Low dose darunavir

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University of the Witwatersrand
WITS RHI

Thanks DoH, WHO, PEPFAR, CHAI, UCT, Michelle Moorhouse, Celicia Serenata, Polly Clayden

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

Optimize

- Led by Wits RHI, the PEPFAR-supported, USAID-managed OPTIMIZE consortium focuses on accelerating access to PEPFAR's priority first- and second-line treatment products. OPTIMIZE, formed through an innovative co-formulation effort, partners with five leading private and public sector organizations and leverages co-funding from Unitaid, SAMRC and pharma
- Supporting PEPFAR's TLD Transition & Global ART Optimization
- Coordinates with several countries for TLD introduction
- Close coordination in SA with Pretoria office – critical for TLD
- ADVANCE and the low-dose darunavir study (052 are two studies in OPTIMIZE (with several related and sub-studies)

USAID FROM THE AMERICAN PEOPLE

SOUTH AFRICANS AND AMERICANS IN PARTNERSHIP TO FIGHT HIV/AIDS
PEPFAR

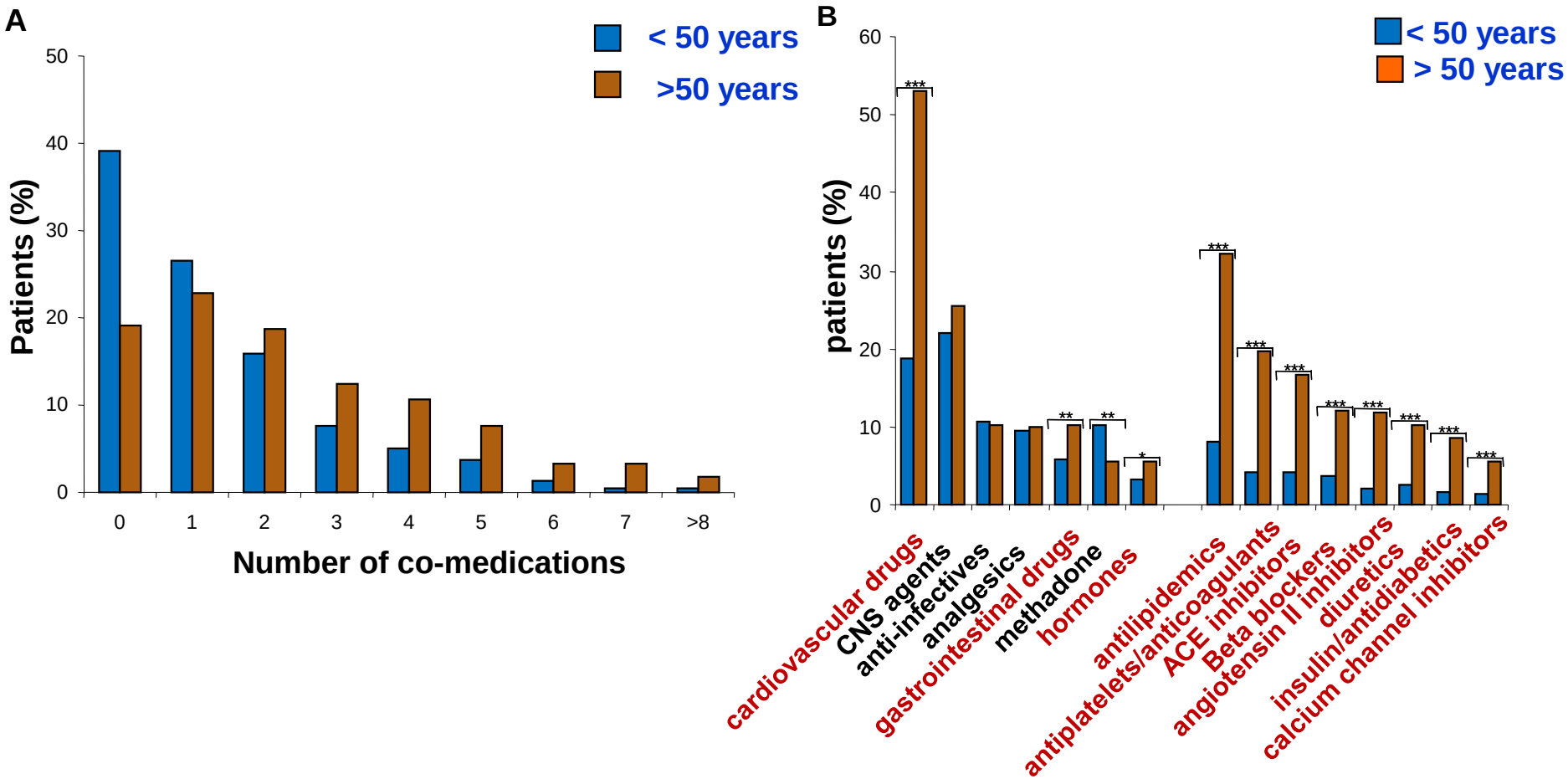
Unitaid

saMRC advancinglife

Optimizing Drug Regimens
Major Strategies

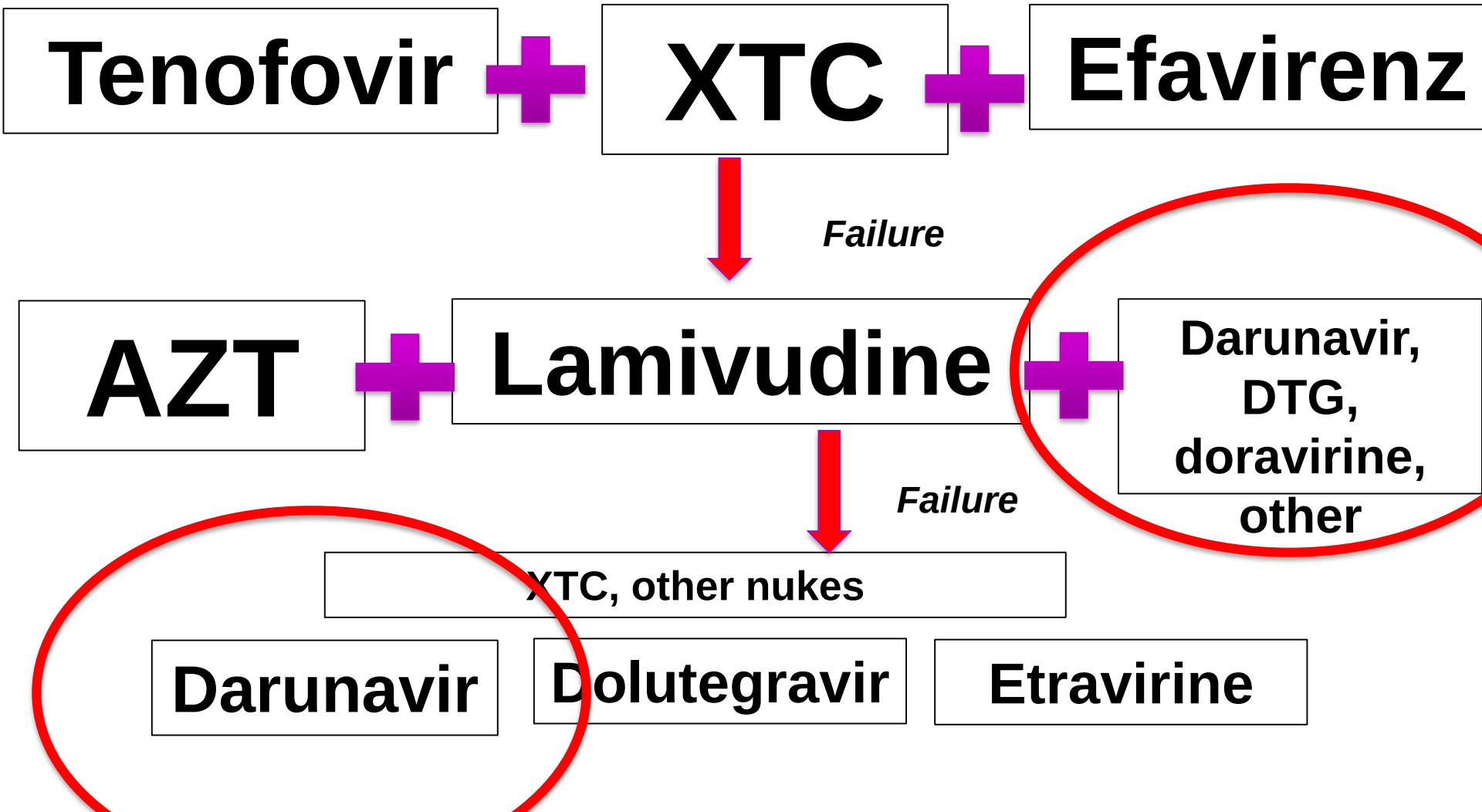
- ✓**Co-formulation** (use FDCs or co-blister pack)
- ✓ **Reformulation** (use extended release formulation; improve drug bioavailability)
- ✓ **Dose adjustment** (improve toxicity, reduce pill burden/size)
- ✓**New drugs** (substitution to improve toxicity or increase efficacy)
- ✓ **New strategies** (eg: induction-maintenance; intensification)
- ✓ **Drug manufacturing process** (improve API route synthesis and reduce cost)

Drug Interactions will be greater as patients age

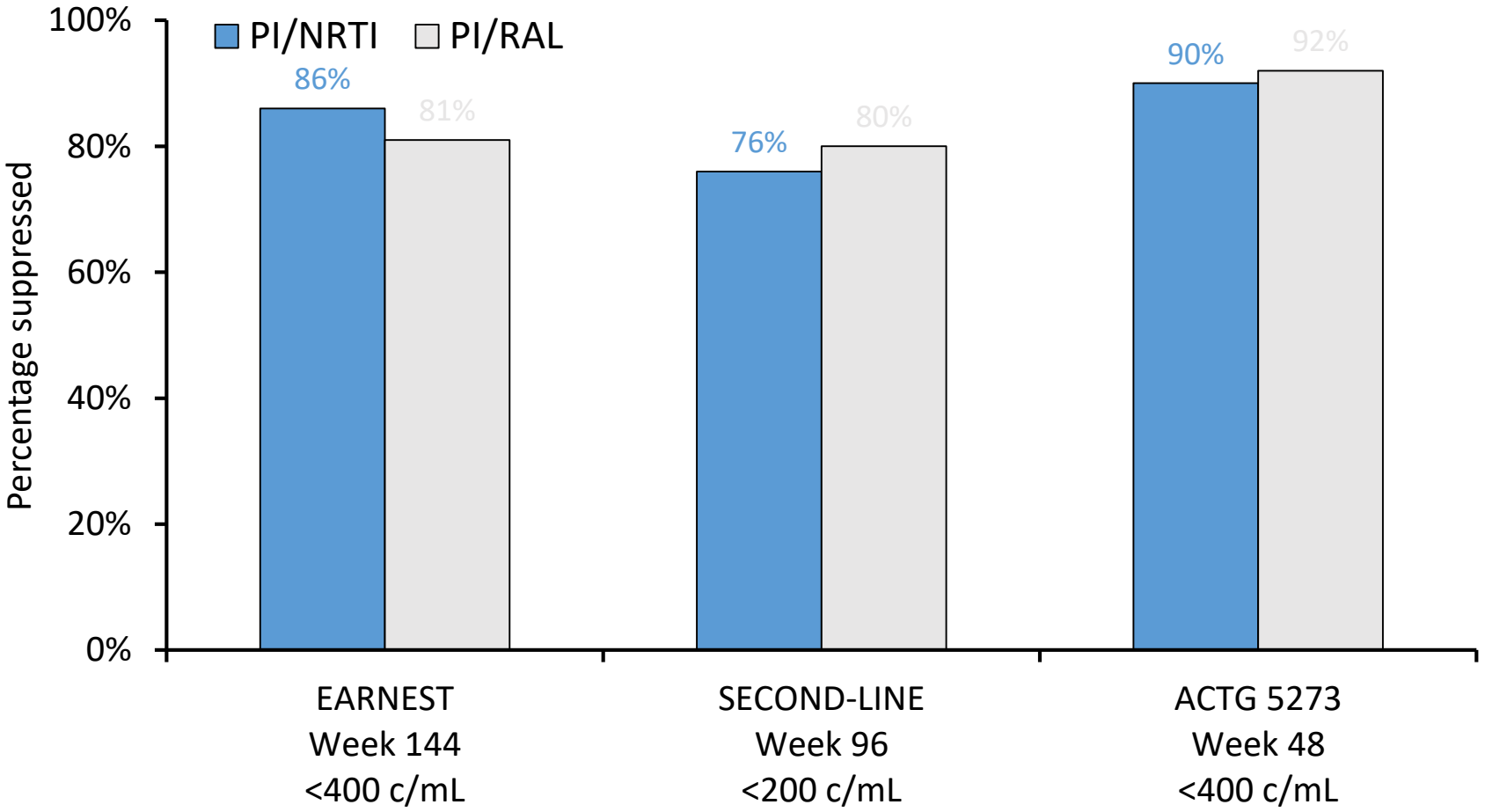


Marzolini C et al J Antimicrob Chemother 2011;66:210

WHO regimens 2018/soon



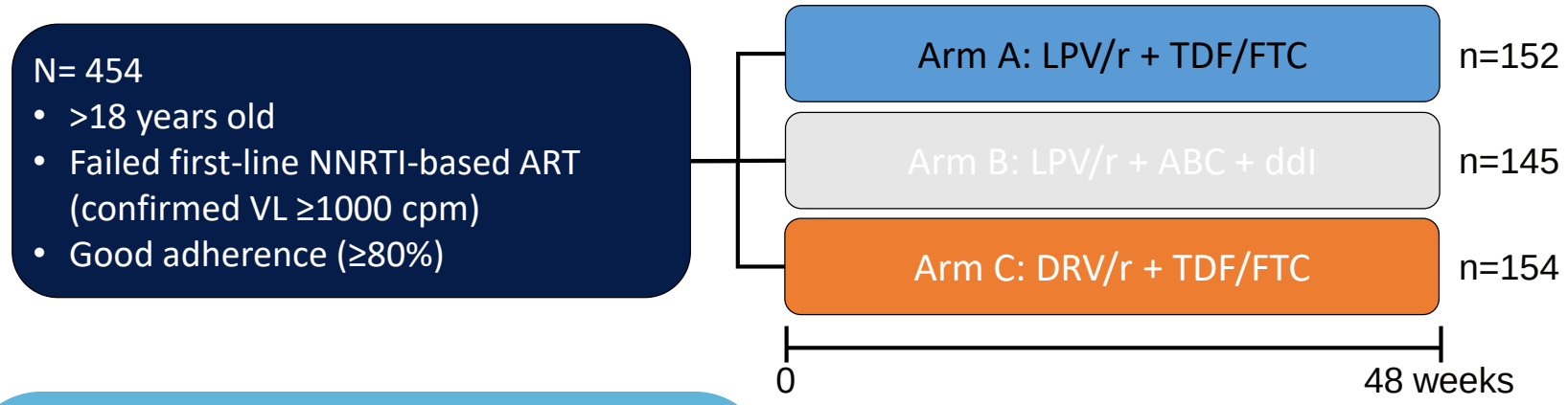
Efficacy of LPV/r-Based Therapy in Second-Line ART



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

Randomized Comparison of 3 Second-Line ART Regimens in Africa: The 2Lady/ANRS/EDCTP Study

- A 48-week, randomized, open label, non-inferiority trial in 3 African cities—Yaoundé (Cameroun), Bobo-Dioulasso (Burkina Faso), Dakar (Senegal)—comparing efficacy and safety of 3 second-line regimens from Jan 2010 to Oct 2012:



Baseline characteristics:

- 72% women
- Median duration on ART — 49 months (IQR 33–69)
- Median CD4 count of 183 cell/mm^3 (IQR 87–290)
- Median VL of 4.5 Log_{10} (IQR 4–5.1).
- ~99% had resistance to at least 1 first-line drug and 95% to 2 classes

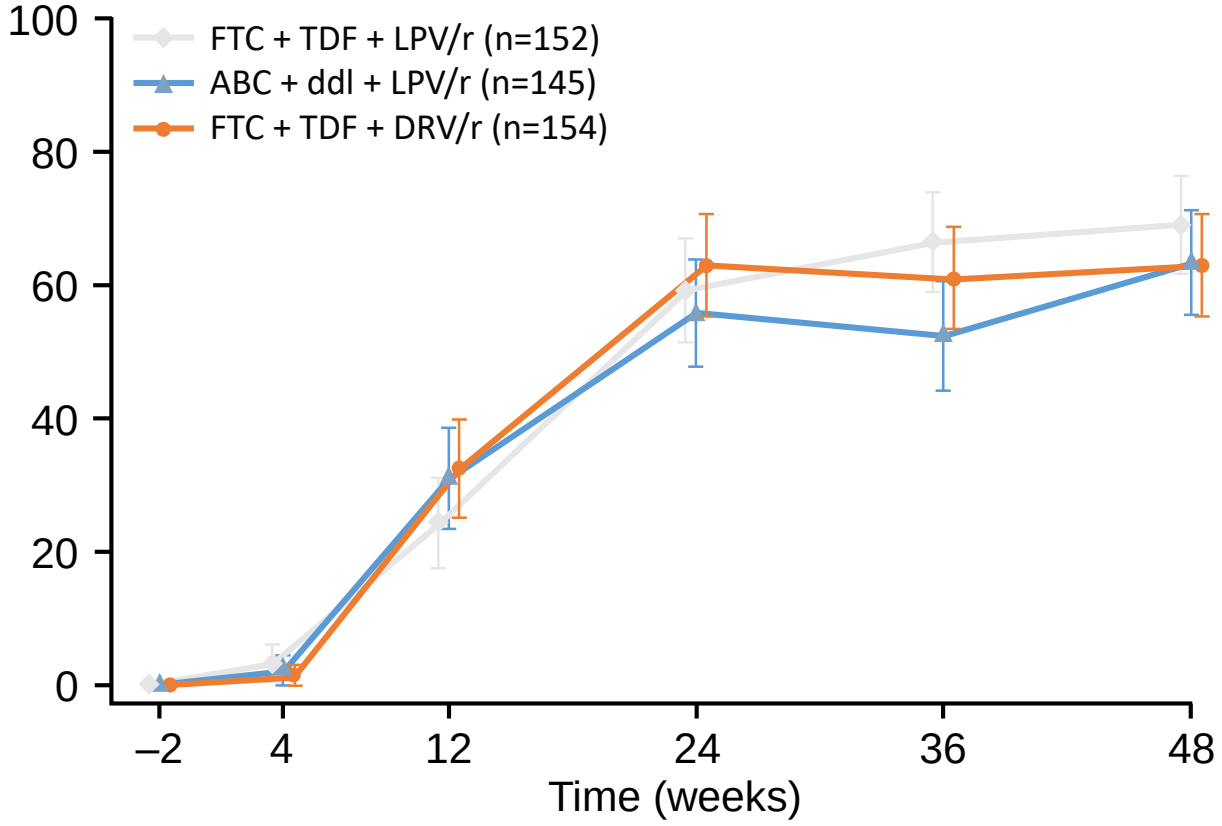
Primary efficacy endpoint:

- HIV-1 RNA <50 c/mL at 48 weeks

(ITT and per protocol; non inferiority margin of 15%)

Koulla-Shiro S, et al. CROI 2014. Poster 541LB

ITT: Proportion in Each Arm of Patients With VL <50 Copies/mL With CI 95%



The 2Lady/ANRS/EDCTP Study: Results

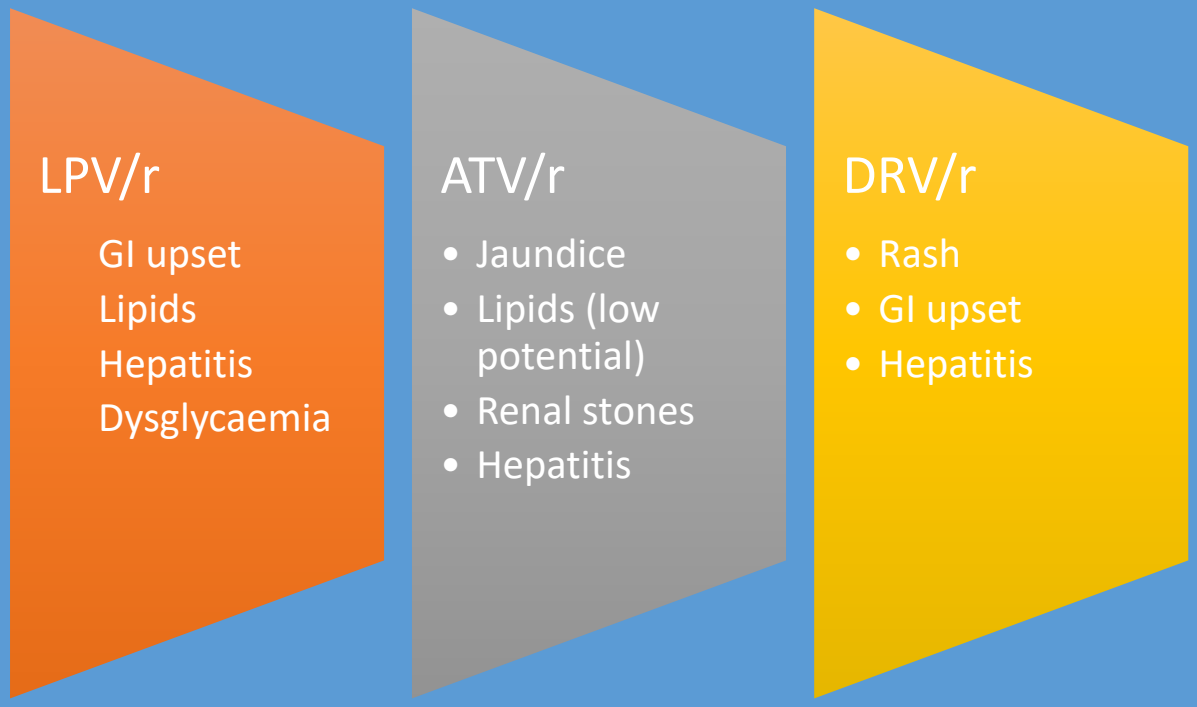
- In multivariate analysis, VL ≤100,000 copies/mL at baseline was an independent predictor of viral suppression
- No difference among arms was observed in:
  - Median CD4 gain (+127 cells/uL)
  - Mortality
  - Severe adverse events
- No protease mutations were observed in patients failing second-line therapy

Conclusions:

- Despite multiple NRTI mutations, PI/b-based second-line regimens showed satisfactory results
- However, results for patients with high VL at switch to second-line are of special concern
- The WHO recommended regimen (LPV/r + 2NRTIs) remains a valid option

Safety issues with PIs and AZT

- AZT associated with gastrointestinal upset, anaemia, long term lipoatrophy, lactic acidosis
- LOTS of tablets twice daily



Safety issues with Pis and AZT

AZT associated with gastrointestinal ups…, long term lipoatrophy, lactic acidosis

Switching to second line is a big deal!

LP…

…patitis

Dysglycaemia

ATV/r

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

DRV/r

- Rash
- GI upset
- Hepatitis

WHO Guidelines – Dec 2015

Options	First-Line	Second-Line
Preferred*	• TDF + 3TC (or FTC) + EFV	• 2 NRTIs + ATV/r or LPV/r
Alternative	• AZT + 3TC + EFV • AZT + 3TC + NVP • TDF + 3TC (or FTC) + NVP	• **2 NRTIs + DRV/r**
	• TDF + 3TC (or FTC) + **DTG**† • TDF + 3TC (or FTC) + **EFV_{400}**†	• **LPV/r + RAL**

NRTI=nucleoside reverse transcriptase inhibitor

*FDC and once-daily regimens preferred

†Safety and efficacy data on use of DTG and EFV400 in pregnant women, people with HIV/TB coinfection is still pending and thus not currently recommended

WHO technical update and 2018 guidelines

Population	First-line regimens	Second-line regimens	Third-line regimens
Adults and adolescents (incl. women of childbearing potential and pregnant women)	**Two NRTIs + DTG**	Two NRTIs + (ATV/r or LPV/r)	DRV/r + DTG + 1–2 NRTIs (if possible, consider optimisation using genotyping)
	~~Two NRTIs + EFV~~	Two NRTIs + DTG	
Children (0–10 years)	**Two NRTIs + DTG**	Two NRTIs + (ATV/r or LPV/r)	
	Two NRTIs + LPV/r	Two NRTIs + DTG	
	~~Two NRTIs + NNRTI~~	Two NRTIs + DTG	

- Guidelines include recommendations on the selection of ARV drugs in response to high levels of DR[1]
  - Recommend countries consider changing their first-line ART regimens away from NNRTIs if levels of NNRTI DR reach 10%

1. http://www.who.int/hiv/pub/arv/arv-2016/en/World Health Organization. HIV treatment interim guidance. Accessed August 2018

SA guidelines (state)

TDF + FTC + EFV

JAIDS Journal of Acquired Immune Deficiency Syndromes Publish Ahead of Print
DOI: 10.1097/QAI.0000000000001883

Third-line antiretroviral therapy programme in the South African public sector: cohort description and virological outcomes

Michelle Moorhouse MBBCh (Wits), DA (SA), FRSPH[1], Gary Maartens, MBChB, MMed[2], Willem Daniel Francois Venter, MBBCh, MMed, FCP (SA), DTM&H, Dip HIV Man (SA)[1]

Darunavir

Dolutegravir

Etravirine

Current recommendations re DRV dosing: SAHCSA

- ATV/r 300/100 mg 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” – now available
- If on PI and VL LDL – switch to 800/100
- DRV/r 600/100 mg bd third-line - switch to 800/100 if no baseline VL

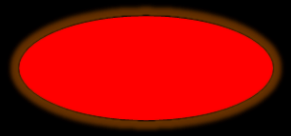
Using DRV/r 800/100 mg in third-line ART

- 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

So why low dose DRV?

- Most drugs titrated against toxicity – THEN think about efficacy (VL) – and dose stopped once they harmonise
- Little impetus to lower dose further
- Lots of examples of dose reduction - AZT, d4T, EFV, ATV
- DRV registration studies mainly in treatment experienced patients
- Lots of excitement in 2012 – ‘’red pill then blue pill’’ – TDF/3TC/EFV400 then DRV/DTG

Pill "A" to Pill "B" – two single tablet regimens?



Pill "A" TDF/3TC/EFV400 $100

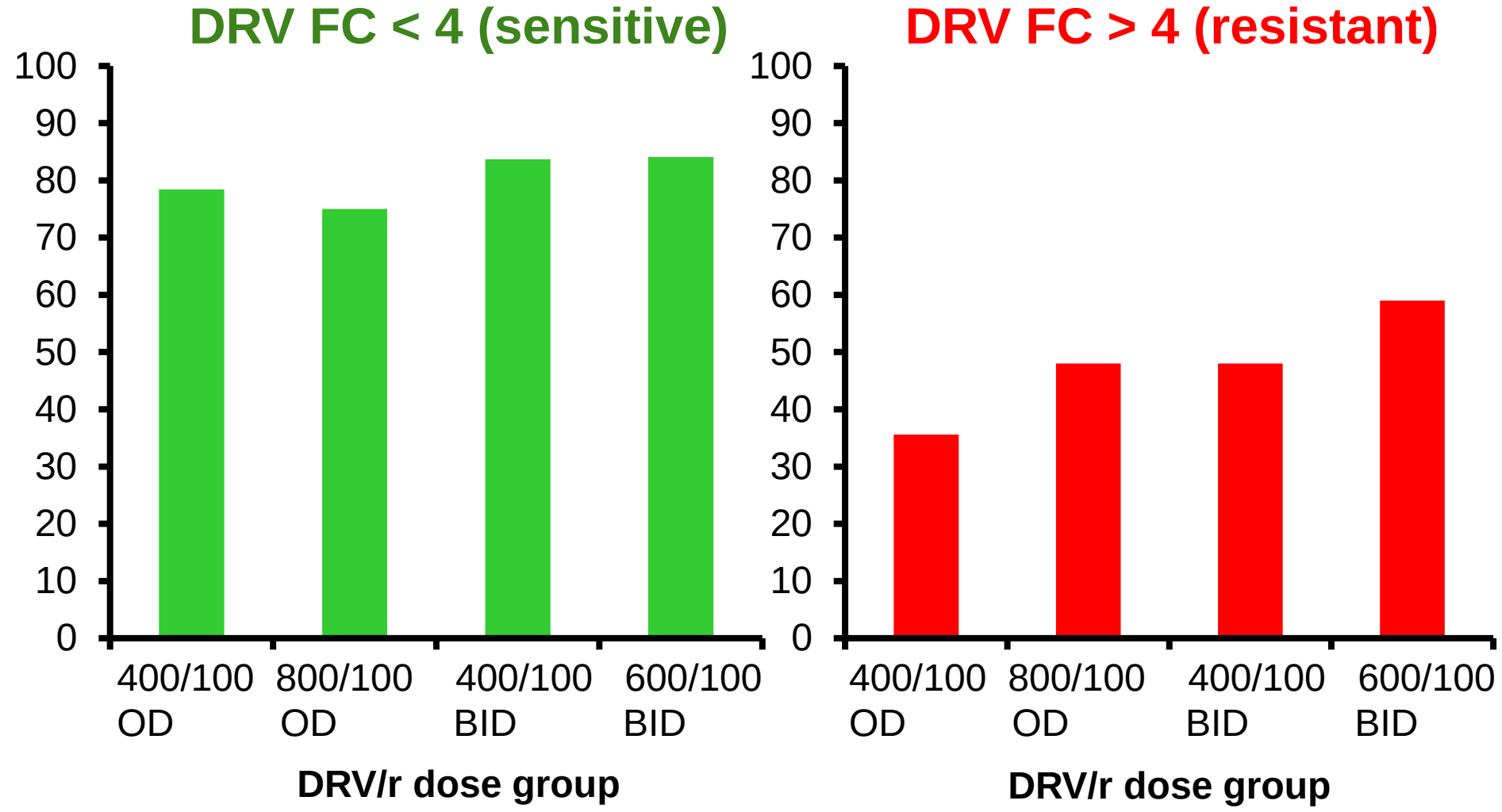
Pill "B" DRV400/r/DTG $250

- Two pills, used in sequence
- Simple treatment rule – task shifting
- No overlapping drug resistance
- Mass generic production
- Low cost: $100 and $250 per person-year

Background

- The approved dose DRV/r is 800/100 mg once daily for PI-naïve patients
- DRV/r is the most highly recommended PI in international treatment guidelines
- However, DRV/r is rarely used in sub-Saharan Africa, because of high treatment costs
- Results from several pilot studies and PK/PD analyses suggest that DRV/r 400/100 mg once daily shows equivalent efficacy to the standard dose
- Therefore the WHRI 052 study was designed to evaluate efficacy and [illegible] of DRV/r 400/100 mg once daily as a switch option

POWER trials: % HIV RNA > 1 log reduction at Week 24, by dose and baseline DRV resistance



Katlama C et al. AIDS 2007, 21: 395-402
Haubrich et al. AIDS 2007, 21: F11-F18

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

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Optimize

Non-inferior efficacy for darunavir/ritonavir 400/100 mg once daily versus lopinavir/ritonavir, for patients with HIV RNA below 50 copies/mL in South Africa: The 48-week WRHI 052 study

Francois Venter[1], Michelle Moorhouse[1], Ellisha Maharaj[1], Godspower Akpomiemie[1], Bryony Simmons[2], Ambar Qavi[2], Celicia Serenata[1], Simiso Sokhela[1], Andrew Hill[3]

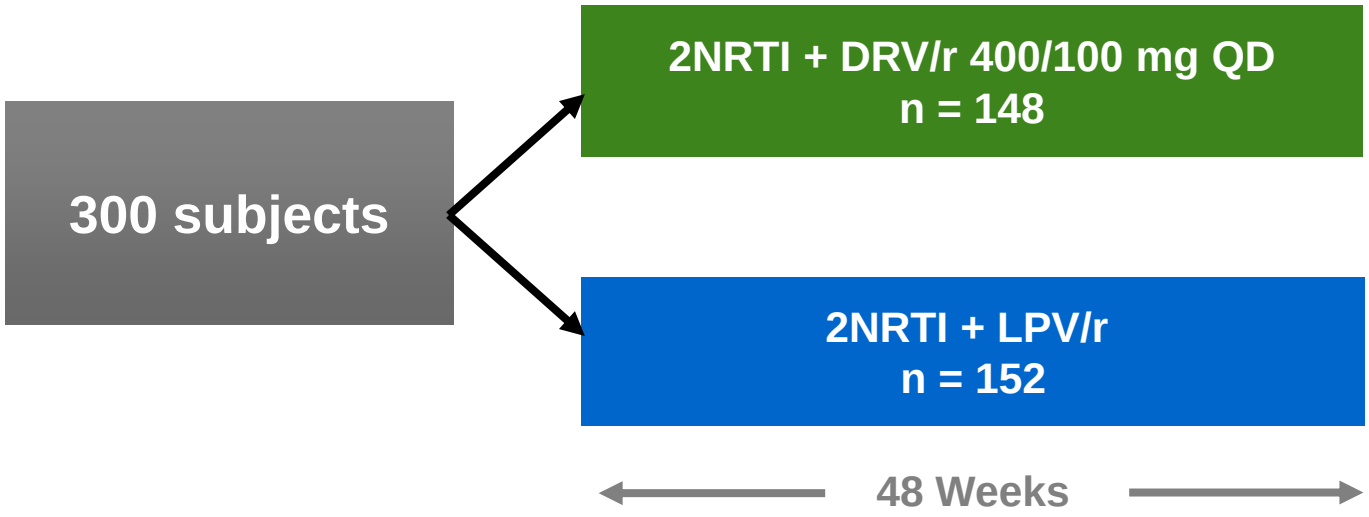
[1]University of Witwatersrand, WITS Reproductive Health and HIV Institute, Johannesburg, South Africa; [2]Imperial College, Faculty of Medicine, London, United Kingdom; [3]Liverpool University, Pharmacology, Liverpool, United Kingdom

22nd International AIDS Conference, Amsterdam, the Netherlands, July 2018
Session B35: Regimen simplification and switch studies [TUAB0107LB]

WRHI 052 study: Trial design

Inclusion criteria:

- On a LPV/r-containing regimen for > 6 months with no history of other PI use
- HIV-1 RNA level < 50 copies/mL in the last 60 days



Open-label, 48 week study in Johannesburg, South Africa
Study visits at Baseline, Week 12, 24, 36 and 48
Resistance testing for samples with HIV RNA > 200 copies/mL on study

Primary efficacy endpoint: HIV RNA analysis

Main efficacy endpoint: FDA SNAPSHOT: Switch equals failure analysis

If a patient shows a confirmed elevation in HIV RNA > 50 copies/mL at Week 48, this is a failure. Change in randomised treatment or missing data is also a failure.

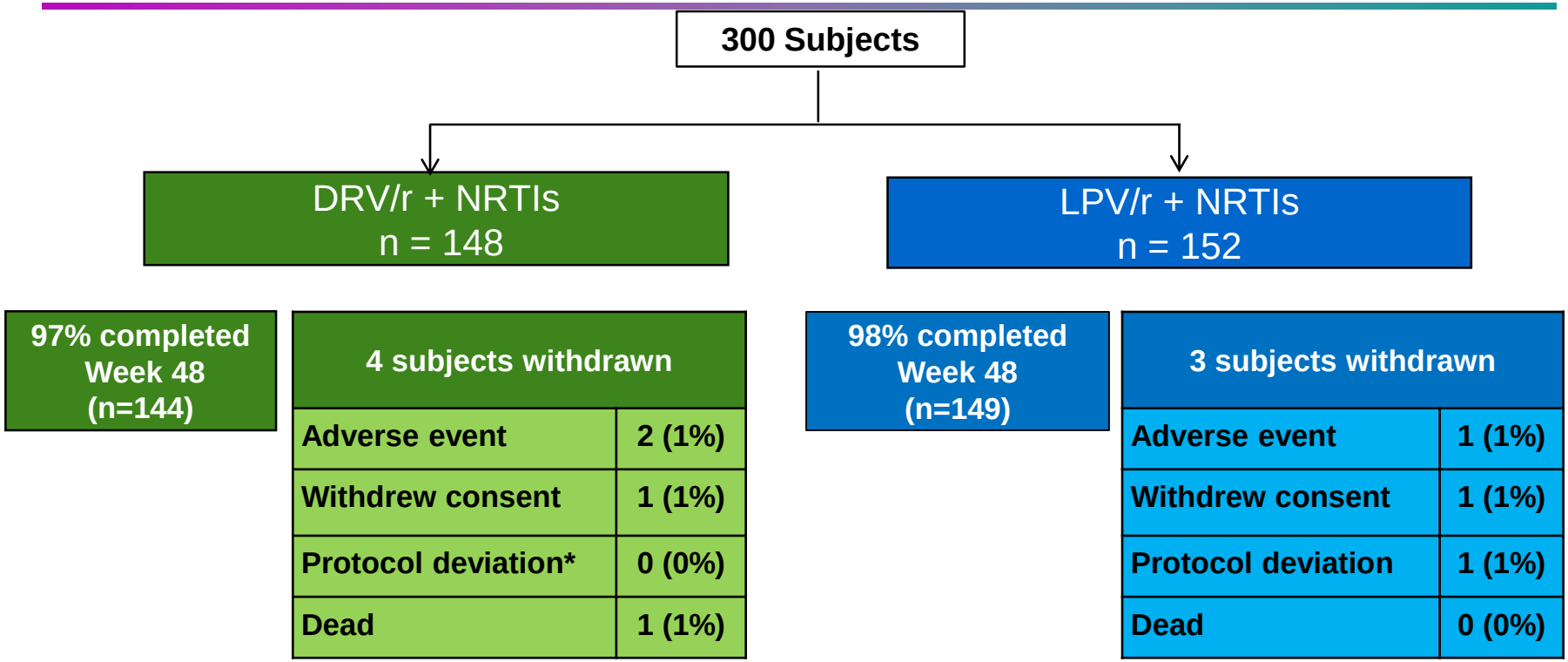
Secondary endpoint: ITT: Switch included analysis

This analysis also includes the HIV RNA levels at Week 48, after changes in treatment. Missing data is failure.

New FDA non-inferiority margin for switch studies = -4%

The trial was originally powered for a -12% NI margin, but the -4% margin was added to the analysis plan after consultation with the trial DSMB.

Study disposition

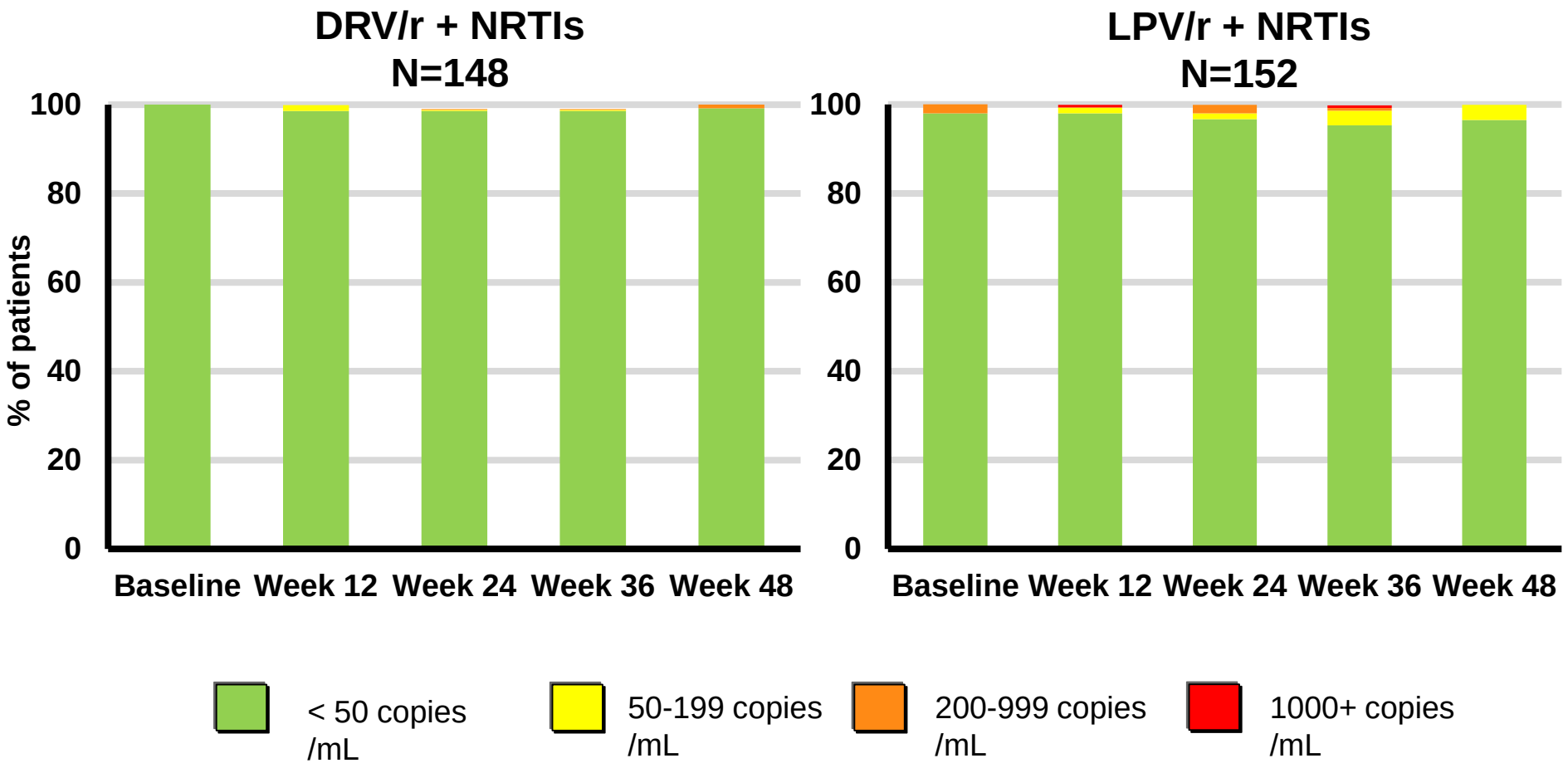


*Protocol deviation in LPV/r arm was due to non-compliance.

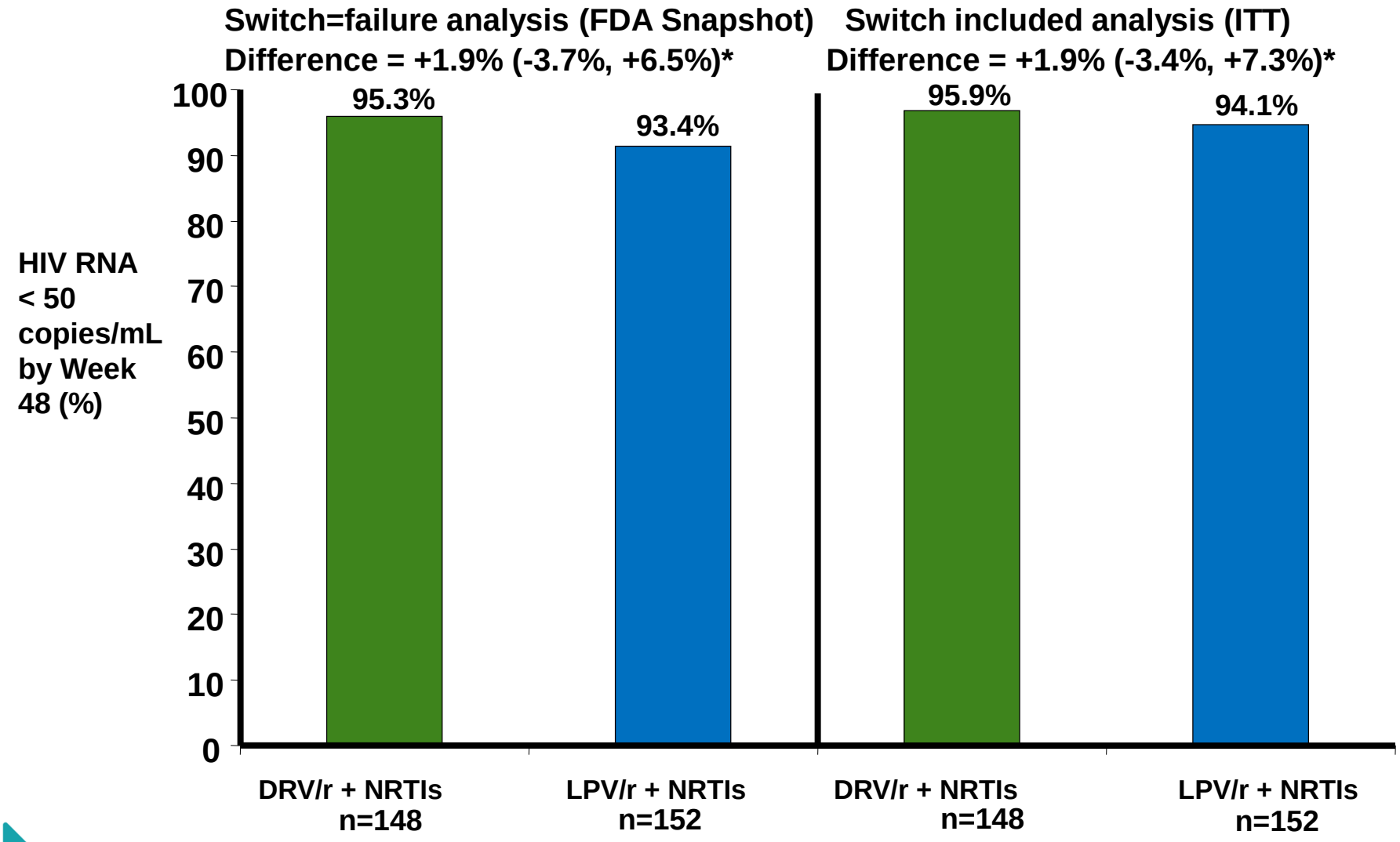
Baseline characteristics (ITT)

	DRV/r + NRTIs (n=148)	LPV/r + NRTIs (n=152)
Age, years (median, years)	42	42
Male (%)	34%	30%
Female (%)	66%	70%
Black (%)	99%	100%
Weight (median, kg)	72	70
BMI (kg/m^2)	26	27
Disease characteristics		
HIV-1 RNA < 50 copies/mL (%)	100%	98%
Mean CD4+ cell count (cells/uL)	623	646

HIV RNA by study visit (observed data)



HIV RNA < 50 copies/mL at Week 48
FDA Snapshot and ITT population



* 95% confidence intervals from univariate analysis

Drug resistance

Genotypic resistance tests on samples with HIV RNA > 200 copies/mL at any visit to Week 48

Resistance analysis	DRV/r +NRTIs (n=4)	LPV/r + NRTIs (n=6)
No PI or NRTI mutations	**3**	**2**
PI	**0**	**0**
NRTI	**1**	**4***
M184V	1	3
K219E	0	1
K65R	0	1
Y115E	0	1
K70R	0	1

***NRTI mutations may have been archived from prior virological failure on first-line treatment**

Summary of adverse events

	DRV/r + NRTIs (n=148)	LPV/r +NRTIs (n=152)
Any adverse event, n (%)	100 (68)	106 (70)
Most common AEs (≥ 4% in either arm)		
Respiratory tract infection	31 (21)	34 (22)
Influenza	14 (9)	13 (9)
Rash	3 (2)	11 (7)
Elevated ALT	8 (5)	5 (3)
Headache	6 (4)	5 (3)
Backache	3 (2)	8 (5)
Hypertension	6 (4)	3 (2)
Transaminitis	7 (5)	2 (1)
Constipation	6 (4)	2 (1)
Drug-related AE	30 (20)	8 (5)
Serious AEs	6 (4)	3 (2)
Drug-related serious AEs**	3 (2)	0 (0)
AEs leading to withdrawal	2 (1)	0 (0)

***1 Patient died from MI after week 12. ** DRV arm: all LFT elevations, 2 led to withdrawal**

Treatment emergent grade 3 or 4 laboratory abnormalities

	DRV/r Grade 3 or 4	LPV/r Grade 3 or 4
Haematology, n (%)		
Haemoglobin	1 (1)	1 (1)
Clinical Chemistry, n (%)		
ALT	3 (2)	0 (0)
AST	3 (2)	0 (0)
LDL	6 (4)	4 (3)
Creatinine, serum	1 (1)	0 (0)
Creatinine clearance	3 (2)	2 (1)

Conclusions

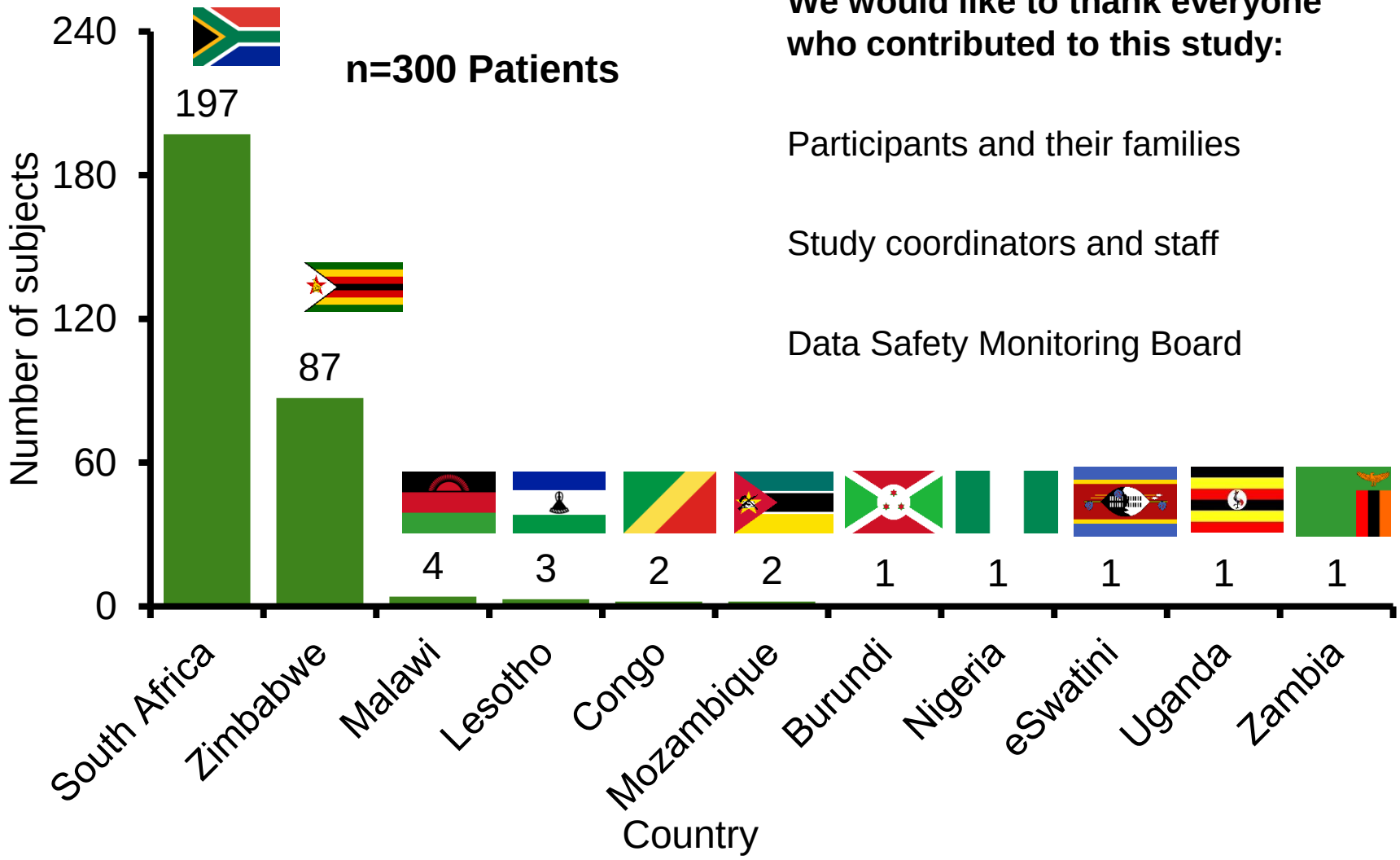
In this 300 patient study, DRV/r at the lower dose of 400/100 mg once daily showed non-inferior efficacy to LPV/r as a switch option for patients with HIV RNA < 50 copies/mL

These results are consistent with pilot studies of low-dose DRV/r, which showed no difference in efficacy versus standard 800/100 mg once daily dosing for PI-naïve patients.

A lower dose of DRV/r would be better tolerated and cheaper to produce than the standard 800/100 mg dose, LPV/r or ATV/r.

This result needs to be confirmed in new studies where DRV/r 400/100 mg once daily is used in PI naïve patients – for example after failure of first-line treatment

Nationality of participants



We would like to thank everyone who contributed to this study:

Participants and their families

Study coordinators and staff

Data Safety Monitoring Board

Thank you…

- South African Medical Research Council and USAID for funding
- South African Department of Health
- OPTIMIZE Consortium, especially Andrew Hill and colleagues, Wits RHI staff and Clinton Health Access Initiative (CHAI)
- Scientific Advisory Committee

Now what?

- Article under review
- BUT: No manufacturer – J&J make product - ?role of WHO
- ?role of DTG