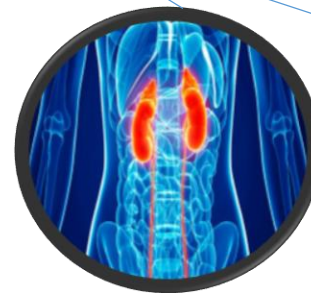
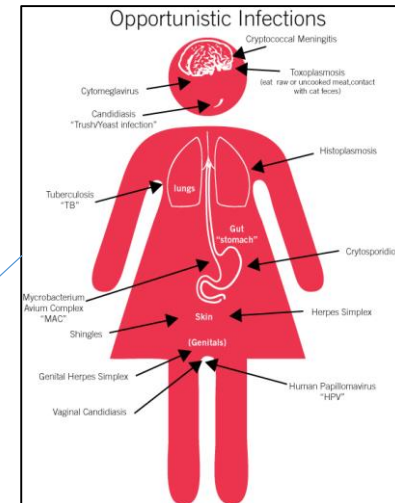
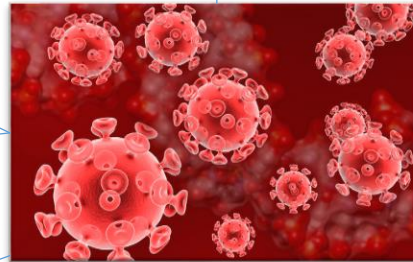
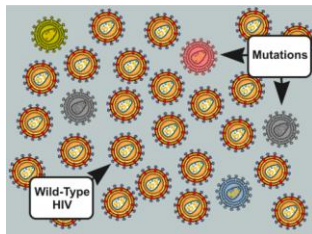
Treatment failure is defined by a confirmed VL of > 1000 copies/mL on two measurements taken 2–3 months apart. Several factors can influence the measurement of the VL. The

A VL > 50 copies/mL while receiving ART should be an indication for *urgent* action to improve adherence. A

subsequent ART change must be considered if the patient meets the criteria for a switch to a second-line ART regimen at the subsequent 2–3-month follow-up VL measurement (see the section 'Indications for changing antiretroviral therapy').

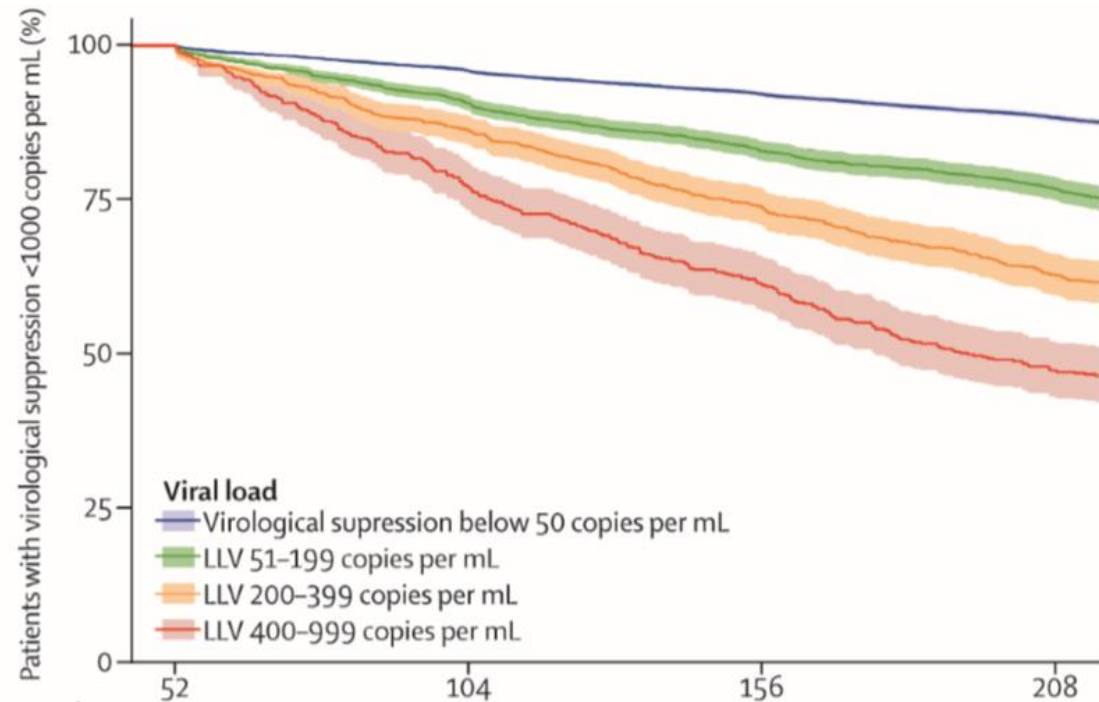


Consequences of viraemia



Data from SA: What are the consequences?

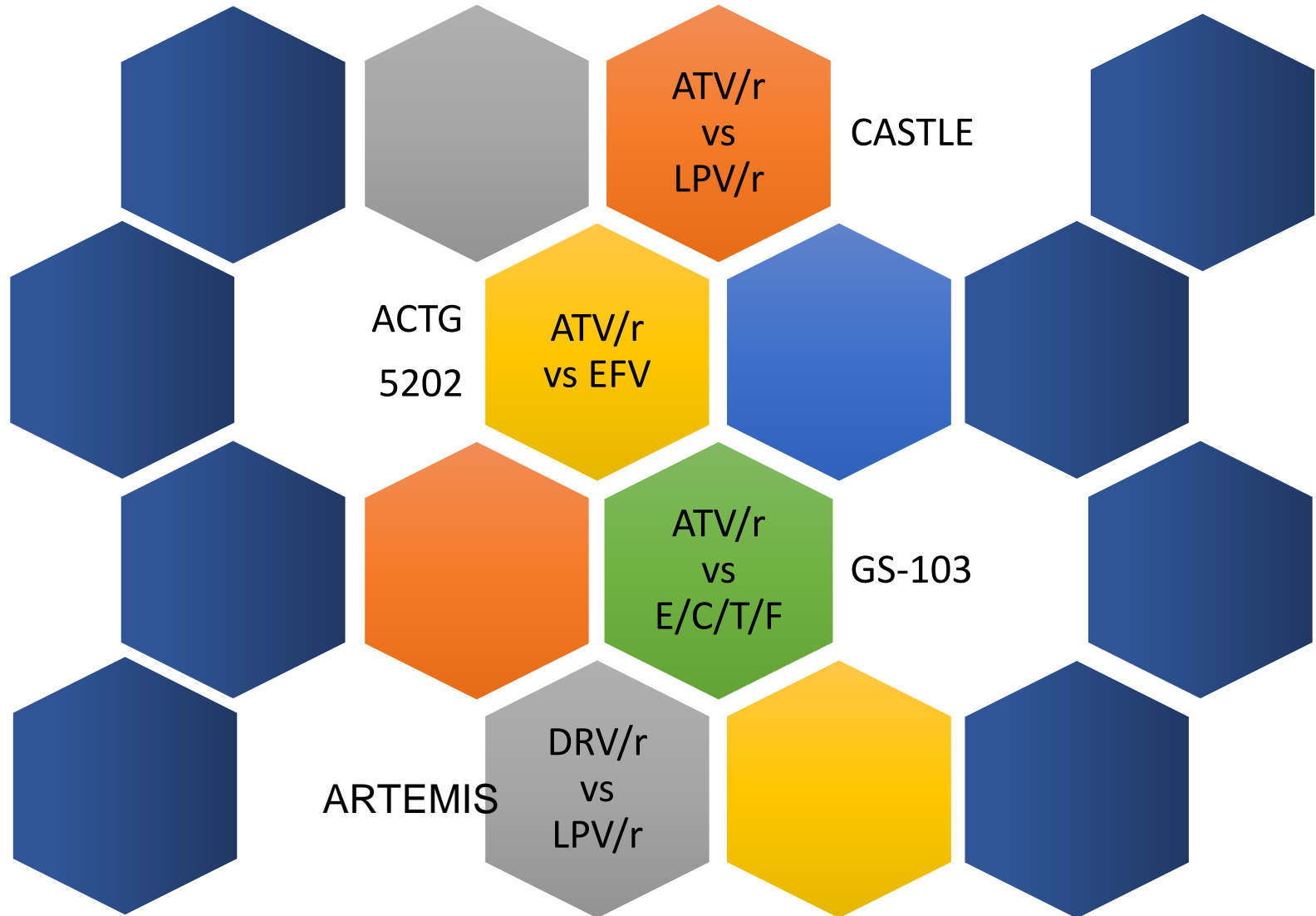
- If LLV occurs, what is the likelihood of VL >1000 c/mL at the next viral load?
- Stratified LLV
 - 51-199 c/mL
 - 200-399 c/mL
 - 400-999 c/mL
- Association corrected for demographics, baseline CD4



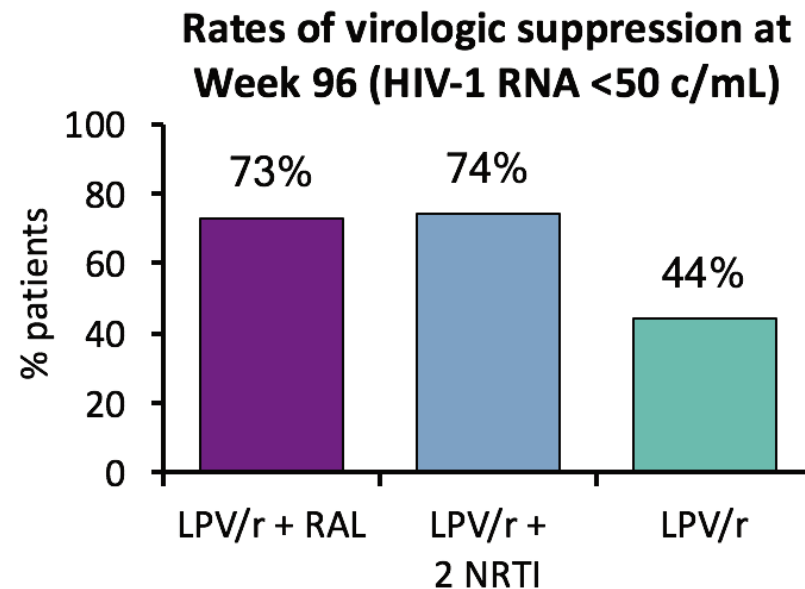
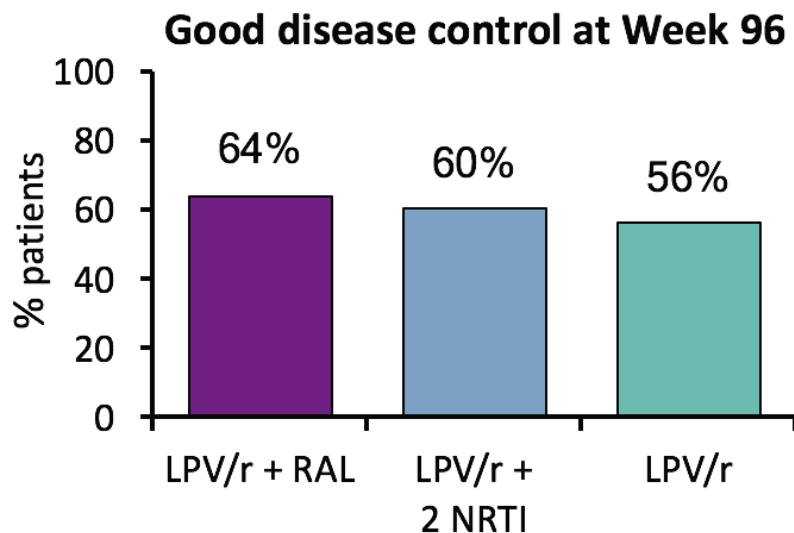
	Adjusted HR (95% CI)	p value
Virological suppression <50 copies per mL	1 (ref)	..
LLV 51-999 copies per mL	2.6 (2.5-2.8)	<0.0001
LLV 51-199 copies per mL	1.9 (1.8-2.1)	<0.0001
LLV 200-399 copies per mL	3.2 (2.9-3.5)	<0.0001
LLV 400-999 copies per mL	4.7 (4.2-5.2)	<0.0001



PIs work



EARNEST study: Efficacy



- Increase in mean CD4 counts did not significantly differ between groups
- LPV/r + NRTI had excellent outcomes
 - LPV/r + RAL was not superior to LPV/r + NRTI
 - LPV/r was inferior to LPV/r + NRTI

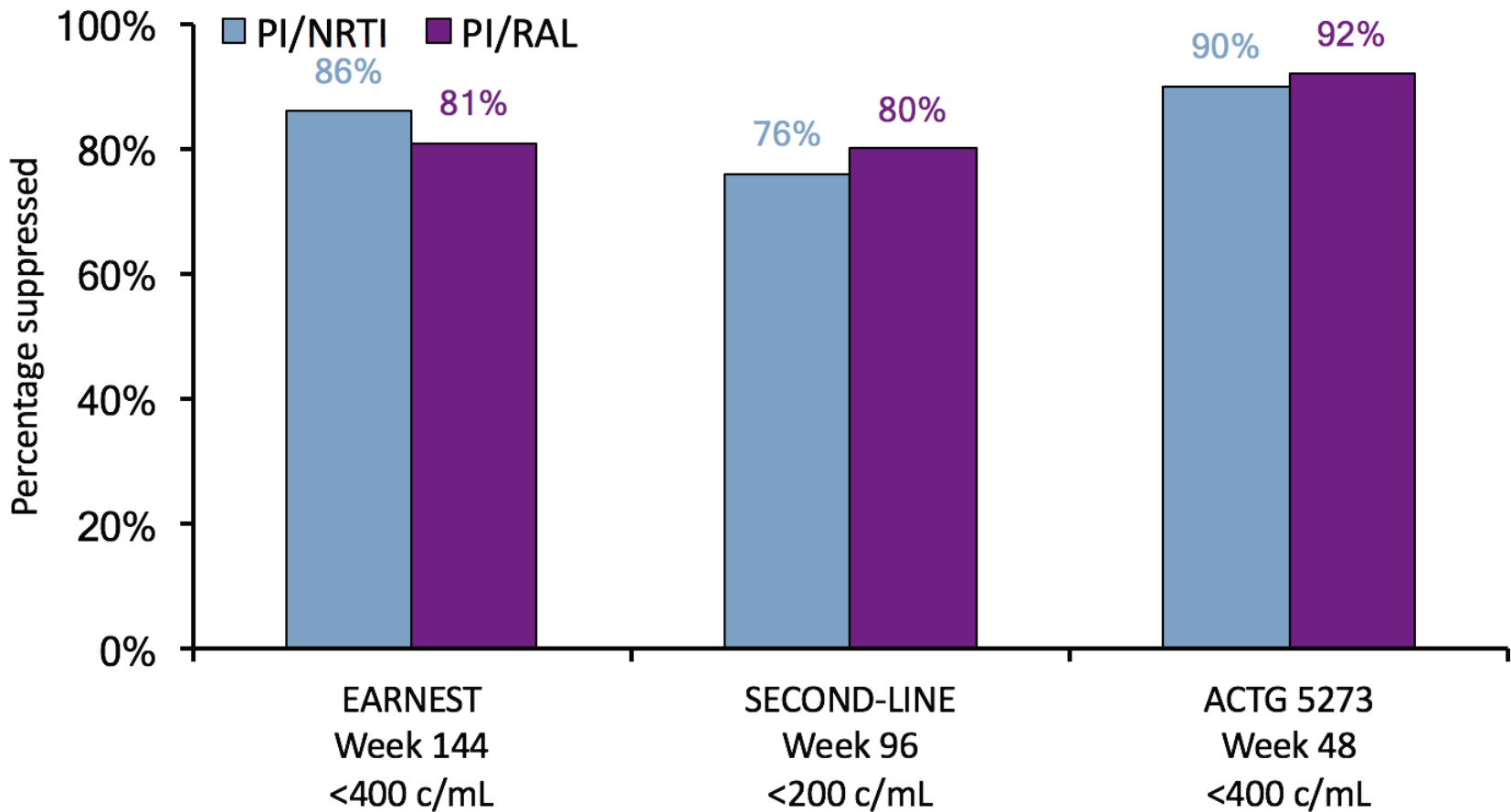
- AEs were similar across the arms
- 18% of patients receiving LPV/r monotherapy had intermediate/high-level LPV resistance at Week 96
 - Versus 2% and 1% in patients receiving LPV/r + NRTI or LPV/r + RAL, respectively

Some learnings from EARNEST et al

- PI/r + 2NRTIs work well in real world LMIC settings
- PI/r + InSTI is an option for those needing NRTI sparing regimens
- Good outcomes can be achieved without genotypes at BL and first-line failure
- Functional monotherapy debunked



Summary of second-line studies



EARNEST: Hakim J, et al. CROI 2015; Poster 552

SECOND-LINE: Amin J, et al. PLoS ONE 10:e0118228

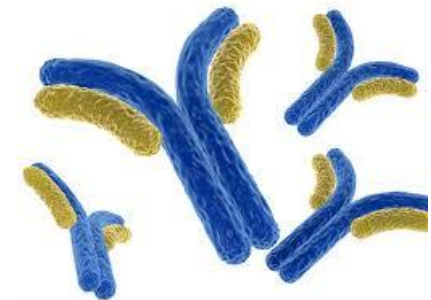
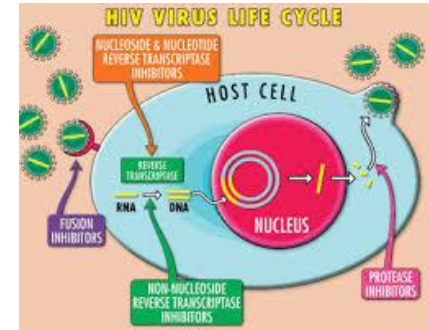
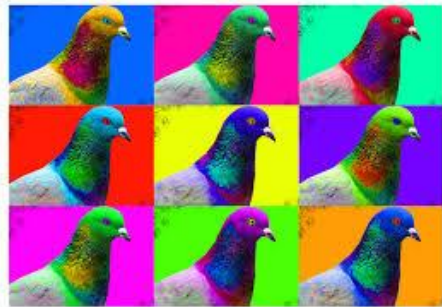
ACTG 5273: La Rosa AM, et al. CROI 2016; Abstract 30

So how do we make second-line better?

Use current drugs differently

New(er) drugs

New drug classes



Current PI replacements

- ATV dose reduced
- DRV/r will get cheaper with increased use
- DRV/r 600/100 switch studies did well
- DRV/r 400/100?
- Booster: RTV replacements?

So what to switch to? 2019 pending....



Adult antiretroviral therapy guidelines 2017

We recommend a regimen of two NRTIs and a RTV-boosted (/r) PI. Boosting of PIs involves the addition of low-dose

we suggest that the preferred PI in second-line therapy should be ritonavir-boosted atazanavir (ATV) 300 mg/RTV

tablet for DRV/r 800/100 mg dosing became available, DRV/r 800/100 mg would be a feasible option in second-line ART, with fewer side effects than the DRV/r 600/100 mg twice-daily dosing.

Whence darunavir?

- Looking like will be available soon at lower cost
- Cant use in TB
- See SAHCS guidelines on dosing
- Discussion re 400mg/100mg



Third line eligibility

Adults on PI regimen not fully suppressed at 12 months

Genotype resistance test

PI resistance: full treatment history to third-line panel

Documented resistance to PI/r in current regimen

Access to third-line drugs, including **DRV/r**, **etravirine** and **raltegravir**



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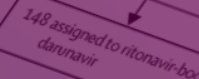


Subsc

Low-dose ritonavir-boosted darunavir once daily versus ritonavir-boosted lopinavir for participants with less than 50 HIV RNA copies per mL (WRHI 052): a randomised, open-label, phase 3, non-inferiority trial

Prof Willem D F Venter, FCP • Michelle Moorhouse, FRSPH • Simiso Sokhela, MBChB • Celicia Serenata, MBA • Godspower Akpomiemie, MPH • Ambar Qavi, MPH • et al. [Show all authors](#)

Published: June 12, 2019 • DOI: [https://doi.org/10.1016/S2352-3018\(19\)30081-5](https://doi.org/10.1016/S2352-3018(19)30081-5)



Articles

Low-dose ritonavir-boosted darunavir once daily versus ritonavir-boosted lopinavir for participants with less than 50 HIV RNA copies per mL (WRHI 052): a randomised, open-label, phase 3, non-inferiority trial



Willem D F Venter, Michelle Moorhouse, Simiso Sokhela, Celicia Serenata, Godspower Akpomiemie, Ambar Qavi, Nonkululeko Mashabane, Natasha Arufappan, Joel W Sim, Phumla Z Sinxadi, Lubbe Wiesner, Elisha Maharaj, Carole Wallis, Tom Boyles, David Ripin, Sarah Stacey, Gilo Chitauri, Andrew Hill

Summary

Background Pilot studies suggest that ritonavir-boosted darunavir could show high efficacy at doses below those currently approved. We investigated whether switch to 400 mg of darunavir boosted with 100 mg ritonavir once daily could show equivalent efficacy to continuation of ritonavir-boosted lopinavir (a protease inhibitor commonly used in

Lancet HIV 2019
Published Online
June 12, 2019
<https://doi.org/10.1016/>

HIV RNA < 50 copies/mL at Week 48

FDA Snapshot and ITT population

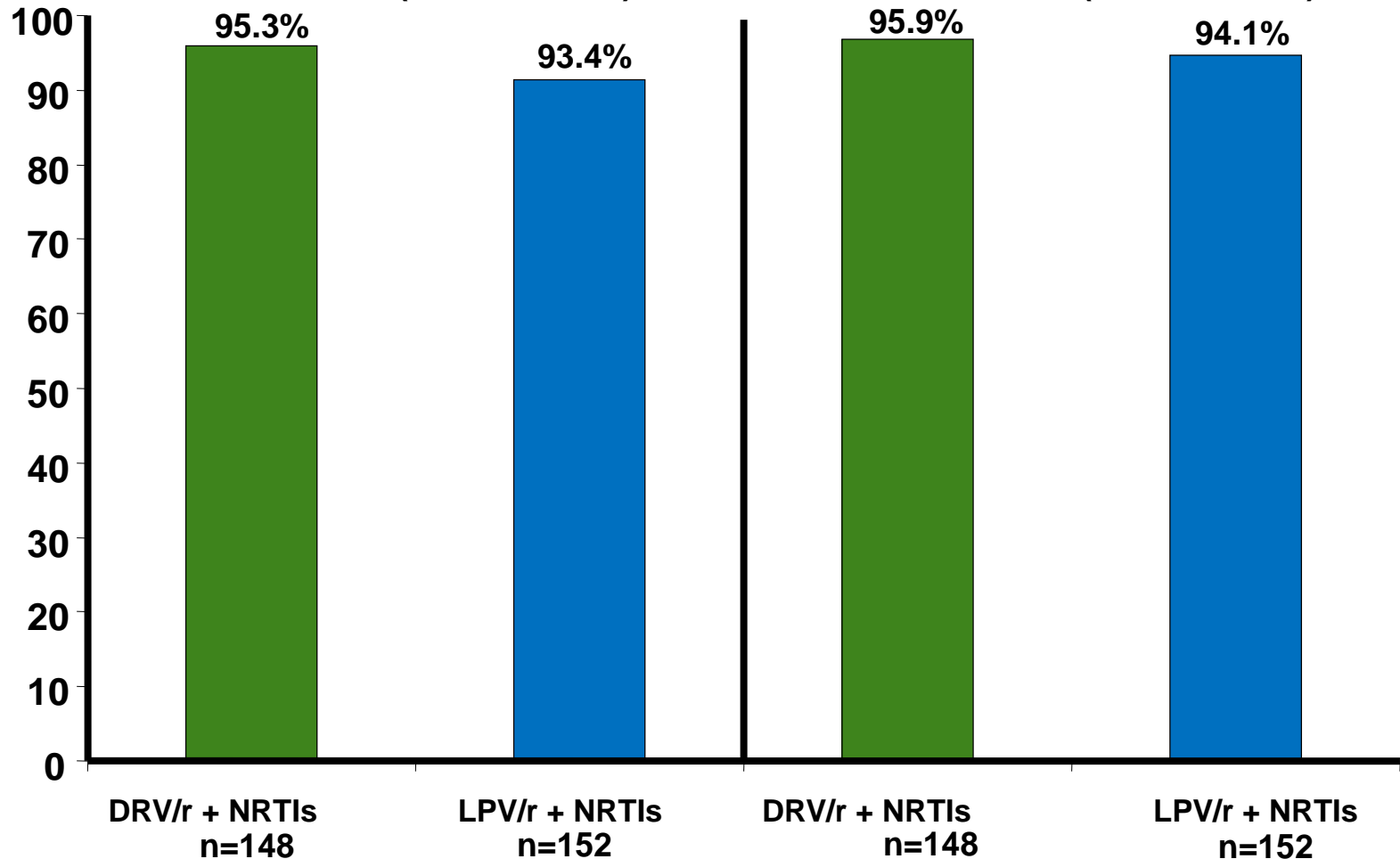


Switch=failure analysis (FDA Snapshot)

Difference = +1.9% (-3.7%, +6.5%)*

Switch included analysis (ITT)

Difference = +1.9% (-3.4%, +7.3%)*



DRV/r + NRTIs
n=148

LPV/r + NRTIs
n=152

DRV/r + NRTIs
n=148

LPV/r + NRTIs
n=152

* 95% confidence intervals from univariate analysis

22nd International AIDS Conference, Amsterdam, the Netherlands, July 2018 [TUAB0107LB]

Final thoughts

- DTG is going to change the landscape
- But there will be some EFV in the system (and probably PIs)
- Ongoing need to optimise ART beyond first-line
- Many of the challenges of lifelong ART have nothing to do with the ARVs themselves
- Virological suppression is achievable with prompt action and appropriate support
- LPV – TB; ATV – may disappear!

