Pretreatment drug resistance and new treatment paradigms in first-line ART

Michelle Moorhouse

25 October 2018

SAHCS 2018

University of the Witwatersrand
WITS RHI

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

Disclosures/disclaimers

- 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

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

saMRC advancinglife

Unitaid

Factors influencing drug resistance

Drug toxicities

Social / personal issues

Poor adherence

Lack of API, drug supply and delivery

Lack of continuous support and monitoring

Drug stockouts

Increasingly stretched healthcare systems

Interruption of treatment

Poor potency

Adding 1 drug to failing regimen

Insufficient drug level

Prolonging a failing regimen

Treatment with < 3 drugs

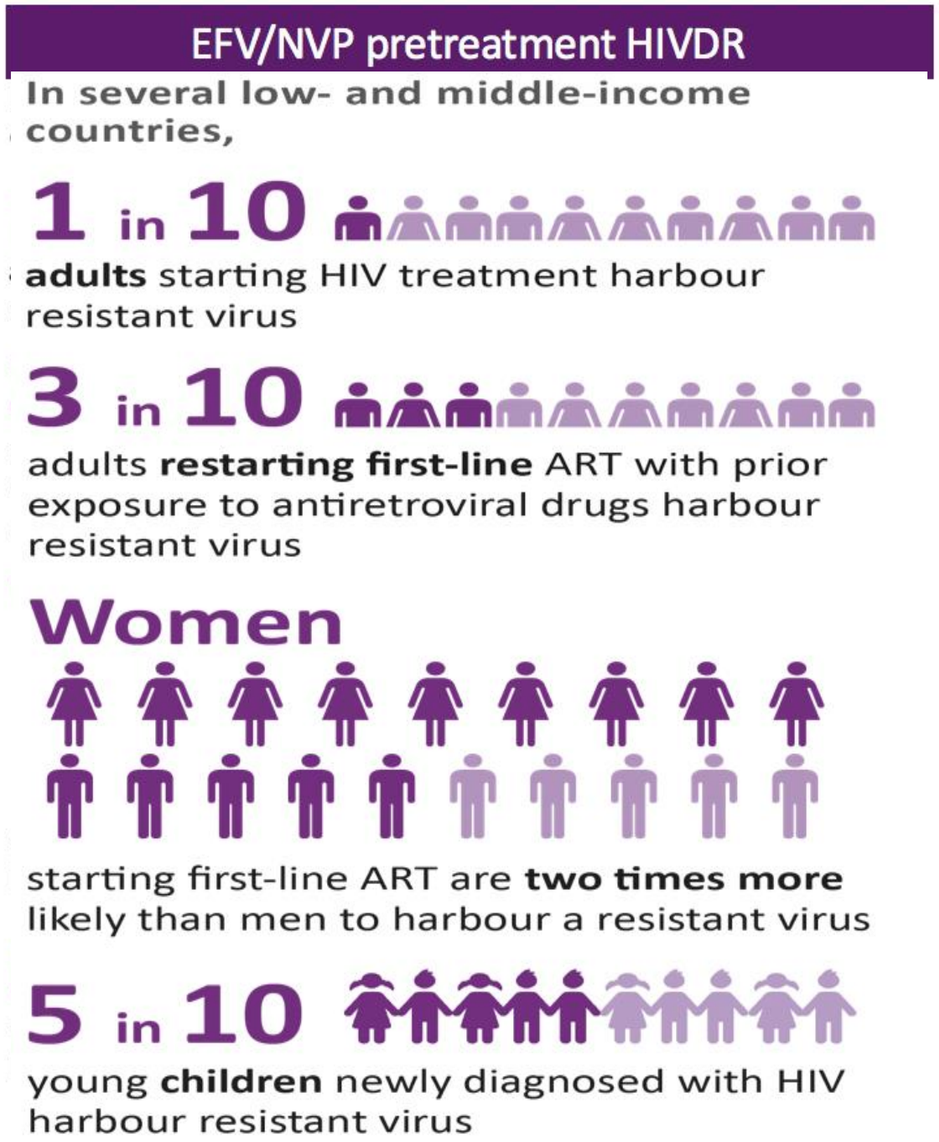
Inappropriate drug selection

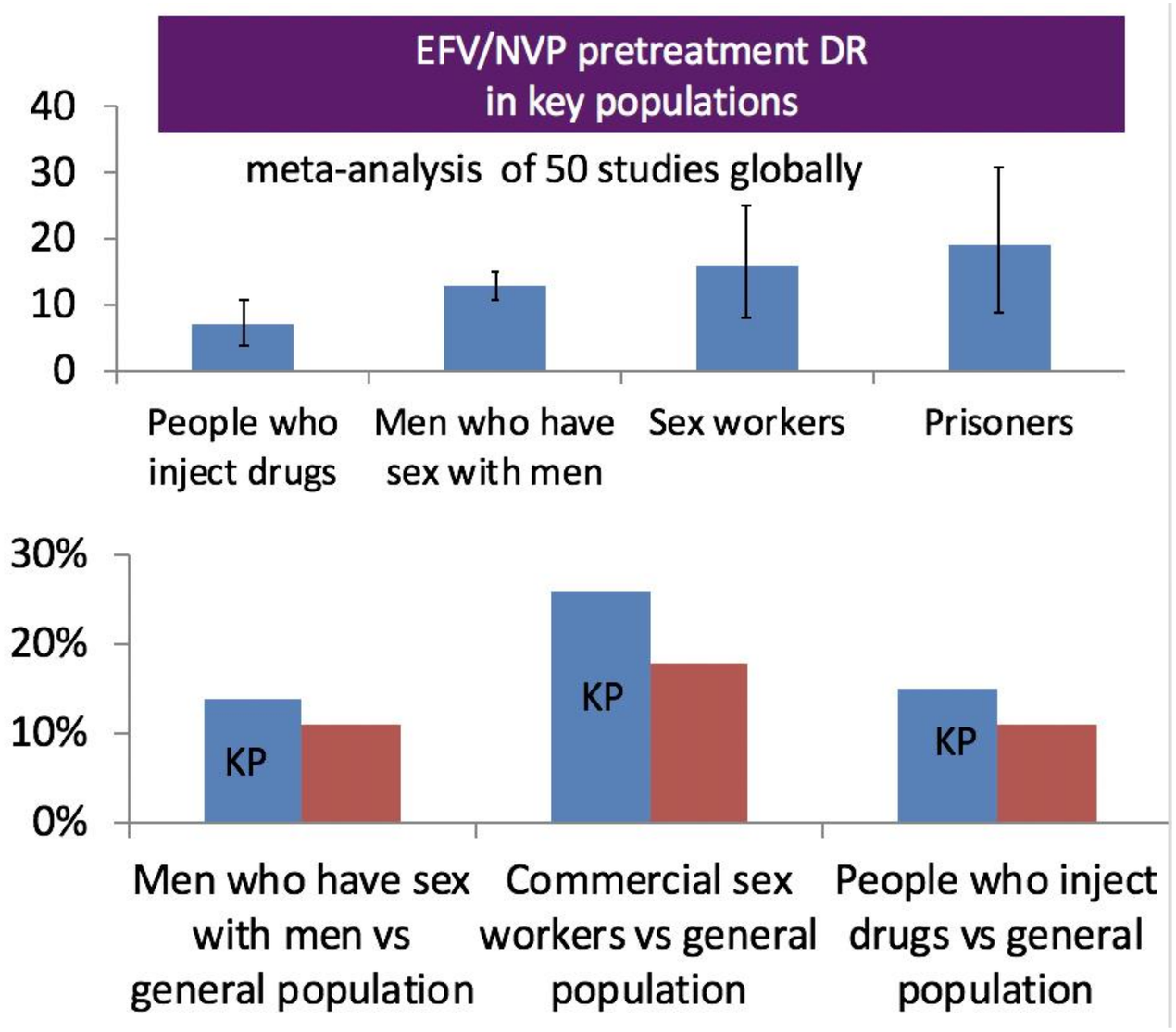
Viral replication in the presence of drug

HIV DR

TDR = transmitted drug resistance

Levels of pretreatment HIVDR (PDR)





Thanks: Silvia B (WHO)

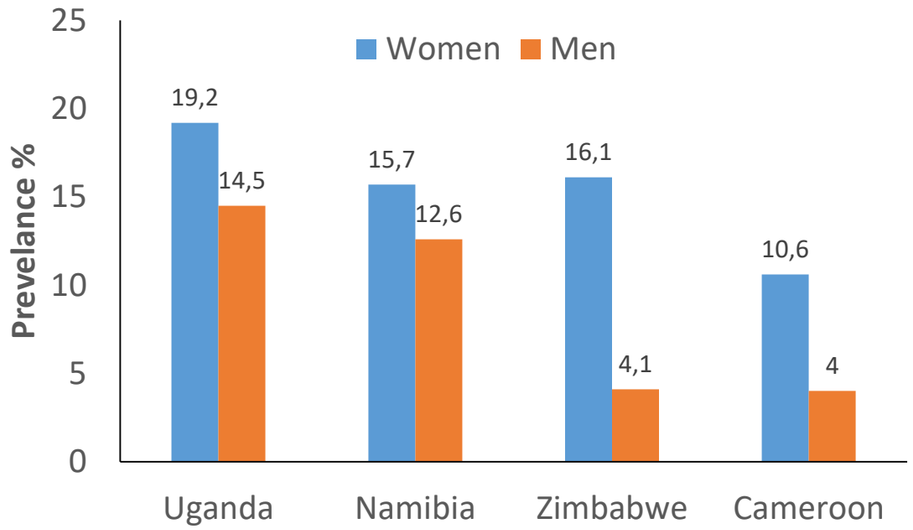
Pretreatment NNRTI drug resistance in special populations

- In children < 18 months, NNRTI resistance = **63.7%** (95% CI: 59.0–68.4) (single study, South Africa, 2014–16)

- In children 0–18 years starting ART, NNRTI resistance = **49.3%** (range 7.5–100%) (meta-analysis, 2014–17)
  - Particularly in PMTCT-exposed children (4/7 studies found > 50% of PMTCT-exposed children had NNRTI DR)

- Prevalence of any TDR and NNRTI resistance is higher among women than men in the majority of surveys

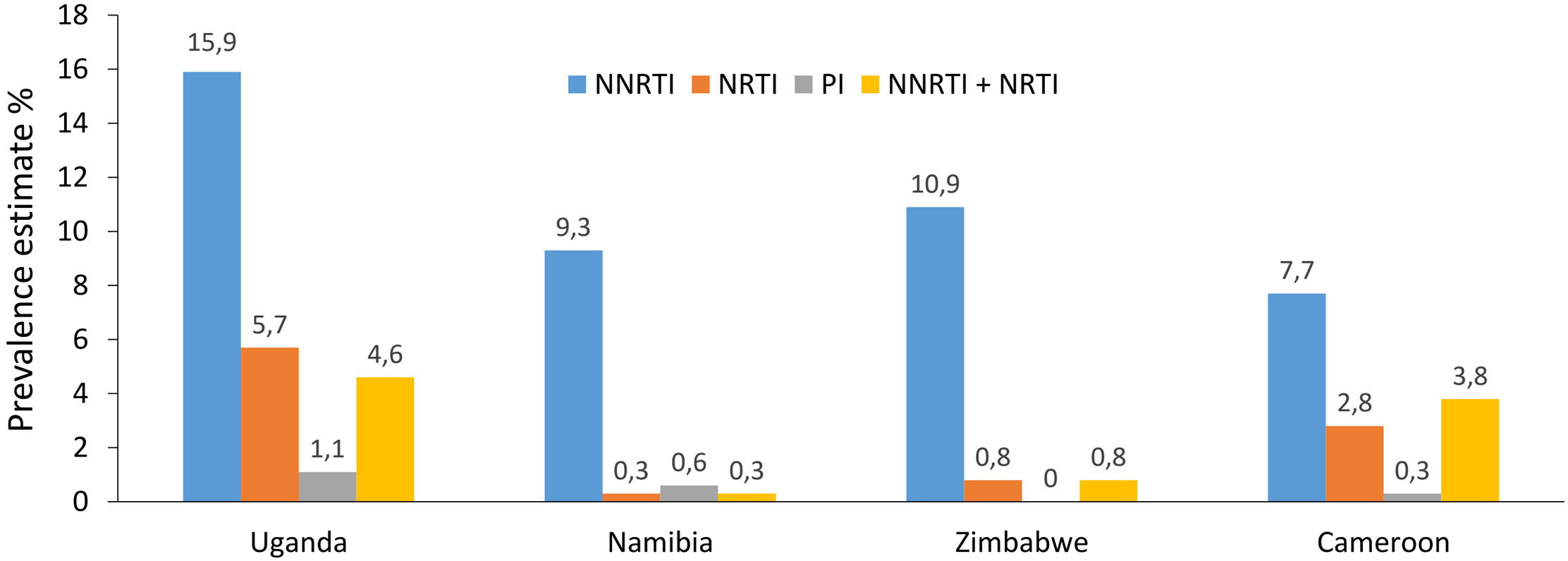
Prevalence estimates of pretreatment HIV DR



WHO. HIV drug resistance report 2017; http://apps.who.int/iris/bitstream/handle/10665/255896/9789241512831-eng.pdf

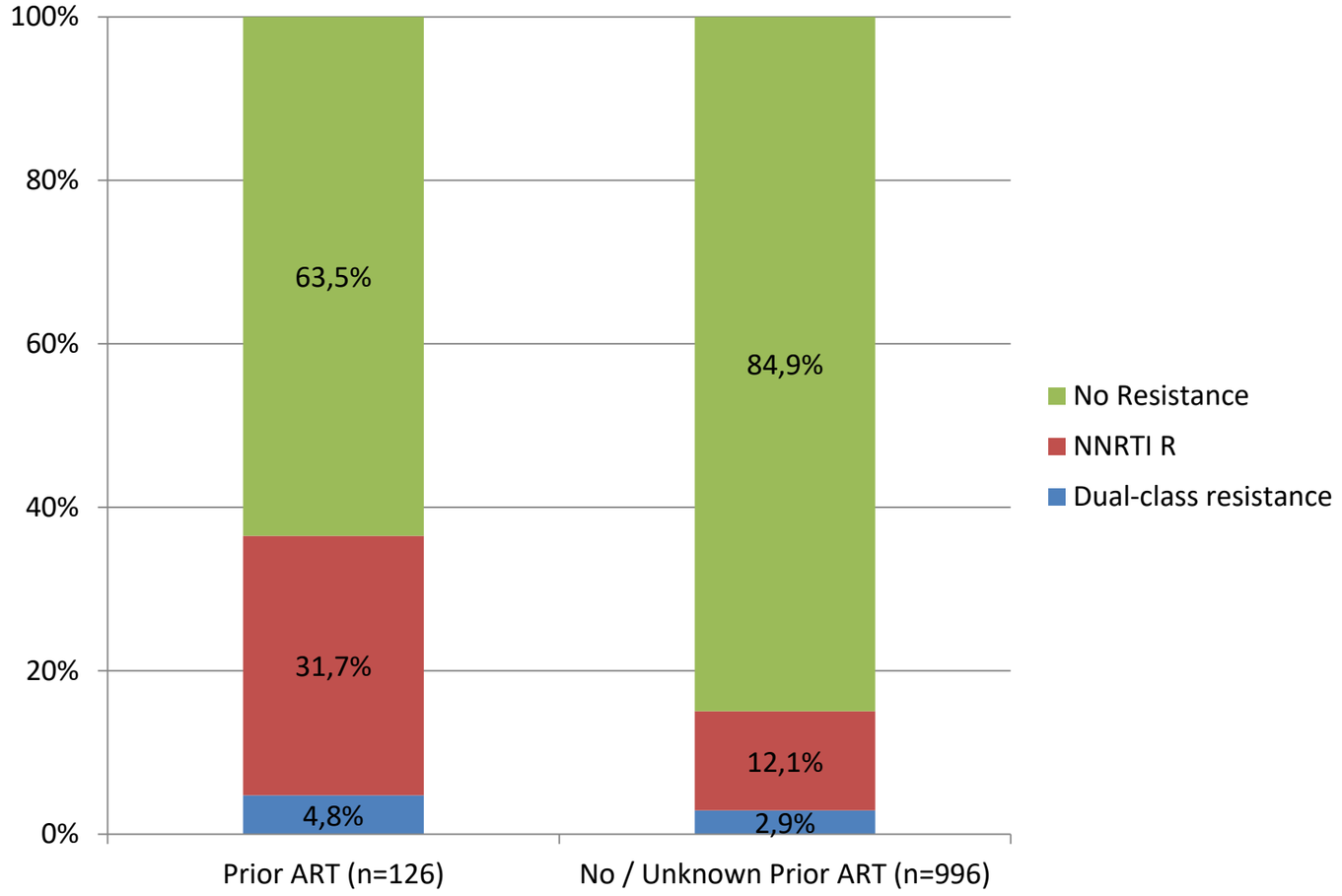
PDR in treatment-naïve patients in selected countries

- Most pretreatment DR is **NNRTI resistance**



WHO. HIV drug resistance report 2017; http://apps.who.int/iris/bitstream/handle/10665/255896/9789241512831-eng.pdf

NNRTI and dual-class resistance detected amongst patients enrolled according to prior ART exposure (SA)



HIVDR:
37% in ART starters with prior exposure to ARVs

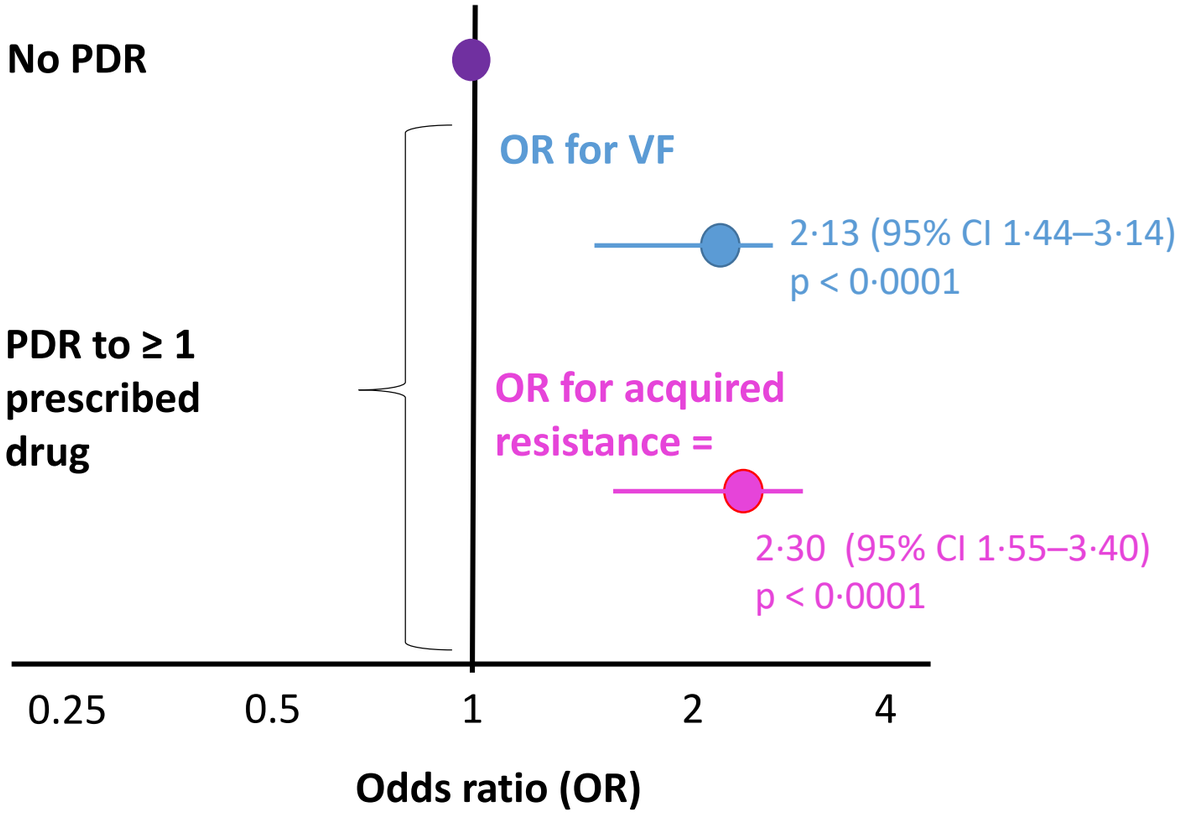
15% in ARV-naive

Hunt et al 2017

Magnitude of effect of PDR on long-term virological outcomes

- Cohort data 2007–09; 6 countries in sub-Saharan Africa[1]
- PDR results available for 2579 patients
  - 2404 (93%) had no pretreatment DR
  - 123 (5%) had PDR to ≥ 1 prescribed drug
  - 52 (2%) had PDR and received fully active ART
- **CD4+ count** increased less in patients with PDR than in those without (△ 35 cells/μL at 12 months; 95% CI 13–58; p = 0·002)

- A separate retrospective study of 801 HIV-1-infected ARV-naive patients from 2001–09
  - Presence of transmitted NNRTI resistance → 1.5-fold increased risk for treatment failure in the first 48 weeks after ART initiation[2]

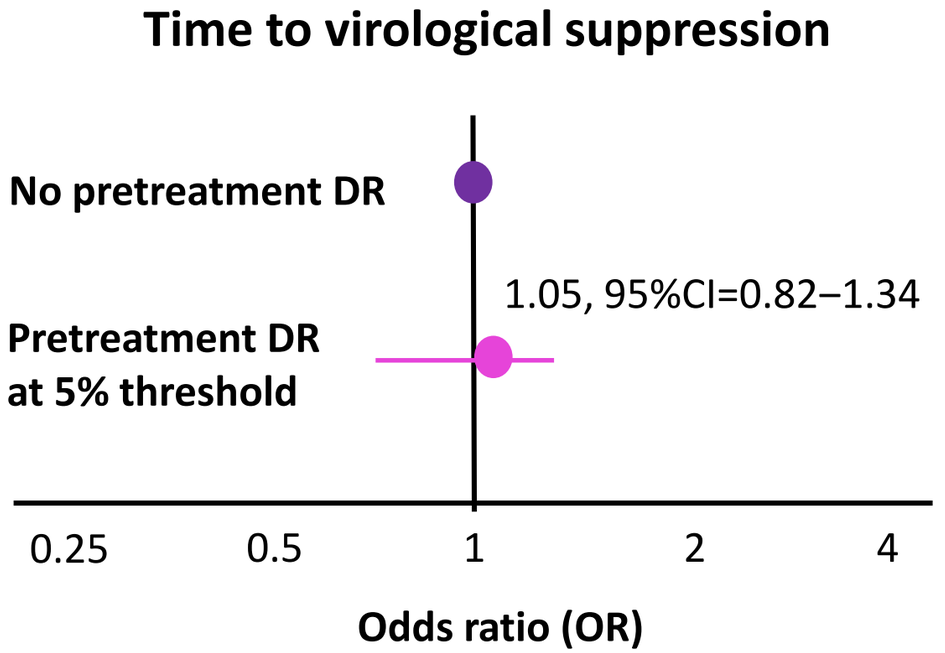


1. Hamers RL et al, Lancet Infect Dis. 2012;12:307–17 2. Taniguchi T et al. AIDS Res Hum Retroviruses 2012; 28:259-264
VF = virologic failure

More recently

- 1 148 HIV-positive treatment-naïve patients enrolled in trial clinics in rural KwaZulu-Natal
- Pretreatment drug resistance prevalence was **9.5%** (109/1,148) at 20% interval and **12.8%** (147/1,148) and 5% thresholds
- Median of 1.36 years (IQR 0.91-2.13), mostly on TDF/FTC/EFV

No difference between those with only NNRTI PDR vs. no PDR at the **5%** threshold



Derache A et al, Clin Infect Dis. 2018 Oct 15. doi: 10.1093/cid/ciy881

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

WHO technical update and 2018 guidelines

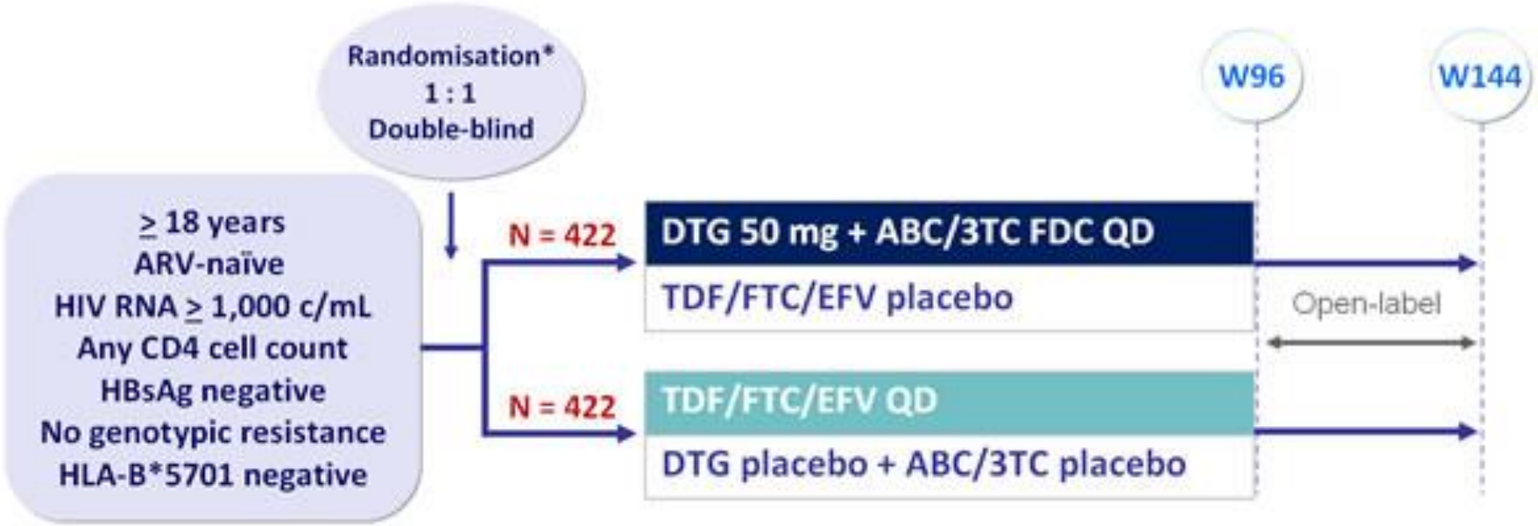
Population	First-line regimens	Second-line regimens	Third-line regimens
Adults and adolescents (incl. women of childbearing potential and pregnant women)	**Two NRTIs + DTG**	Two NRTIs + (ATV/r or LPV/r)	DRV/r + DTG + 1–2 NRTIs (if possible, consider optimisation using genotyping)
	~~Two NRTIs + EFV~~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

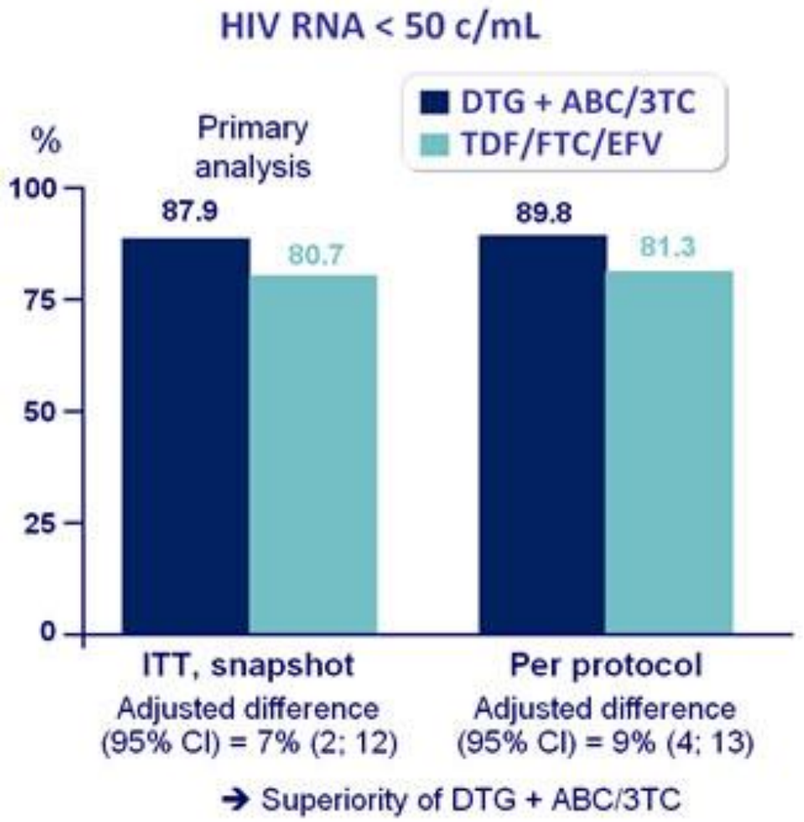
1. http://www.who.int/hiv/pub/arv/arv-2016/en/World Health Organization. HIV treatment interim guidance. Accessed August 2018

SINGLE: ABC/3TC/DTG vs TDF/FTC/EFV

Study design



48 Week efficacy results



Primary objective

- Non inferiority of DTG at W48: % HIV RNA < 50 copies/mL by ITT, snapshot analysis (1-sided significance level of 2.5%, lower margin of the 95% CI for the difference = -10%, 90% power)

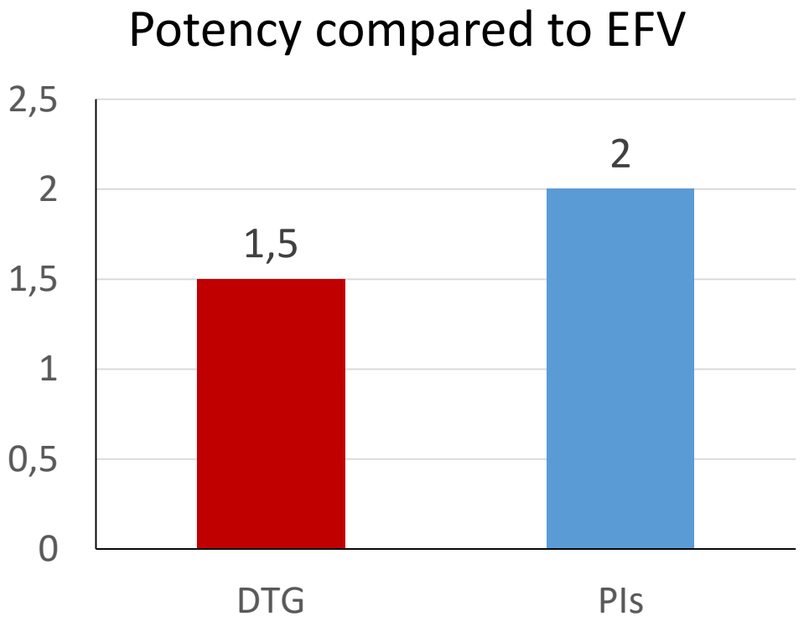
Conclusions

- Virologic superiority of DTG + ABC/3TC over TDF/FTC/EFV was confirmed at Weeks 96 and 144

Walmsley SL, N Engl J Med. 2013 Nov 7;369(19):1807-18;
Walmsley SL, JAIDS 2015; 70:515-9; Walmsley SL, ICAAC 2012. Abs.H556b;
Pappa K, ICAAC 2014, Abs. H-647a; Tebas P, AIDS 2015; 29:2459-64

DTG in first-line treatment when NNRTI DR is prevalent

- Rate of HIV DR acquisition of DTG at a similar level to that of ATV/r
- DTG generally found to be associated with lower risk of toxicity than both EFV and PIs
  - Risk of neurological toxicity is half that of EFV → reduced risk of toxicity → less discontinuation

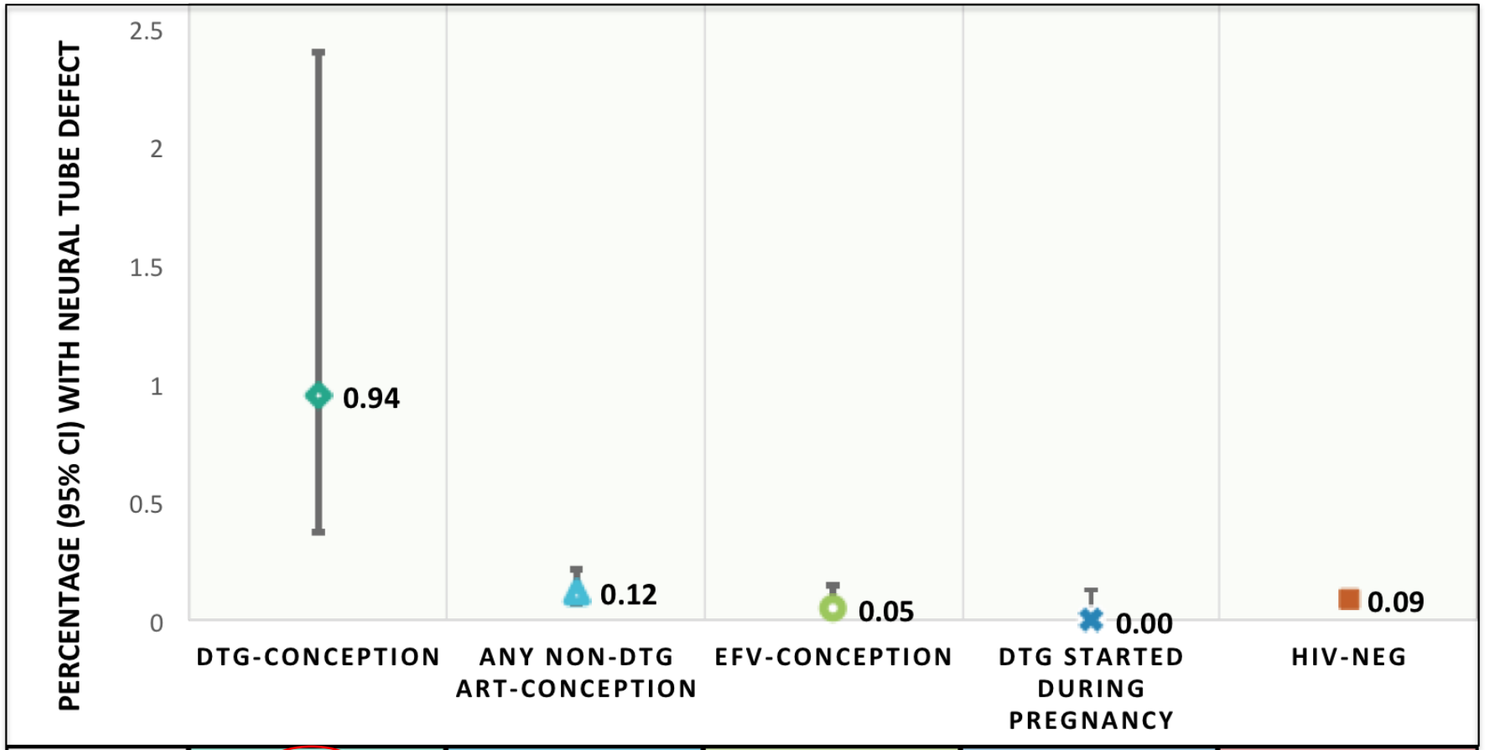


Countries in sub-Saharan Africa with **substantial prevalence of NNRTI drug resistance** in ART initiators should transition from EFV to DTG in first-line ART regimens

Phillips A et al, Lancet HIV 2017; 5: e146–54

Dolutegravir NTD signal

Tsepamo study, Botswana



NTDs/Exposures	4/426	14/11,300	3/5,787	0/2.812	61/66,057
% with NTD (95% CI)	0.94% (0.37%, 2.4%)	0.12% (0.07%, 0.21%)	0.05% (0.02%, 0.15%)	0.00% (0.00%, 0.13%)	0.09% (0.07%, 0.12%)
Prevalence Difference (95% CI)	ref	**-0.82% (-0.24%, -2.3%)**	**-0.89% (-0.31%,- 2.3%)**	**-0.94% (-0.35%, -2.4%)**	**-0.85% (-0.27%, -2.3%)**

Neural tube defects in 4/426 pregnancies **(0.94%)**

Updated data since 01 May 2018: 4/596 **(0.67%)**

95% CI still does not overlap with other groups

Zash, TUSY15

Guidance on the use of DTG in women

Approach to use of DTG across different guideline making bodies

ART history	Clinical scenarios	DHHS	BHIVA	WHO
ART-naive or using a non-DTG containing regimen	Early pregnancy*			
	Late pregnancy			
	Childbearing age potential, not using contraception			
	Childbearing age potential, using effective/consistent contraception			
On DTG containing regimen	Early pregnancy*			
	Late pregnancy			
	Childbearing age potential, not using contraception			
	Childbearing age potential, using effective/consistent contraception			

* The definition of early pregnancy period varies in different guidelines.
DHHS: < 8 weeks from LMP; BHIVA : 1st trimester; WHO: < up to 8 weeks from conception.

Do not initiate DTG/ switch to other effective options

Initiate /continue to DTG or switch to other effective options

Initiate/ switch to DTG

WHO 2018; https://www.bhiva.org/BHIVA-statement-on-Dolutegravir; https://aidsinfo.nih.gov/news/2109/recommendations-regarding-the-use-of-dolutegravir-in-adults-and-adolescents-with-hiv-who-are-pregnant-or-of-child-bearing-potential

Safety and Efficacy of DTG and EFV600 in first-line ART
(summary 2018 WHO Systematic Review and NMA)

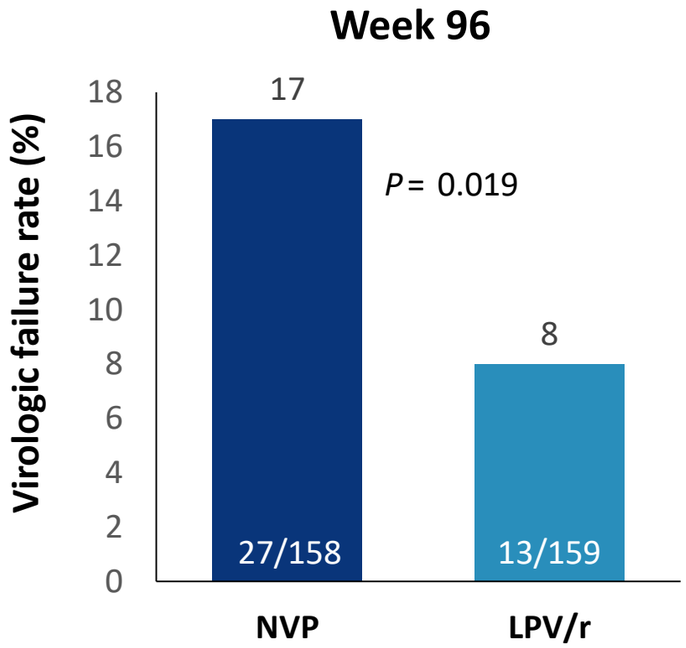
Major outcomes	DTG vs EFV_{600}	QUALITY OF EVIDENCE
Viral suppression (96 weeks)	DTG better	moderate
Treatment discontinuation	DTG better	high
CD4+ recovery (96 weeks)	DTG better	moderate
Mortality	comparable	low
AIDS progression	comparable	low
SAE	comparable	low

Reference: Steve Kanters, For WHO ARV GDG, 16-18 May 2018

LPV/r in first-line treatment when NNRTI DR is prevalent

425 treatment-naive adults patients randomised

- **NVP + TDF/FTC or ZDV/3TC**
- **LPV/r + TDF/FTC or ZDV/3TC**



- At baseline, major DRMs were found in 3/27 NVP-failing patients and in 0/13 patients who failed in the LPV/r group

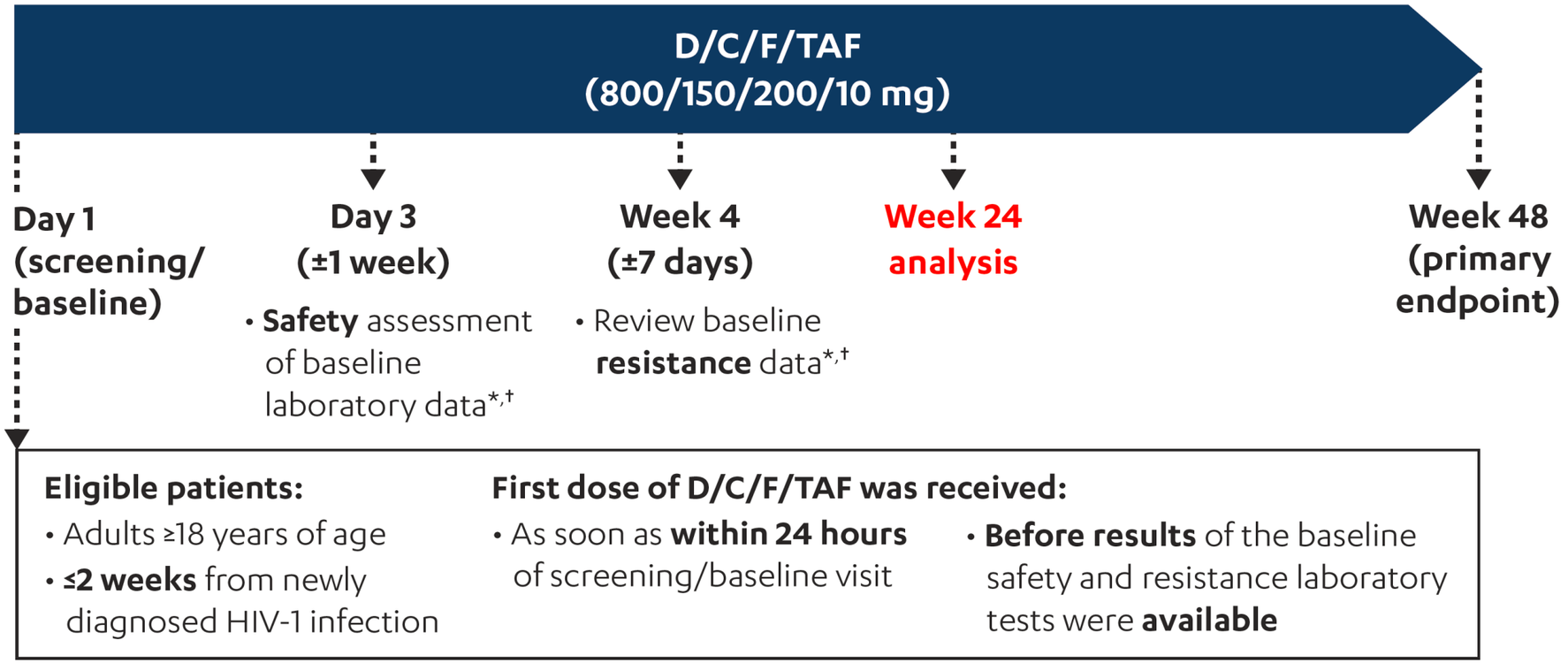
In RLS, LPV/r-based regimen was associated with significantly **fewer virologic failures** and **resistance mutations**

- Additionally, high levels of NNRTI resistance observed in children in South Africa and Togo support WHO's 2013 recommendation that all children < 3 years be started on **LPV/r-based regimens**, irrespective of PMTCT exposure[1]

Clumeck N et al, AIDS. 2014; 28: 1143–53 1. WHO. HIV drug resistance report 2017; http://apps.who.int/iris/bitstream/handle/10665/255896/9789241512831-eng.pdf

DIAMOND: Study design

- DIAMOND is an ongoing, phase 3, single-arm, open-label, prospective, multicentre study evaluating DRV/Cobi/FTC/TAF in a rapid initiation model of care over 48 weeks
- Objective: Assess efficacy and safety of DRV/Cobi/FTC/TAF in a rapid initiation model of care in newly diagnosed, HIV-1–infected, treatment-naive patients; **baseline viral resistance in the study population**

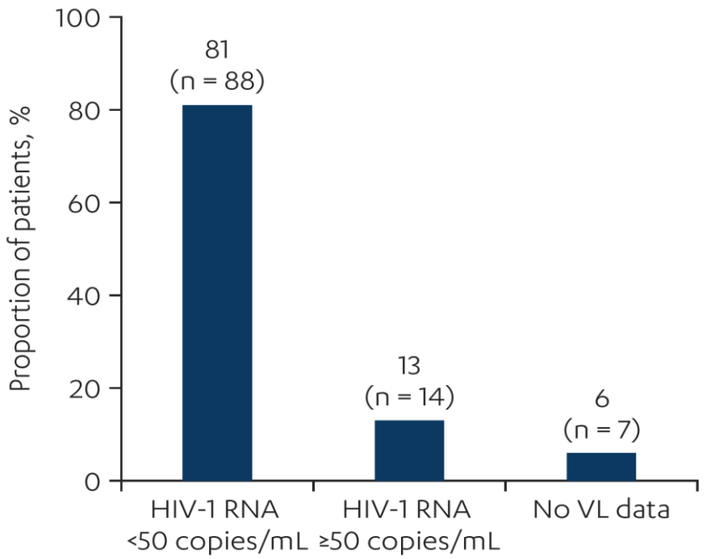


*Evaluations could be performed sooner based on the availability of results; †Interim analyses were performed once all patients had been assessed for safety at Day 3 and resistance at Week 4, and were updated when all patients continuing treatment reached Week 24

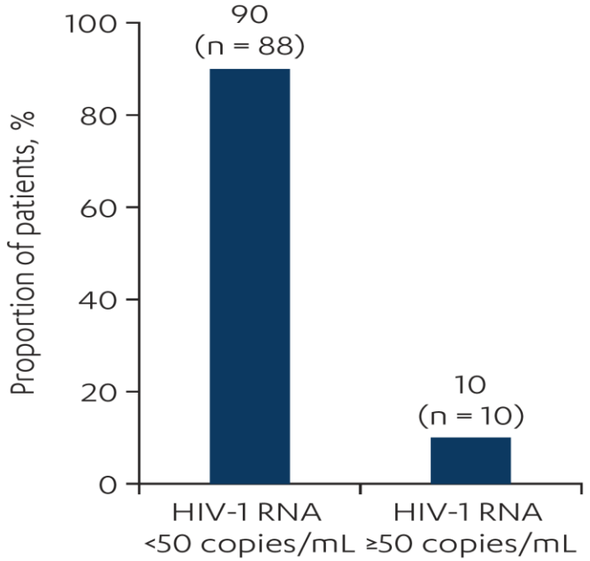
NCT03227861 Huhn G et al. IAC Congress 2018; Poster WEPEC200

DIAMOND: Week 24 efficacy

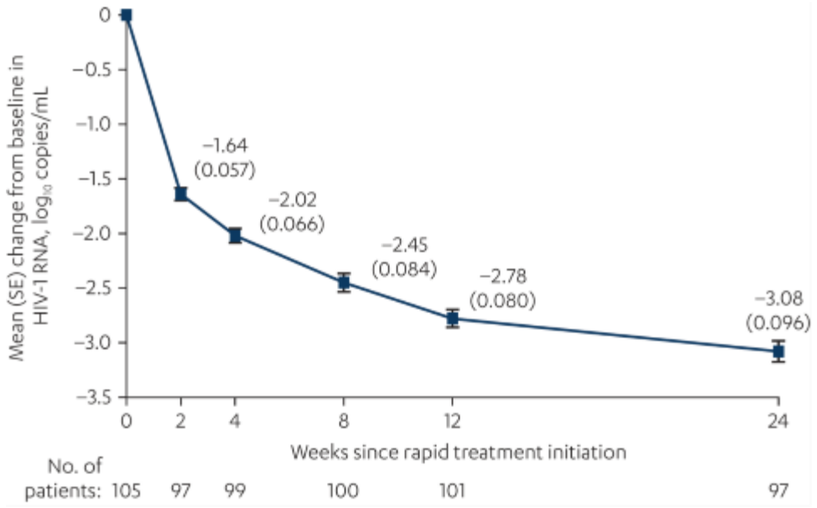
FDA Snapshot (N=109)



Observed (n=98)



Week 24: Change from baseline in log_{10} HIV-1 RNA (Observed)



- 91% (99/109) of patients continued treatment through Week 24 – No patients discontinued due to receipt of baseline resistance and only 3 discontinued due to safety stopping rules
  - No patients discontinued due to lack of efficacy and no patients had protocol-defined virologic failure; there was only 1 discontinuation due to an AE

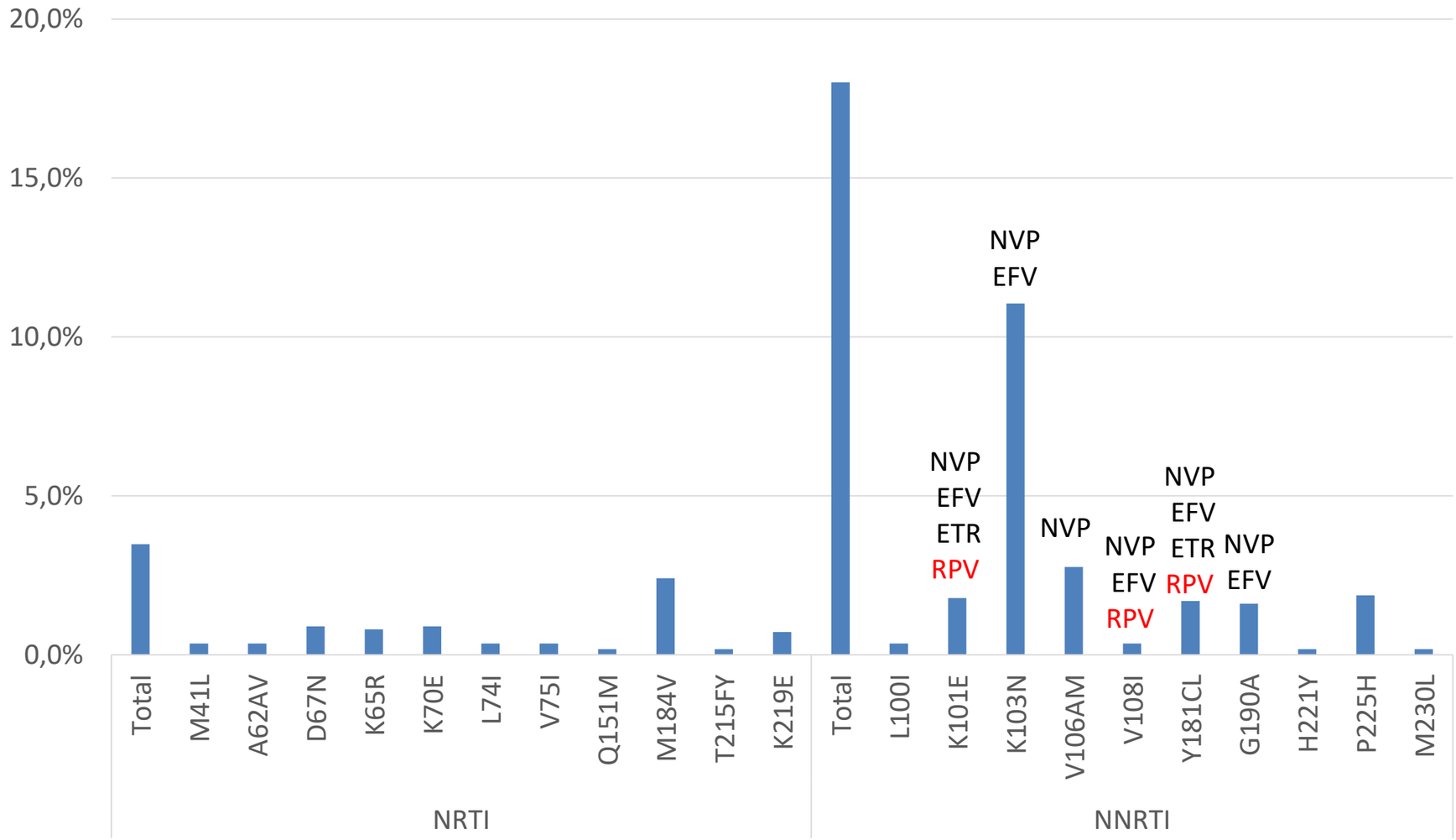
- Mean HIV-1 RNA decreased from baseline to Week 24 by 3.08 log_{10} copies/mL
- Mean ± SE CD4 count was 413 ± 24 at baseline and 589± 30 cells/mm^3 at Week 24

These findings, together with the demonstrated **efficacy, high barrier to resistance, safety profile, and convenience** of the DRV/Cobi/FTC/TAF single-tablet regimen, suggest that D/C/F/TAF should be considered a recommended treatment option in a rapid initiation model of care

Huhn G et al. IAC Congress 2018; Poster WEPEC200

Most prevalent HIVDR mutations contributing to PDR in South Africa

- Pretreatment HIVDR: 17.5%
- 13.9% had NNRTI resistance
- 3.1% of participants had NNRTI and NRTI resistance
- 0.5% are resistant to NRTI
- Three participants harboured single major PI mutations (I54V, I84V)



Hunt et al 2017

Rilpivirine? – active against K103N

- Successful switch to RPV/TDF/FTC in HIV-1-infected patients with an isolated K103N mutation acquired during prior NNRTI therapy

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	None
NNRTI Resistance Mutations:	**K103N**
Other Mutations:	None

Nucleoside RTI		Non-Nucleoside RTI	
lamivudine (3TC)	Susceptible	**efavirenz (EFV)**	High-level resistance
abacavir (ABC)	Susceptible	**etravirine (ETR)**	Susceptible
zidovudine (AZT)	Susceptible	**nevirapine (NVP)**	High-level resistance
stavudine (D4T)	Susceptible	**rilpivirine (RPV)**	Susceptible
didanosine (DDI)	Susceptible		
emtricitabine (FTC)	Susceptible		
tenofovir (TDF)	Susceptible		

RT Comments

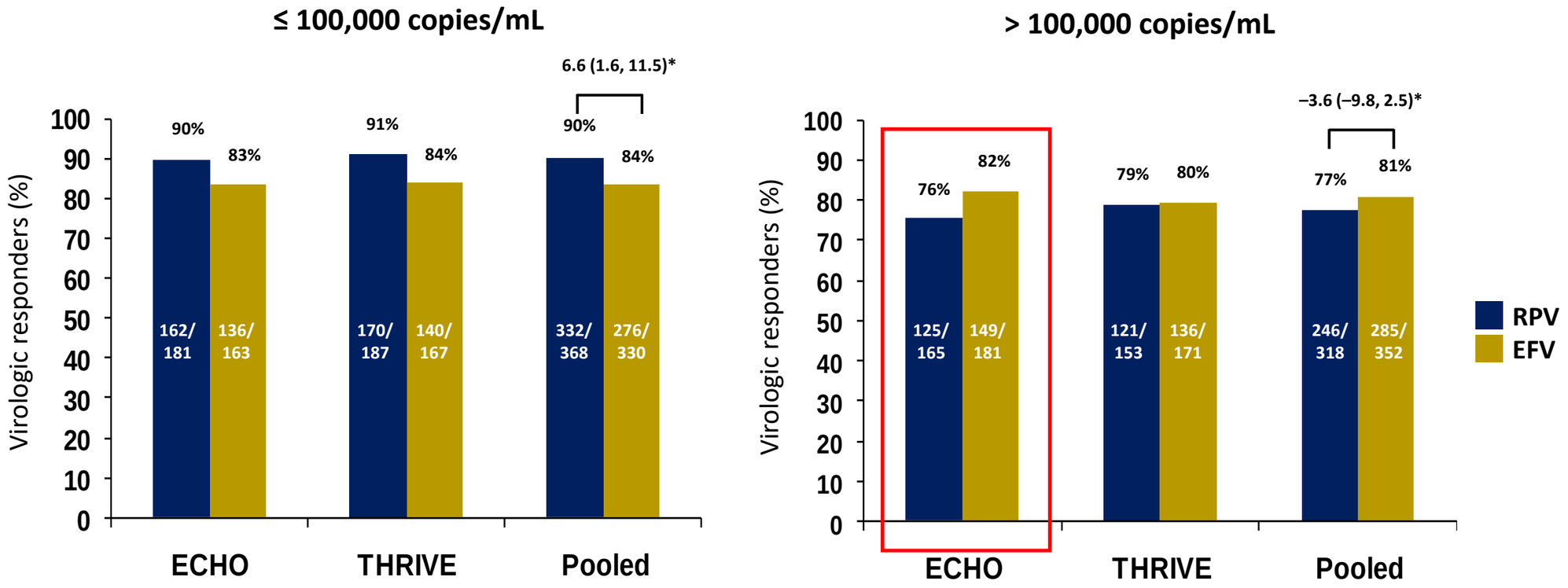
NNRTI

- K103N causes high-level resistance to NVP, and EFV. it has no effect on ETR or RPV susceptibility.

Rokx C et al HIV Med. 2014 Nov;15(10):611-4

ECHO/THRIVE study results: TDF/FTC/RPV vs TDF/FTC/EFV

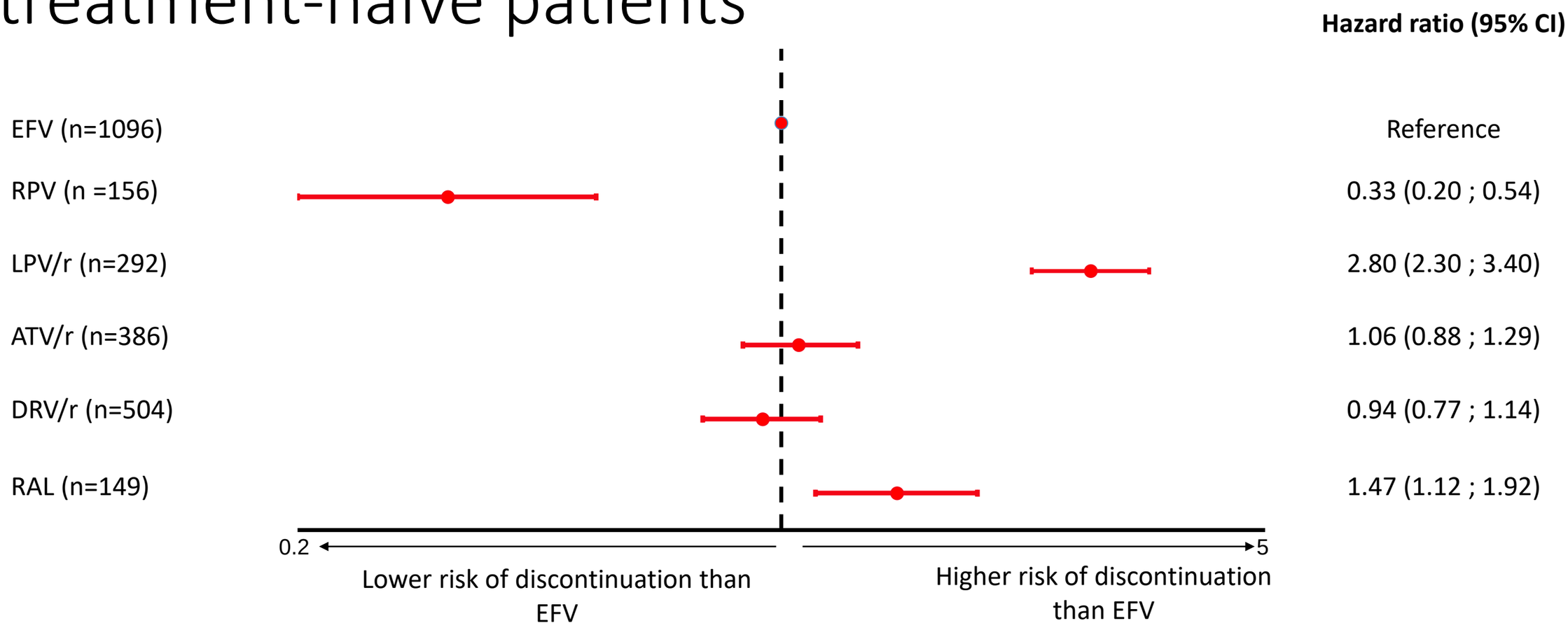
ECHO and THRIVE Week 48 analysis: VL < 50 copies/mL by baseline VL (ITT-TLOVR)



- N(t)RTI background had no effect on virologic response
- No differences between treatment groups in virologic response by gender, region or race

Molina JM, Lancet. 2011;378:238-46; Cohen CJ, Lancet. 2011;378:229-37; Cohen CJ, AIDS. 2013;27:939-50; Rimsky L, J Acquir Immune Defic Syndr. 2012;59:39-46; Rimsky L, Antivir Ther. 2013;18:967-77

Real-world data: Swedish cohort study 2009–2014: treatment-naïve patients



- 2541 treatment-naïve patients started 2583 episodes of treatment with a new third agent
- Compared with EFV, patients on RPV were least likely to discontinue treatment, whilst patients on LPV/r were most likely to discontinue treatment, followed by RAL

Häggblom et al. PLoS One. 2017:12 e0171227

ICONA: Comparison of durability of first-line EFV and RPV with TDF/FTC

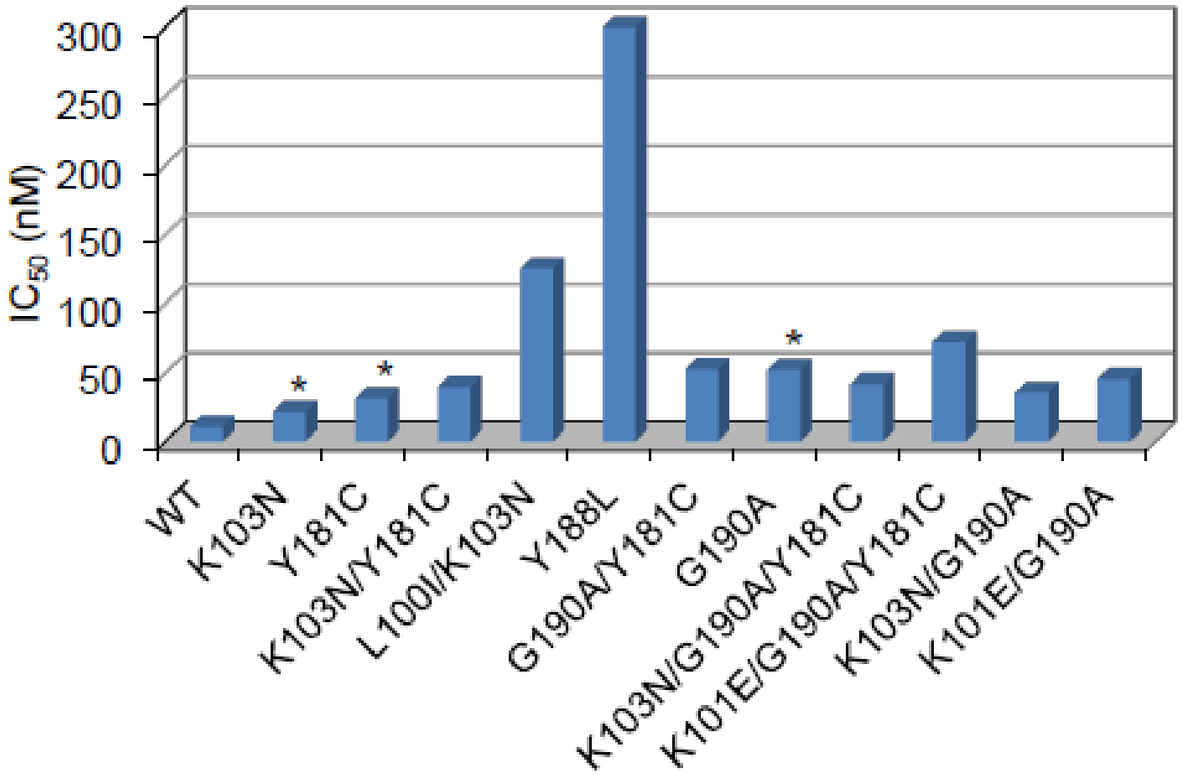
	EFV with TDF/FTC	RPV with TDF/FTC	P value
Discontinue ≥ 1 drug in regimen	**26%**	**13%**	P < 0.0001

- After adjustment, compared to those starting RPV, patients treated with EFV were more likely to discontinue at least one drug
  - for any cause [relative hazard (RH) 4.09; 95% CI 2.89 – 5.80]
  - for toxicity (RH 2.23; 95% CI 1.05 – 4.73)
  - **for intolerance (RH 5.17; 95% CI 2.66 – 10.07)**
  - for proactive switch (RH 10.96; 95% CI 3.17 – 37.87)
- **RPV was better tolerated, less toxic and showed longer durability than EFV, without a significant difference in rates of discontinuation because of failures**

Taramasso L et al, HIV Med. 2018 May 30. doi: 10.1111

Other future options?

Doravirine retains antiviral potency against the most prevalent NNRTI-associated resistant viruses

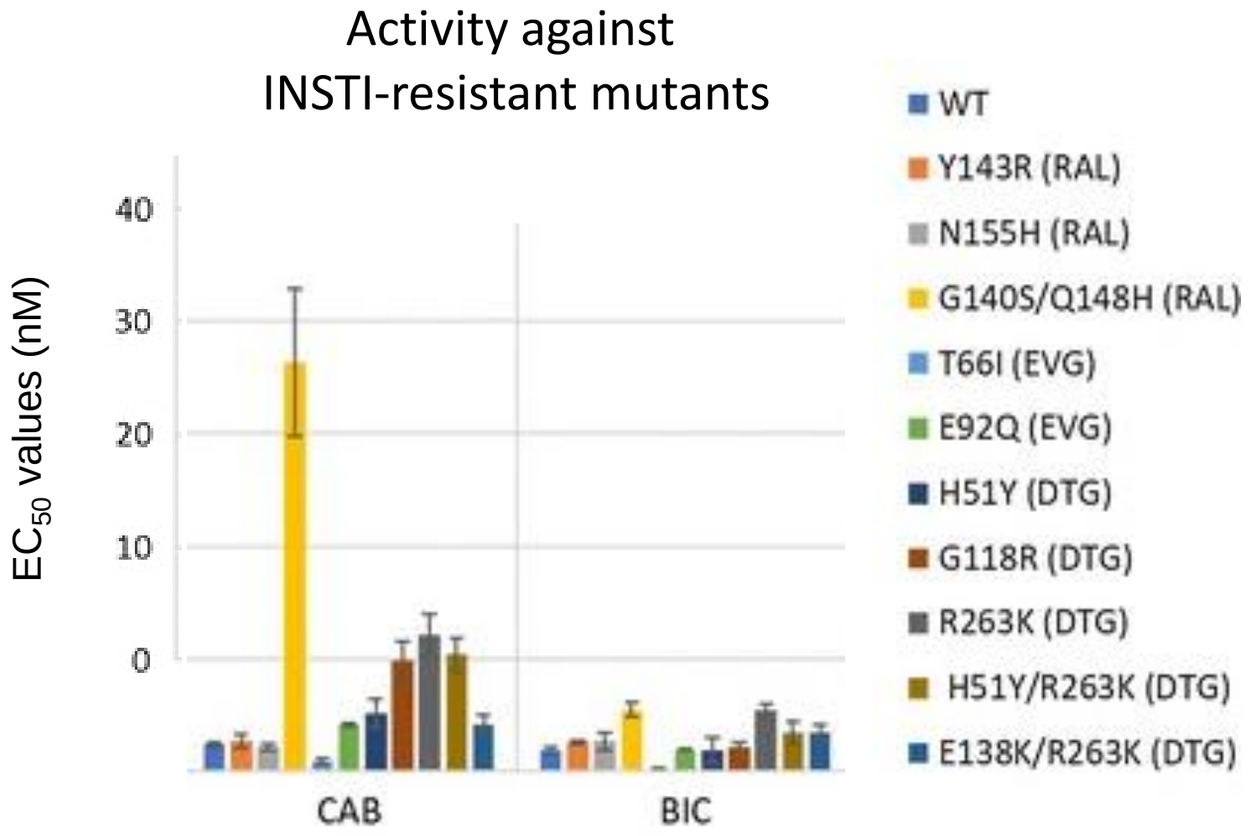


Using clinically relevant concentrations of each drug corrected for protein binding, no viral breakthrough was detected with **doravirine** in resistance selections using K103N, Y181C, and K103N/Y181C mutants

Feng M et al, CROI 2016; Poster 503; http://www.croiconference.org/sites/default/files/posters-2016/506.pdf Feng M et al. Antimicrob Agents Chemother. 2016;60:2241–7

Other future options?

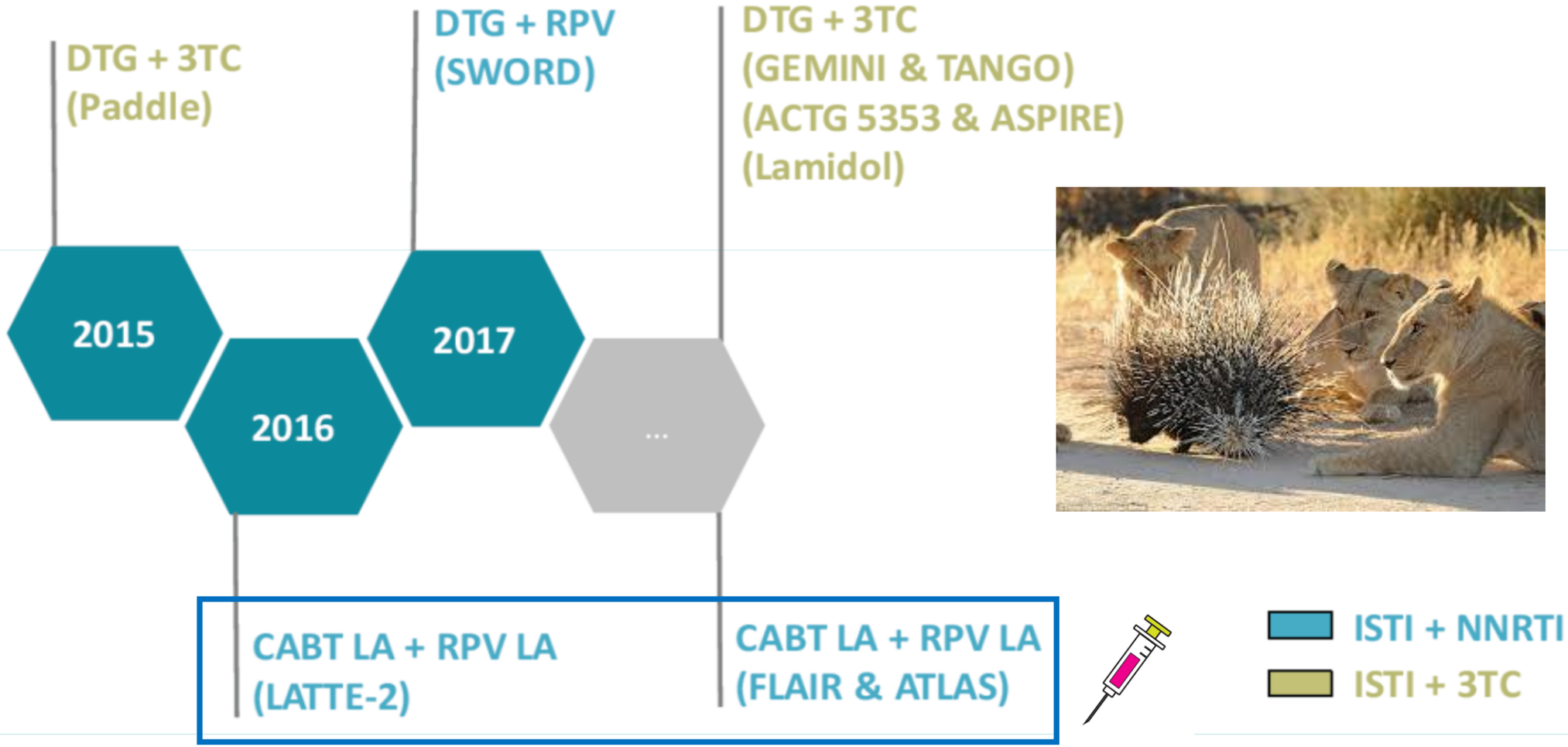
Bictegravir and cabotegravir show activity against InSTI- and NNRTI-associated resistant viruses



Cabotegravir has shown efficacy against five different NNRTI-resistant or NRTI-resistant viruses, with activity equivalent to that against wild-type virus (fold change values ranged from 0.9 to 1.4)

Yoshinaga T et al, Antimicrob Agents Chemother. 2015;59:397-406 Smith et al. Retrovirology 2018;15:37

Reduced drug regimens in ARV-naïve patients



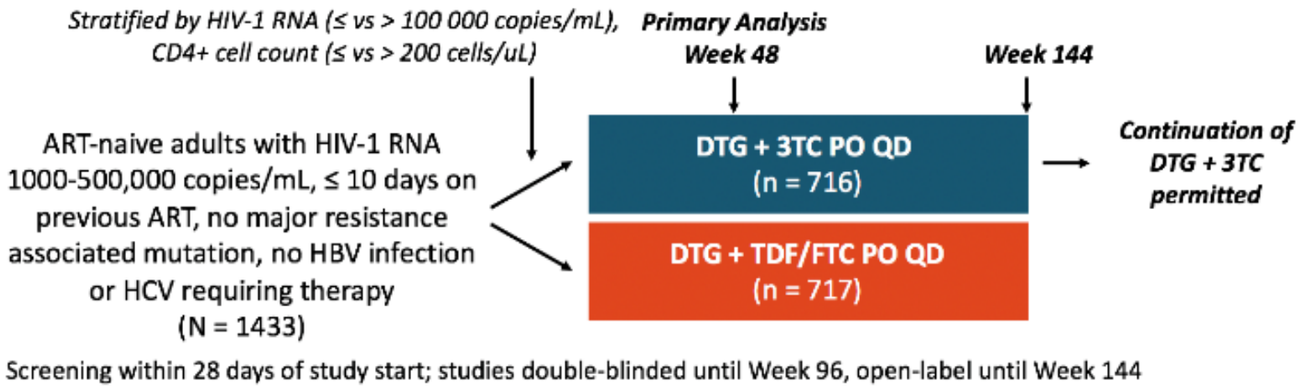
Courtesy: J Arribas

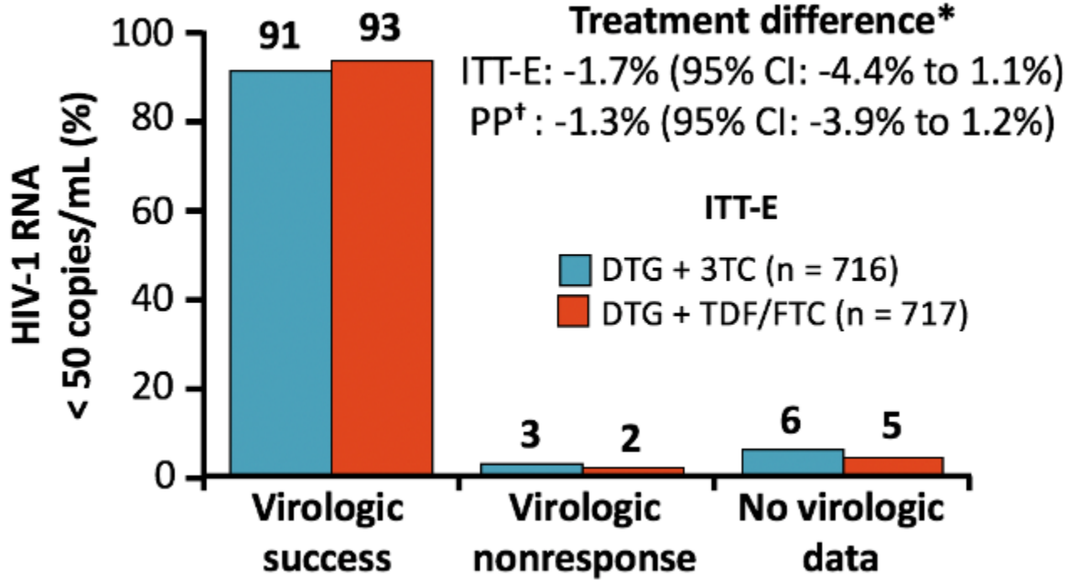
DTG-based dual therapy regimens

Name	Design	Regimen(s)	N	Population
SWORD 1 and 2	Open label RCT switch	DTG/RPV versus continue regimen	1024	Virologically suppressed; no prior VF
PADDLE	Pilot	DTG/3TC	20	ARV-naïve; VL < 100 000 copies/mL
ACTG 5353	Single arm	DTG/3TC	120	ARV-naïve; VL = 1000 – 500 000 copies/mL
GEMINI 1 and 2	RCT double blind	DTG/3TC versus DTG + TDF/FTC	1433	ARV-naïve; VL = 1000 – 500 000 copies/mL
LAMIDOL ANRS 167	Single arm	DTG/3TC	104	Virologically suppressed on first line 2 NRTIs + PI/ NNRTI/InSTI
ASPIRE	RCT switch	DTG/3TC versus continue regimen	89	Virologically suppressed
TANGO	Open label RCT switch	DTG/3TC versus TAF-based regimen	750	Virologically suppressed on TAF-based regimen

GEMINI: DTG + 3TC noninferior at 48 weeks

Parallel randomised double blind phase 3 non-inferiority studies





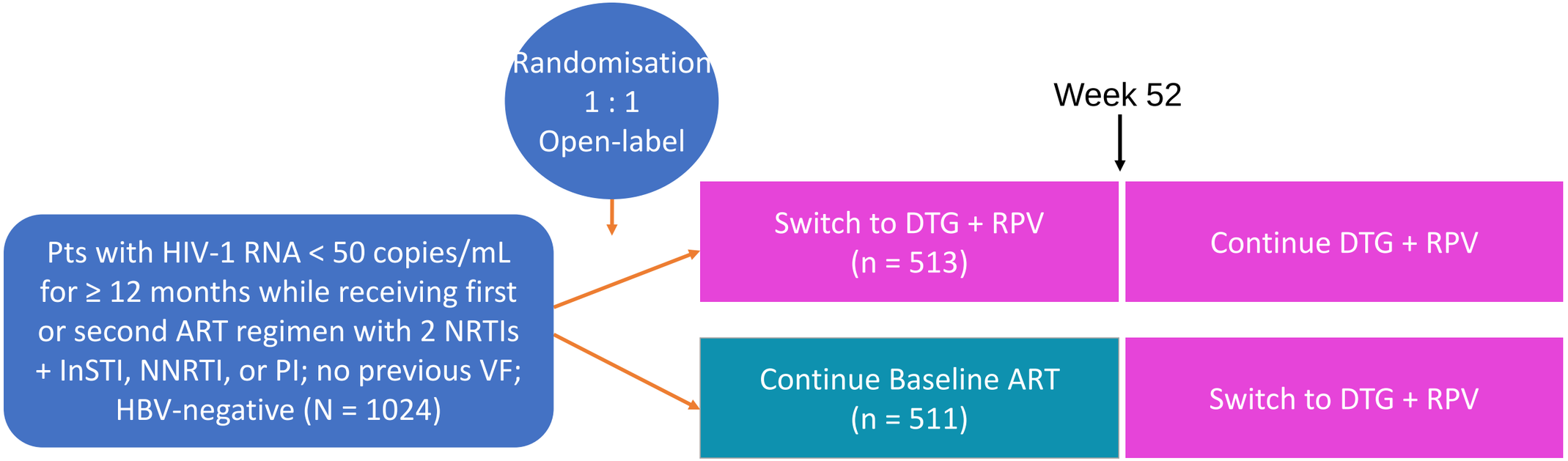
- No treatment-emergent InSTI or NRTI mutations in patients with VF in either arm
- Confirmed VF with DTG + 3TC: n = 6; Confirmed VF with DTG + TDF/FTC: n = 4
- Bone and kidney safety markers more favourable with DTG + 3TC vs DTG + TDF/FTC

DTG + 3TC was noninferior versus 3-drug therapy; no resistance in either arm

*Adjusted for HIV-1 RNA (≤ vs > 100 000 copies/mL), CD4+ cell count(≤ vs > 200 cells/uL), and study (GEMINI-1 vs GEMINI-2).
†PP = the ITT-E population excluding significant protocol violations

Cahn P, et al. AIDS 2018. Abstract TUAB0106LB.

SWORD 1 and 2: Switch from current ART to DTG + RPV dual regimen



Objectives: To evaluate the efficacy and safety of DTG + RPV compared with continuation of current ART regimen (CAR) for 48 weeks in a large randomised population with suppressed viral load

Primary endpoint: Proportion of participants with virologic failure (HIV-1 RNA ≥ 50 copies/mL)

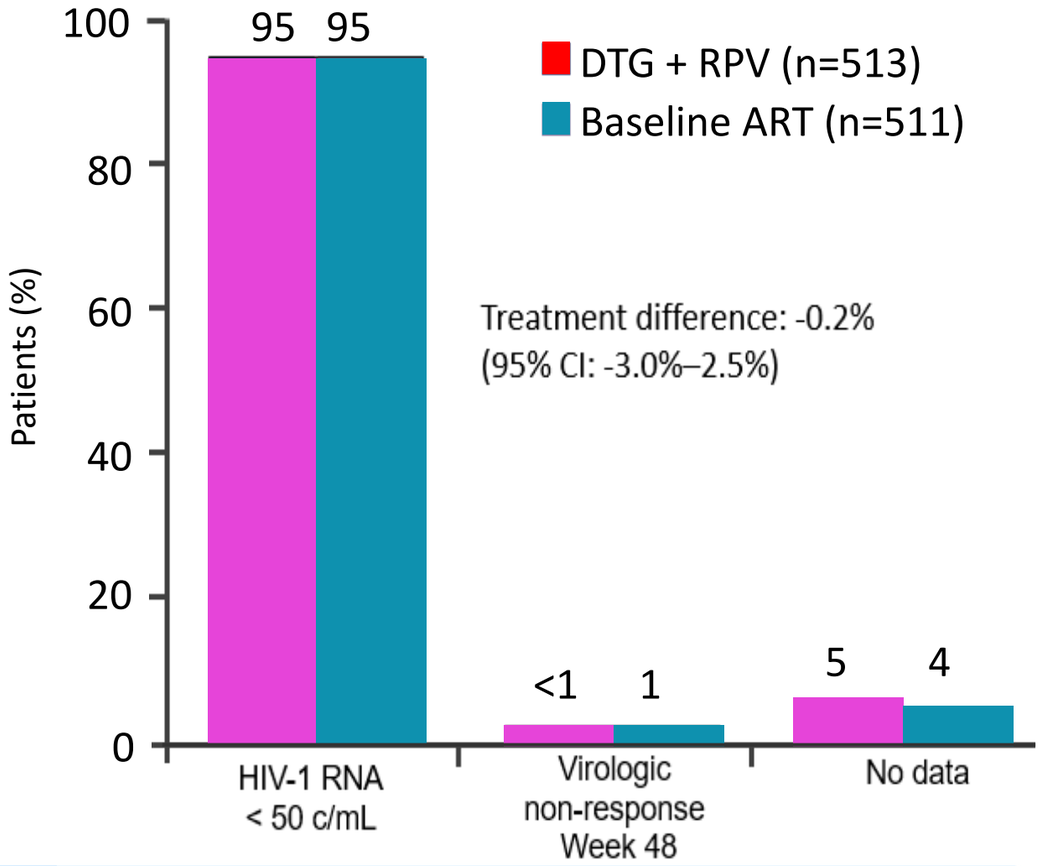
Llibre JM, et al. CROI 2017. Abstract 44LB; Llibre JM, et al. CROI 2017. Abstract 2421; Llibre J, et al Lancet 2018;391:839–49

SWORD 1 and 2: Switch from current ART to DTG + RPV dual regimen

Baseline characteristics

	DTG + RPV (n=513); n (%)	CAR (n=511); n (%)
Age, mean (SD) ≥ 50 years	43 (11.1) 147 (29)	43 (10.2) 142 (28)
Female	120 (23)	108 (21)
Race, non-white	92 (18)	111 (22)
CD4+ cell count, cells/uL (median) ≤500 >500	611 165 (32) 348 (68)	638 149 (29) 362 (71)
Baseline 3rd-agent class PI NNRTI InSTI	 133 (26) 275 (54) 105 (20)	 136 (27) 278 (54) 97 (19)
Baseline TDF use	374 (73)	359 (70)
Months of ART prior to Day 1, median	51	53

Week 48 efficacy



DTG + RPV was non-inferior to CAR (current ART regimen) over 48 weeks in participants with HIV suppression
Results support the use of this two-drug regimen to maintain HIV suppression

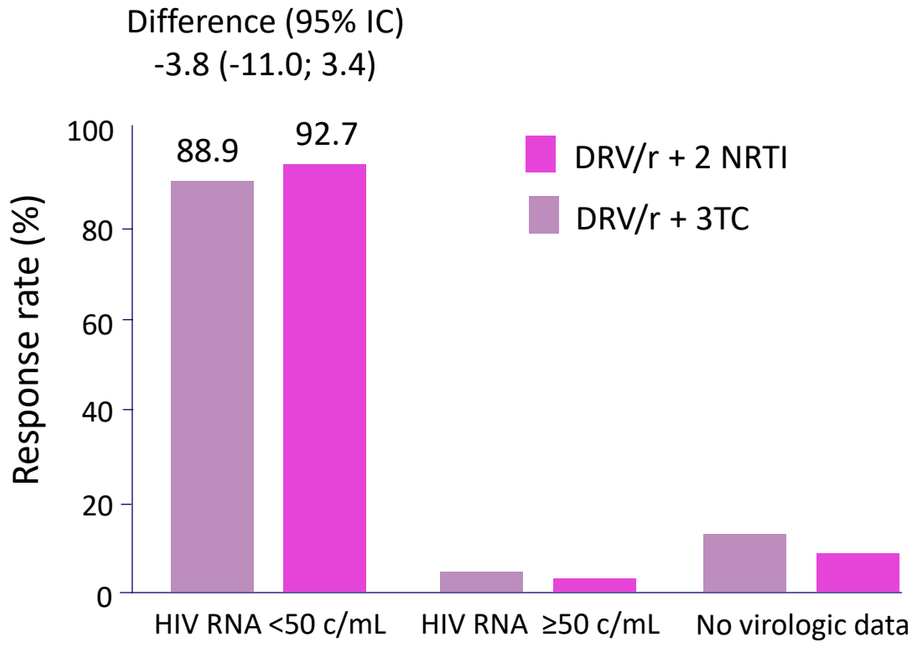
Llibre JM, et al. CROI 2017. Abstract 44LB; Llibre JM, et al. CROI 2017. Abstract 2421; Llibre J, et al Lancet 2018;391:839–49

DUAL: DRV/3TC vs DRV/r + 2NRTIs

Baseline characteristics

	DRV/r + 2NRTI N = 123	DRV/r + 3TC N = 126
Baseline CD4+/uL, median	568	596
Nadir CD4+/uL, median	240	253
Duration of HIV RNA <50 copies/mL (weeks), median	113 (p = 0.014)	79.5
HCV coinfection, %	22.8	25.4
N(t)RTI at baseline, % TDF/FTC ABC/3TC	 76 24	 74 26
Discontinued at Week 48, N (%)	4 (3.3)	9 (7.1)
AE / confirmed VF	2 / 0	1 / 2
Withdrew / lost to f-up	1 / 1	3 / 3

Week 48 efficacy

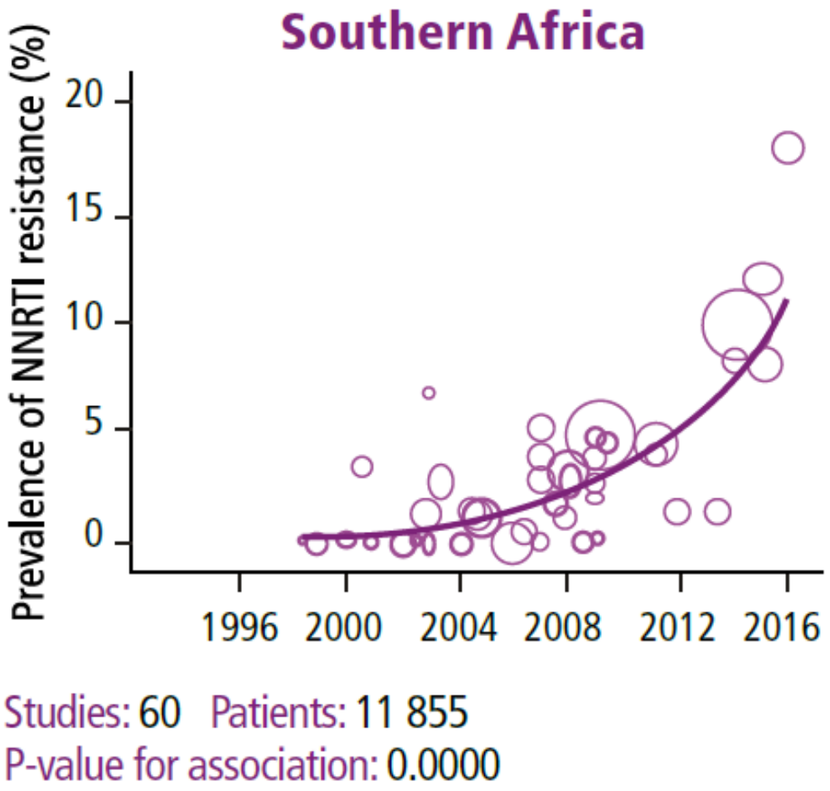


- Dual therapy with **DRV/r plus 3TC was non-inferior** regarding maintenance of viral suppression and **equally well tolerated** as DRV/r plus TDF/FTC (or ABC/3TC)
- Persistent virological suppression was maintained after switching to dual therapy with DRV/r plus 3TC

Pulido F, Clin Infect Dis 2017; 65:2112-8

Prevalence of NNRTI pretreatment resistance by calendar year across studies

Increasing trends in levels of DR observed



Will they continue to increase?

Most DR strains arise independently → ARV regimens with a **high genetic barrier** to resistance and improved patient **adherence** may mitigate DR increases by reducing the generation of new ARV-resistant strains[1]

1. Rhee S-Y et al. PLoS Med. 2015; 12: e1001810 http://apps.who.int/iris/bitstream/handle/10665/255896/9789241512831-eng.pdf

Addressing PDR

↓ chance of transmitting resistant virus

Improve adherence	• Strengthen adherence support
Potent fixed-dose combination regimens	• Suppress HIV-RNA • High adherence
VL monitoring	• Promptly switch individuals with confirmed VF to second-line treatment • Minimise time spent on a failing regimen with resistant virus • Perform viral load monitoring • HIV-DR testing with failure
Use agents with high genetic barrier	• Change first-line regimen at a national level, from an NNRTI-based regimen to DTG- or PI/r-based regimen

Which is the more cost-effective strategy?

http://apps.who.int/iris/bitstream/handle/10665/255896/9789241512831-eng.pdf

Factors influencing drug resistance

Drug toxicities

Social / personal issues

Poor adherence

Lack of API, drug supply and delivery

Lack of continuous support and monitoring

Drug stockouts

Increasingly stretched healthcare systems

Interruption of treatment

Poor potency

Adding 1 drug to failing regimen

Insufficient drug level

Prolonging a failing regimen

Treatment with < 3 drugs

Inappropriate drug selection

Viral replication in the presence of drug

HIV DR

TDR = transmitted drug resistance

Factors influencing drug resistance

Drug toxicities

Social / personal issues

Poor adherence

Lack of API, drug supply and delivery

Lack of continuous support and monitoring

Drug stockouts

Increasingly stretched healthcare systems

Interruption of treatment

Poor potency

Adding 1 drug to failing regimen

Insufficient drug level

Prolonging a failing regimen

Treatment with < 3 drugs

Inappropriate drug selection

Viral replication in the presence of drug

HIV DR

TDR = transmitted drug resistance

Acknowledgements

Pretreatment drug resistance and new treatment paradigms in first-line ART

Michelle Moorhouse

25 October 2018

SAHCS 2018

University of the Witwatersrand
WITS RHI

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

Pretreatment drug resistance and new treatment paradigms in first-line ART

Michelle Moorhouse

October 2018

27th International Workshop on HIV Drug Resistance and Treatment Strategies

University of the Witwatersrand
WITS RHI

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY