

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

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SAHCS 2018



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**WITS RHI**

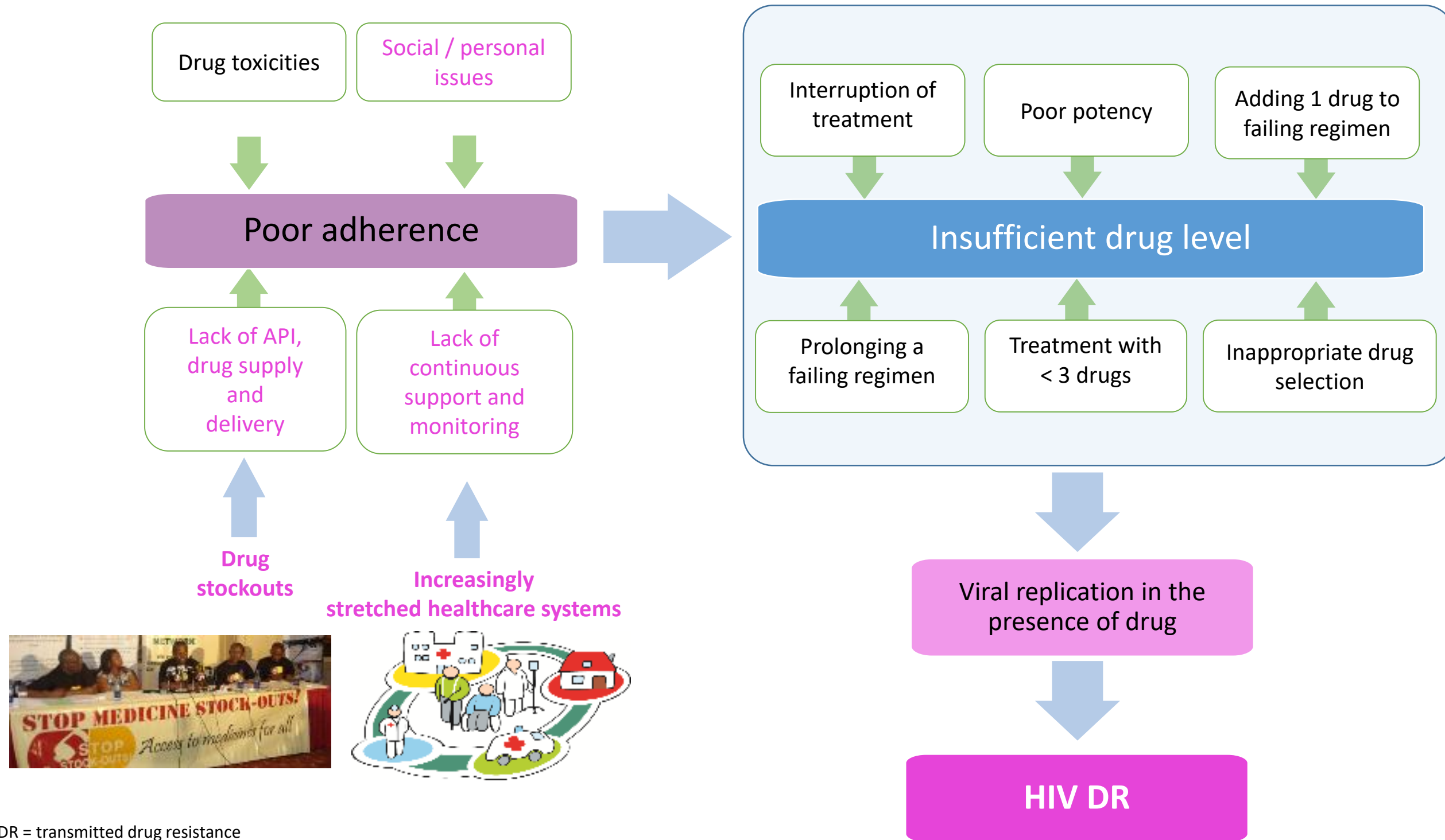


# Disclosures/disclaimers

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- Conference sponsorship from BD, Gilead, Janssen, Merck, Cipla and Mylan
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# Factors influencing drug resistance



# Levels of pretreatment HIVDR (PDR)

## EFV/NVP pretreatment HIVDR

In several low- and middle-income countries,

**1 in 10**  **adults** starting HIV treatment harbour resistant virus

**3 in 10**  **adults restarting first-line ART** with prior exposure to antiretroviral drugs harbour resistant virus

### Women

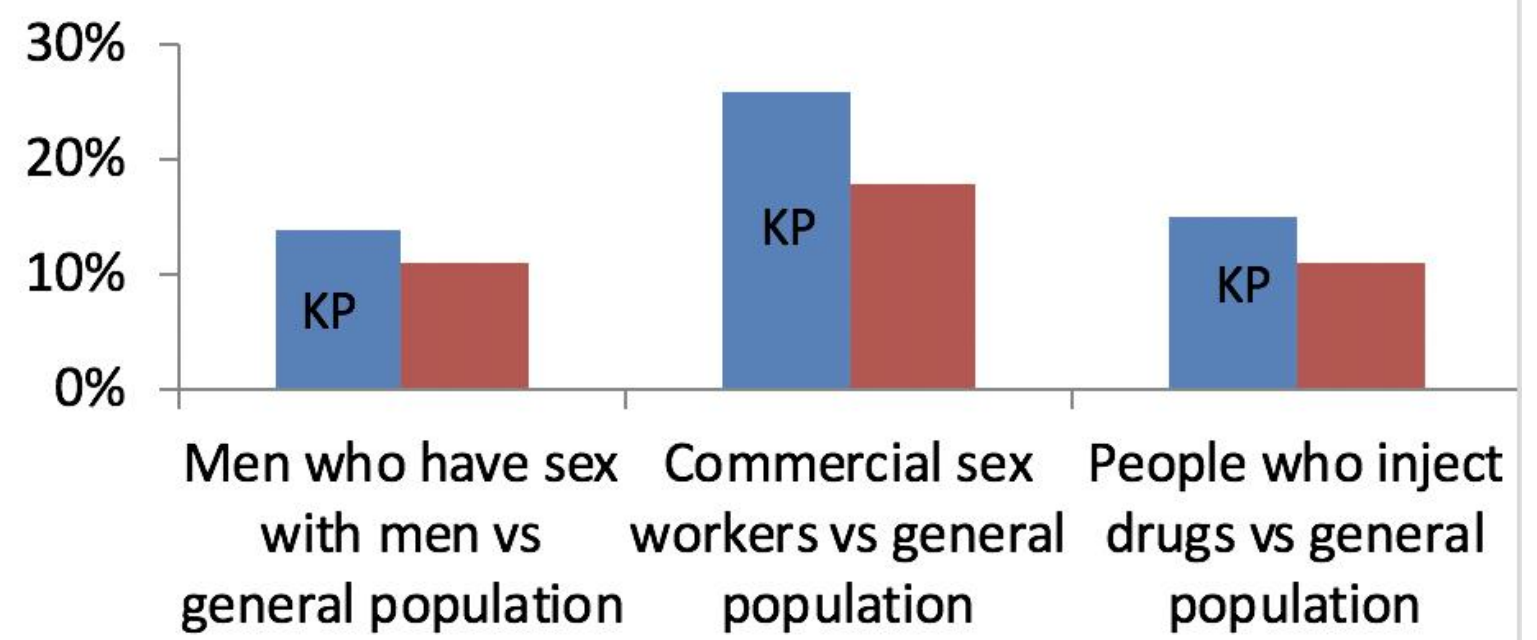
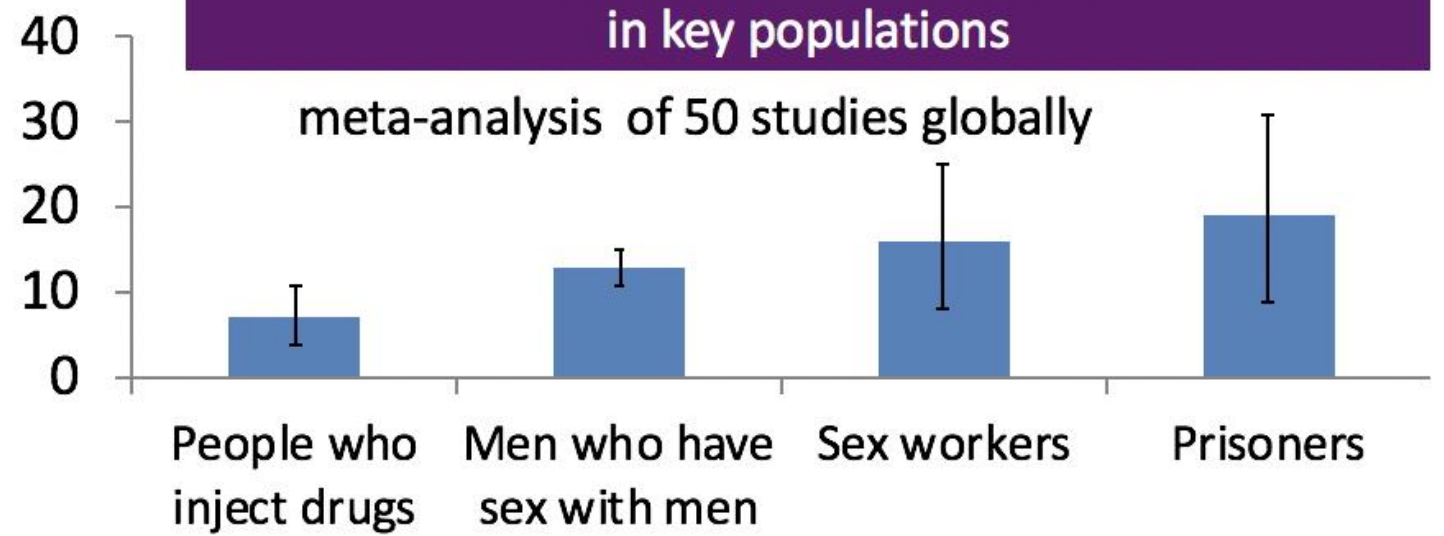


starting first-line ART are **two times more** likely than men to harbour a resistant virus

**5 in 10**  **young children** newly diagnosed with HIV harbour resistant virus

## EFV/NVP pretreatment DR in key populations

meta-analysis of 50 studies globally



# 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)

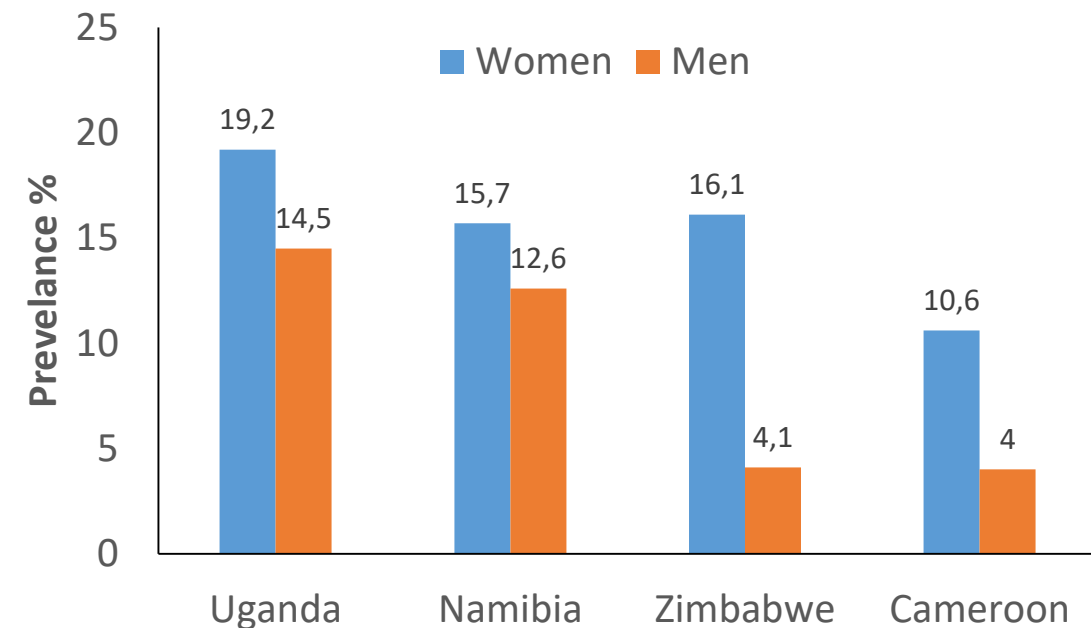


- In children 0–18 years starting ART, NNRTI resistance = **49.3%** (range 7.5–100%) (meta-analysis, 2014–17)
  - Particularly in PMTCT-exposed children (4/7 studies found > 50% of PMTCT-exposed children had NNRTI DR)



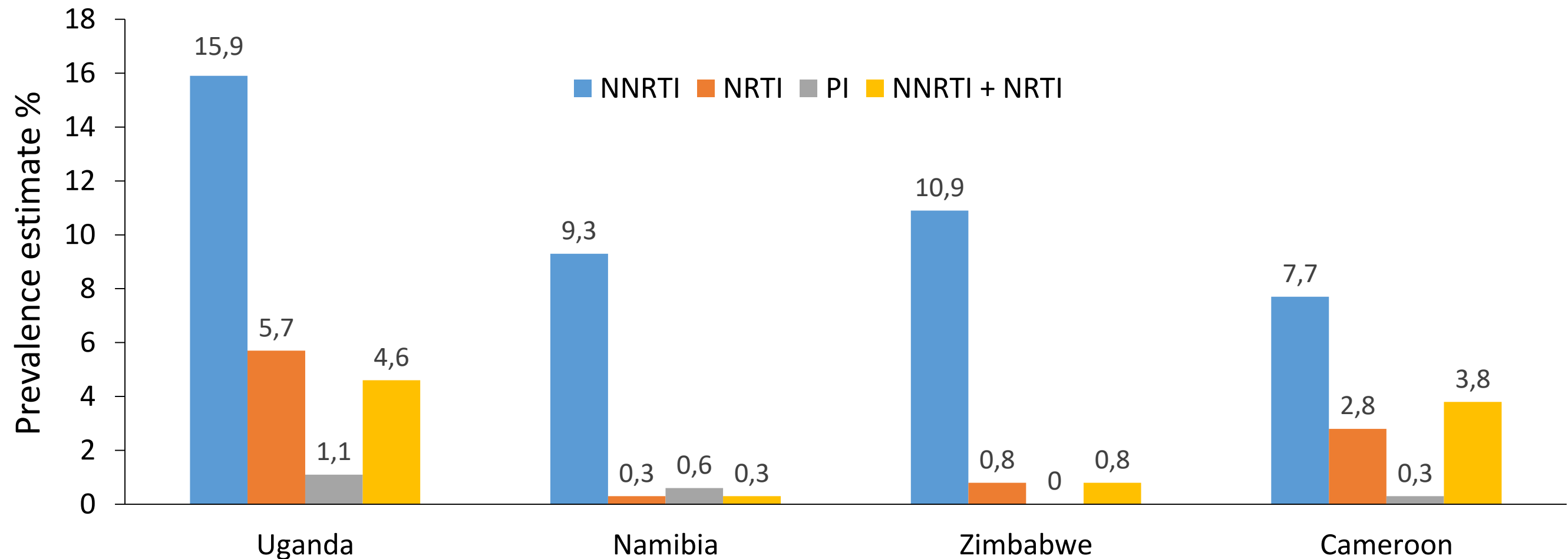
- Prevalence of any TDR and NNRTI resistance is higher among women than men in the majority of surveys

Prevalence estimates of pretreatment HIV DR

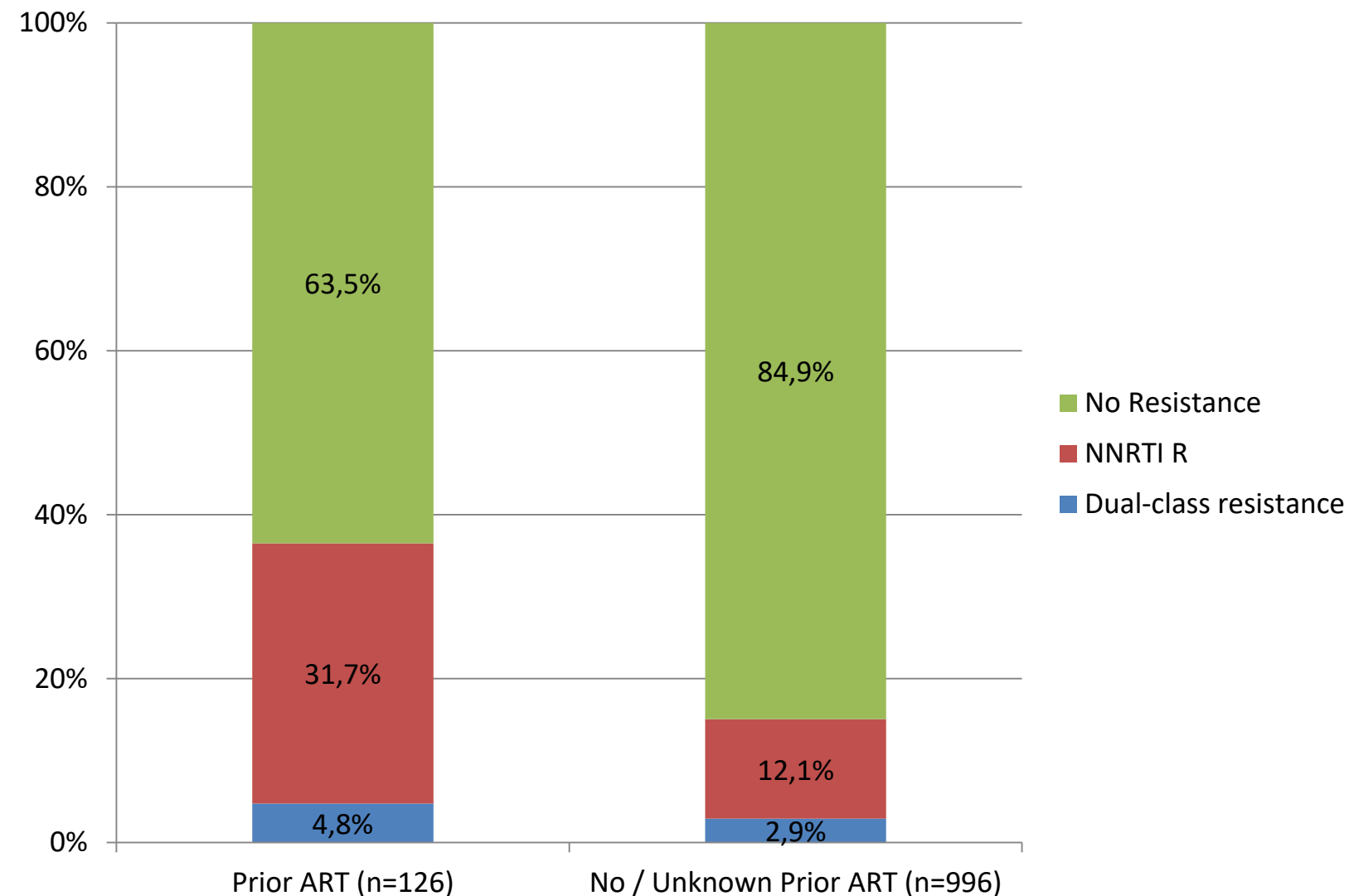


# PDR in treatment-naïve patients in selected countries

- Most pretreatment DR is **NNRTI resistance**



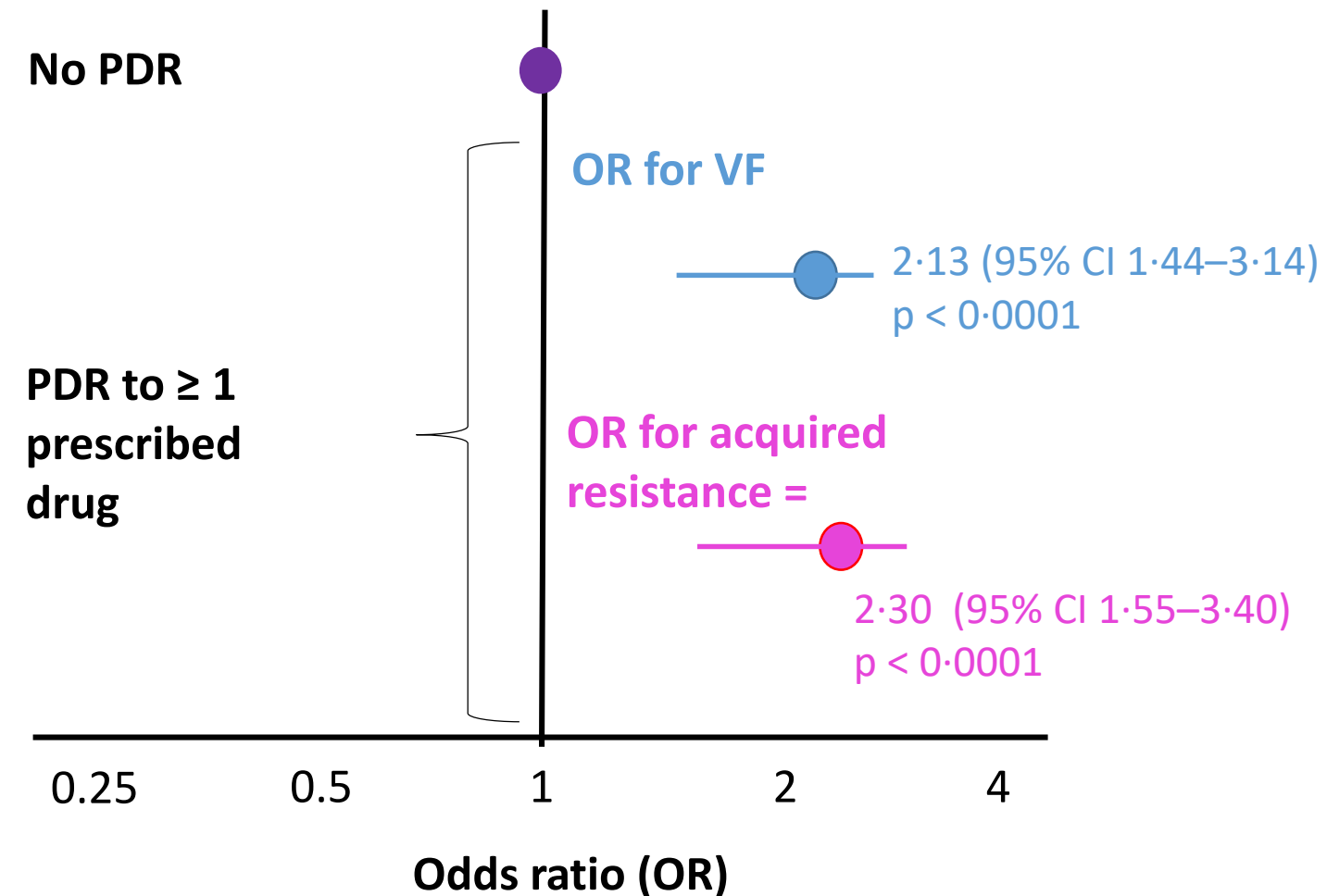
# NNRTI and dual-class resistance detected amongst patients enrolled according to prior ART exposure (SA)



**HIVDR:**  
37% in ART starters with prior exposure to ARVs  
15% in ARV-naive

# Magnitude of effect of PDR on long-term virological outcomes

- Cohort data 2007–09; 6 countries in sub-Saharan Africa<sup>1</sup>
- PDR results available for 2579 patients
  - 2404 (93%) had no pretreatment DR
  - 123 (5%) had PDR to  $\geq 1$  prescribed drug
  - 52 (2%) had PDR and received fully active ART
- **CD4+ count** increased less in patients with PDR than in those without ( $\Delta$  35 cells/ $\mu$ L 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  $\rightarrow$  1.5-fold increased risk for treatment failure in the first 48 weeks after ART initiation<sup>2</sup>

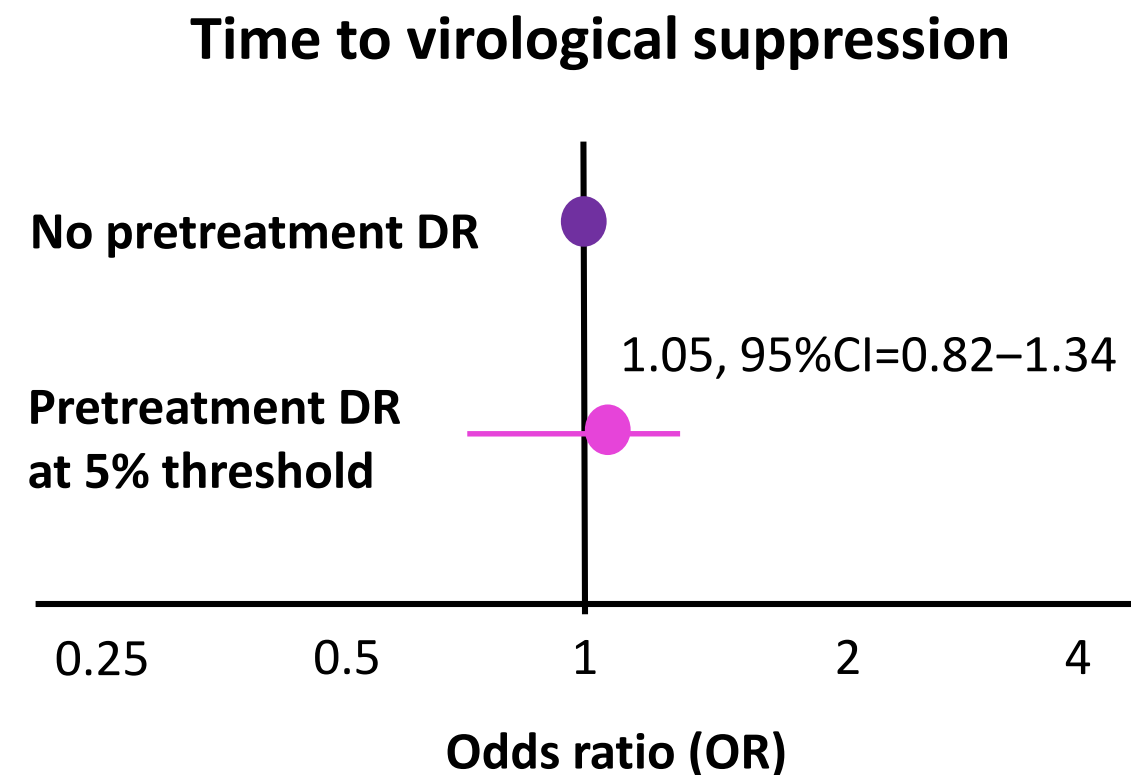




# More recently

- 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) at 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



# 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)
	<b>Two NRTIs + EFV</b>	Two NRTIs + DTG	
Children (0–10 years)	Two NRTIs + DTG ←	Two NRTIs + (ATV/r or LPV/r)	
	Two NRTIs + LPV/r	Two NRTIs + DTG	
	<b>Two NRTIs + NNRTI</b>	Two NRTIs + DTG	

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

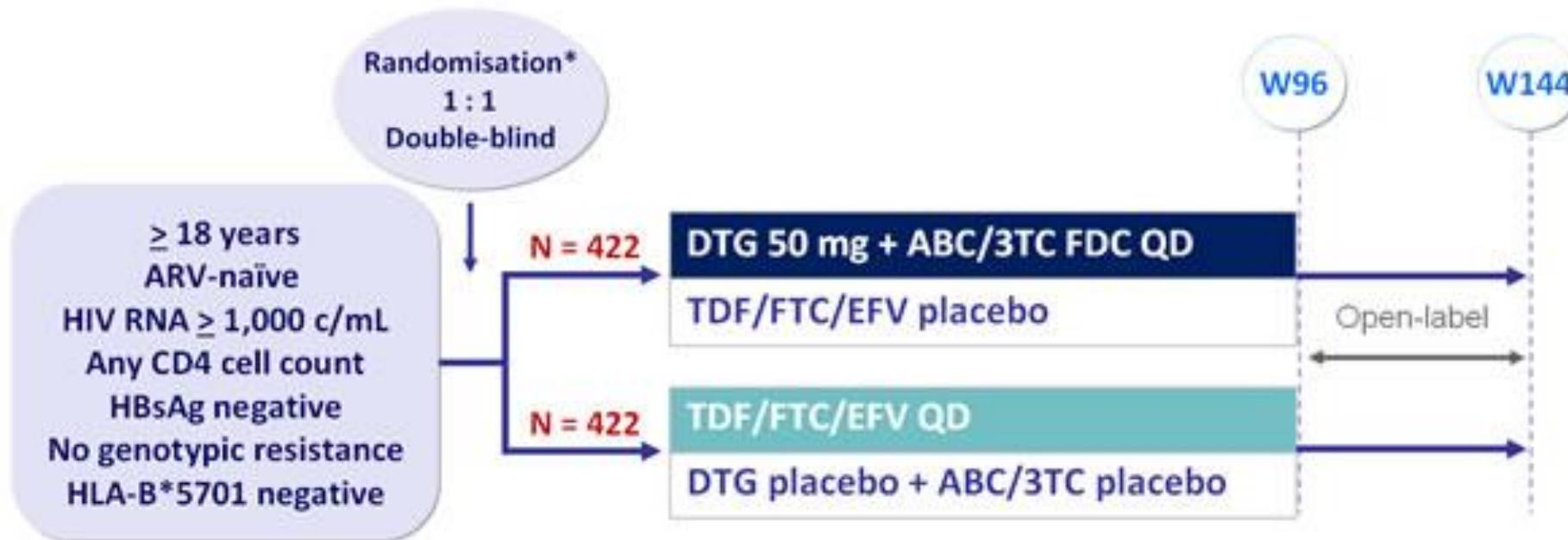
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# SINGLE: ABC/3TC/DTG vs TDF/FTC/EFV

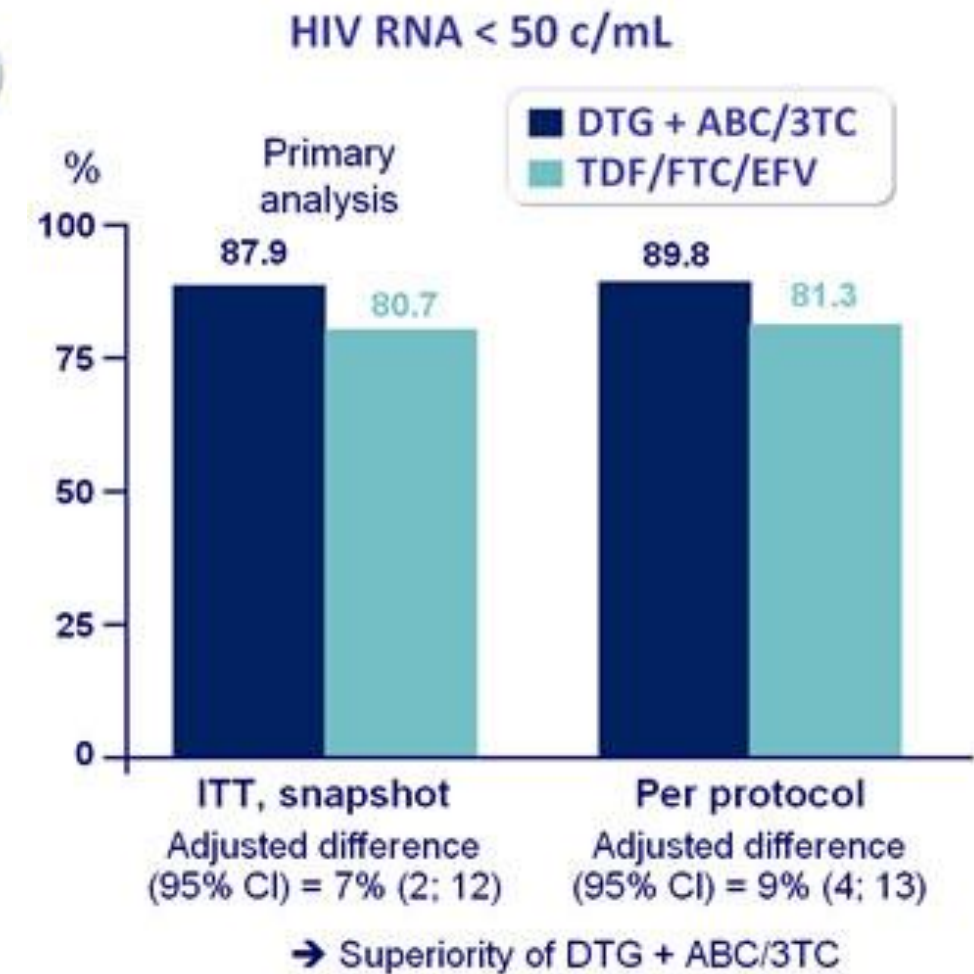
## Study design



## 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)

## 48 Week efficacy results

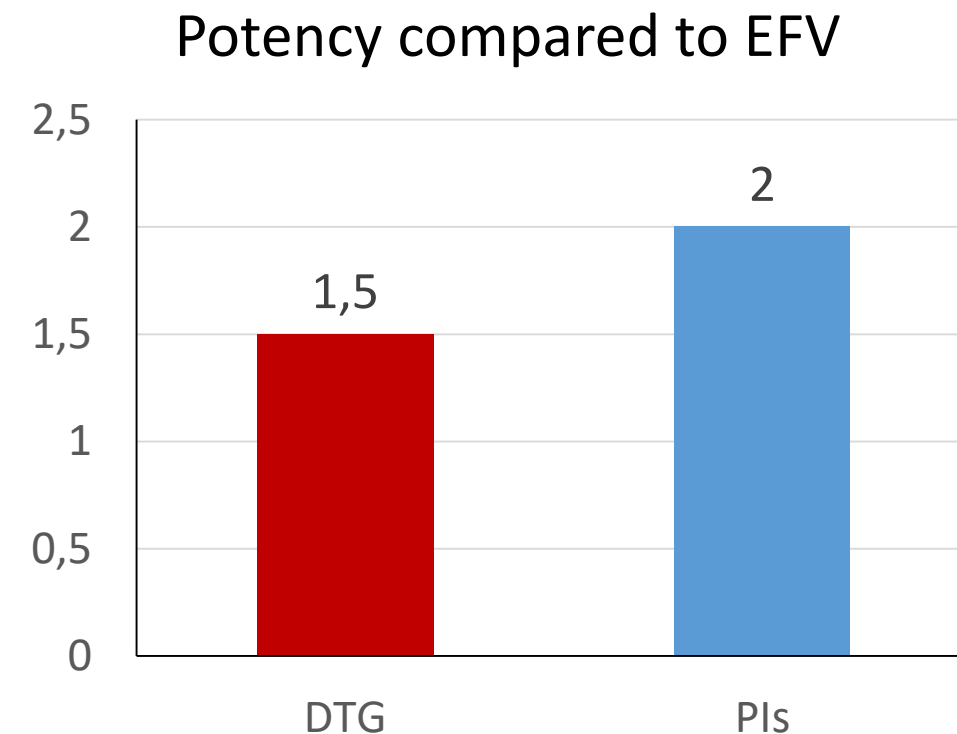


## Conclusions

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

# DTG in first-line treatment when NNRTI DR is prevalent

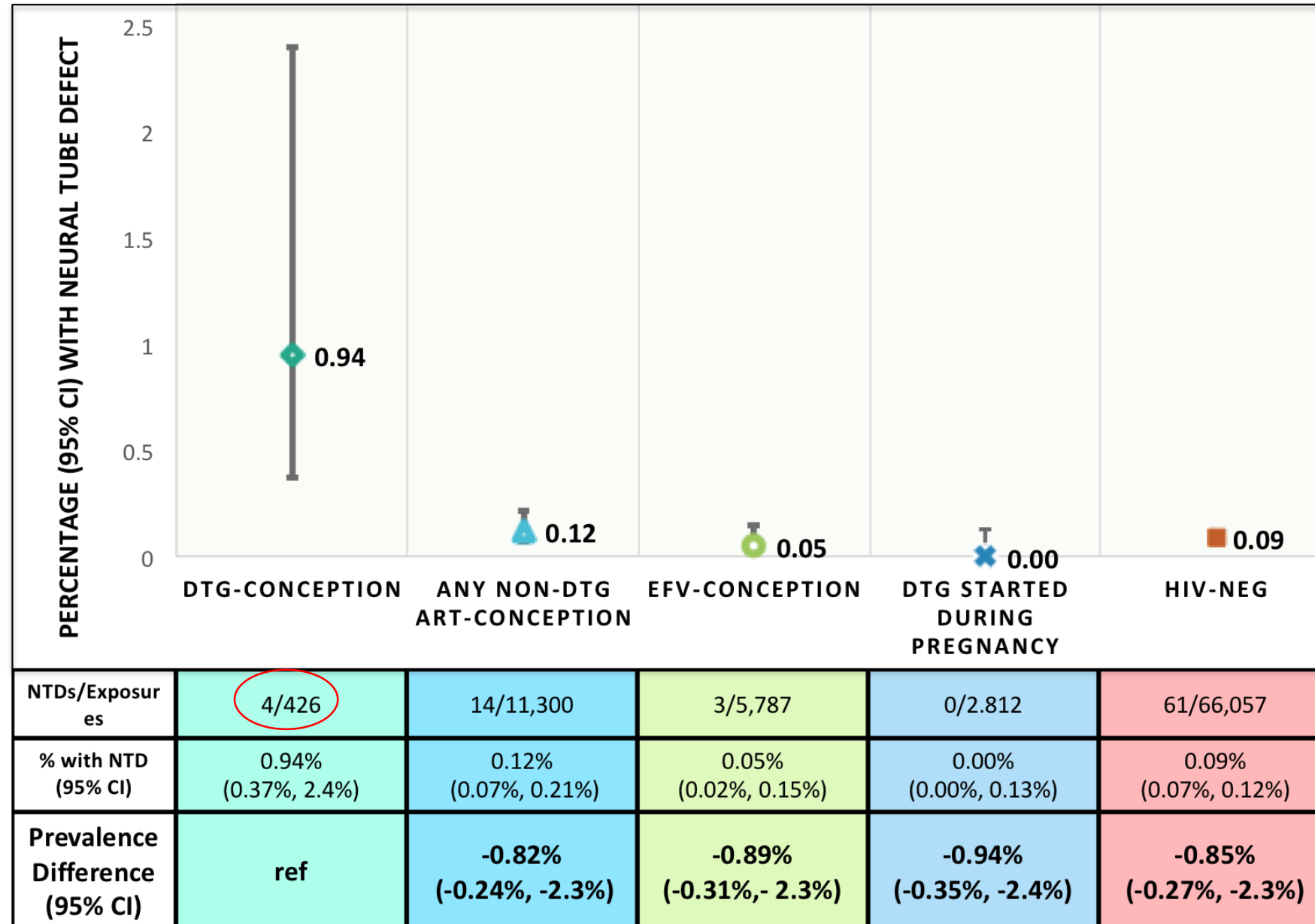
- Rate of HIV DR acquisition of DTG at a similar level to that of ATV/r
- DTG generally found to be associated with lower risk of toxicity than both EFV and PIs
  - Risk of neurological toxicity is half that of EFV → reduced risk of toxicity → less discontinuation



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

# Dolutegravir NTD signal

Tsepamo study, Botswana



**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

# 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*	Red	Red	Red
	Late pregnancy	Yellow	Red	Green
	Childbearing age potential, not using contraception	Red	Red	Red
	Childbearing age potential, using effective/consistent contraception	Green	Green	Green
On DTG containing regimen	Early pregnancy*	Red	Red	Yellow
	Late pregnancy	Green	Green	Green
	Childbearing age potential, not using contraception	Red	Red	Red
	Childbearing age potential, using effective/consistent contraception	Green	Green	Green

\* The definition of early pregnancy period varies in different guidelines.

DHHS: < 8 weeks from LMP; BHIVA : 1<sup>st</sup> 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

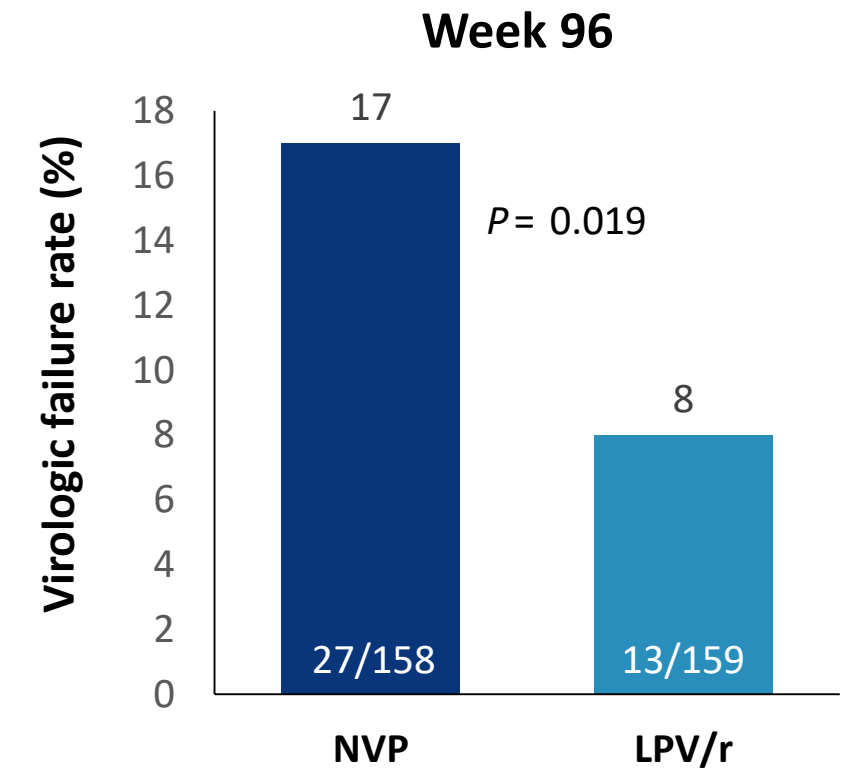
# Safety and Efficacy of DTG and EFV600 in first-line ART (summary 2018 WHO Systematic Review and NMA)

Major outcomes	DTG vs EFV <sub>600</sub>	QUALITY OF EVIDENCE
Viral suppression (96 weeks)	<b>DTG better</b>	moderate
Treatment discontinuation	<b>DTG better</b>	high
CD4+ recovery (96 weeks)	<b>DTG better</b>	moderate
Mortality	<b>comparable</b>	low
AIDS progression	<b>comparable</b>	low
SAE	<b>comparable</b>	low



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

425 treatment-naive adults patients randomised



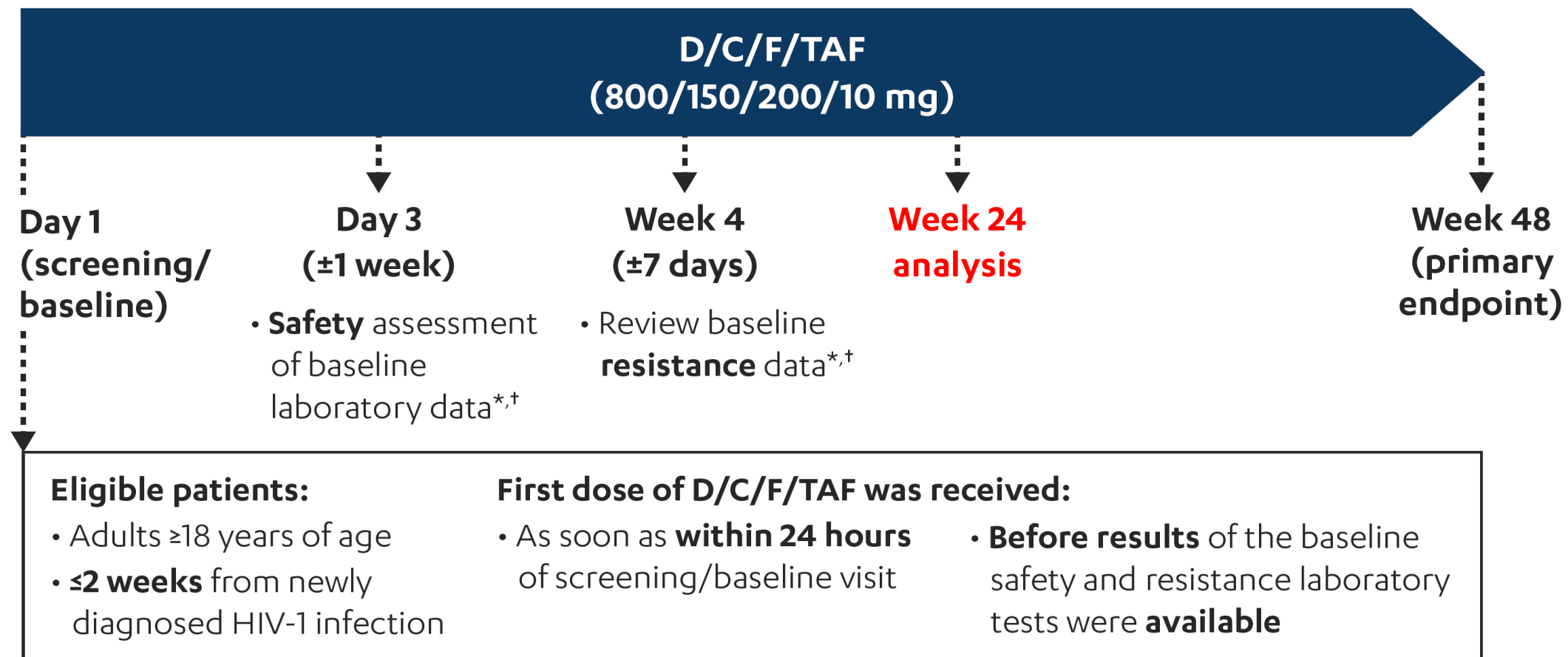
- At baseline, major DRMs were found in 3/27 NVP-failing patients and in 0/13 patients who failed in the LPV/r group

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<sup>1</sup>

# DIAMOND: Study design

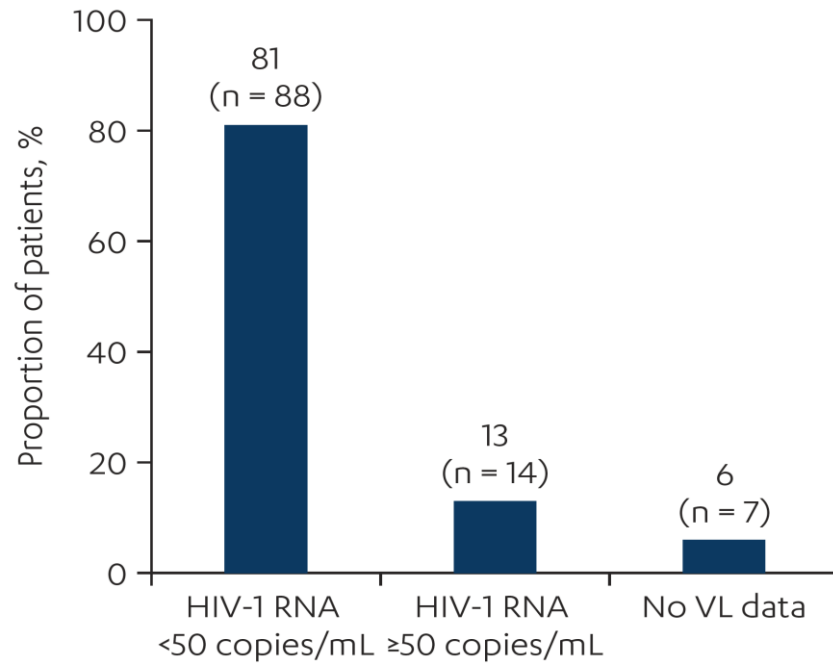
- DIAMOND is an ongoing, phase 3, single-arm, open-label, prospective, multicentre study evaluating DRV/Cobi/FTC/TAF in a rapid initiation model of care over 48 weeks
- Objective: Assess efficacy and safety of DRV/Cobi/FTC/TAF in a rapid initiation model of care in newly diagnosed, HIV-1–infected, treatment-naïve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



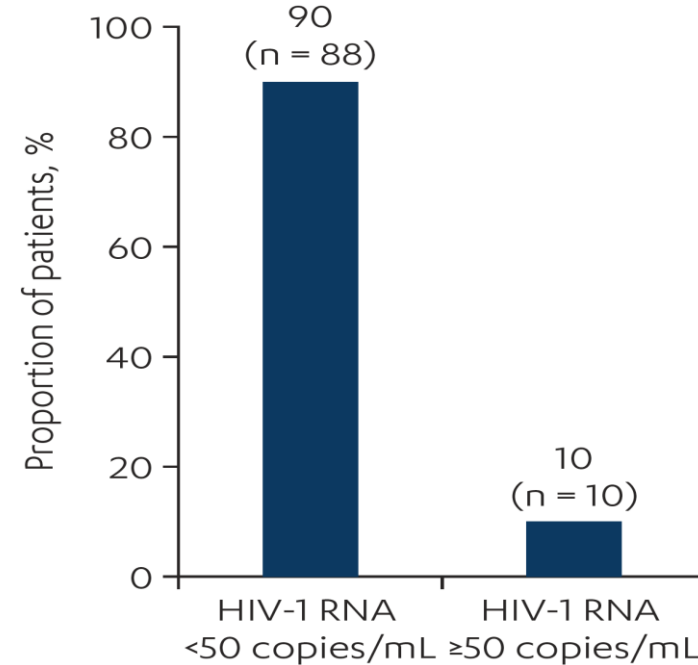
\*Evaluations could be performed sooner based on the availability of results; †Interim analyses were performed once all patients had been assessed for safety at Day 3 and resistance at Week 4, and were updated when all patients continuing treatment reached Week 24

# DIAMOND: Week 24 efficacy

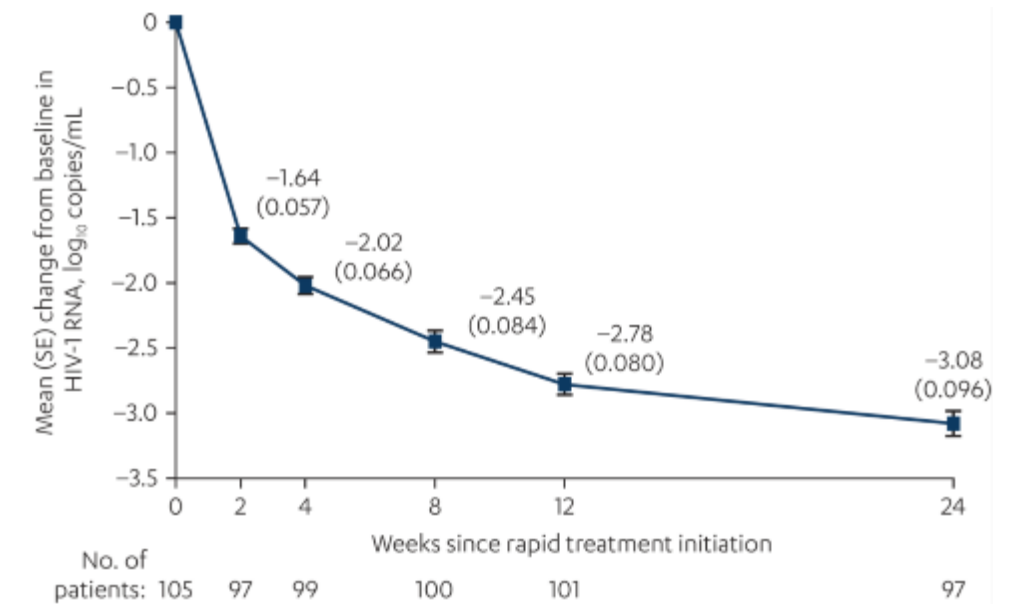
**FDA Snapshot (N=109)**



**Observed (n=98)**



**Week 24: Change from baseline in log<sub>10</sub> HIV-1 RNA (Observed)**



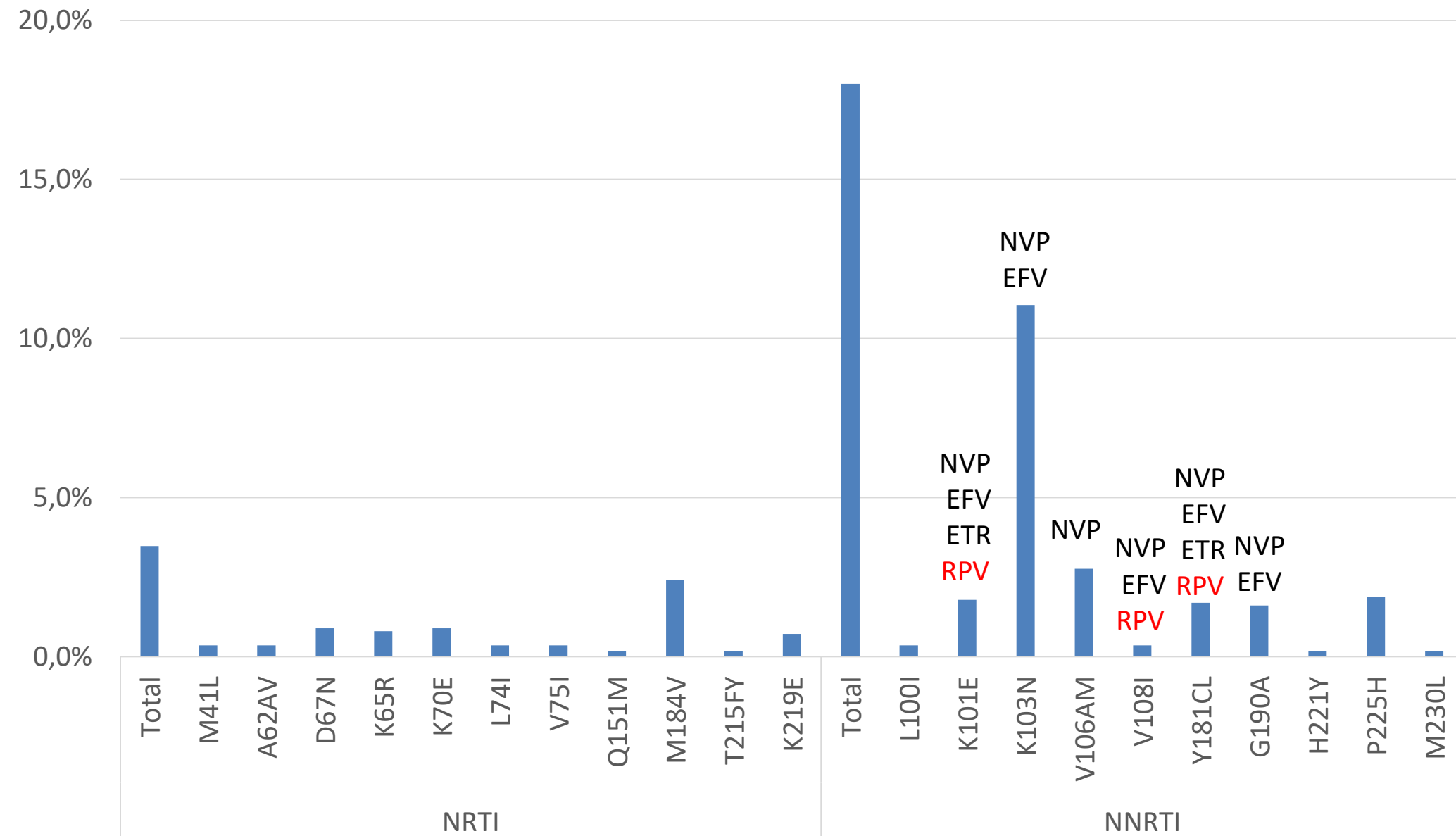
- 91% (99/109) of patients continued treatment through Week 24 – No patients discontinued due to receipt of baseline resistance and only 3 discontinued due to safety stopping rules
  - No patients discontinued due to lack of efficacy and no patients had protocol-defined virologic failure; there was only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

- Mean HIV-1 RNA decreased from baseline to Week 24 by 3.08 log<sub>10</sub> copies/mL
- Mean ± SE CD4 count was 413 ± 24 at baseline and 589 ± 30 cells/mm<sup>3</sup> 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

# 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)



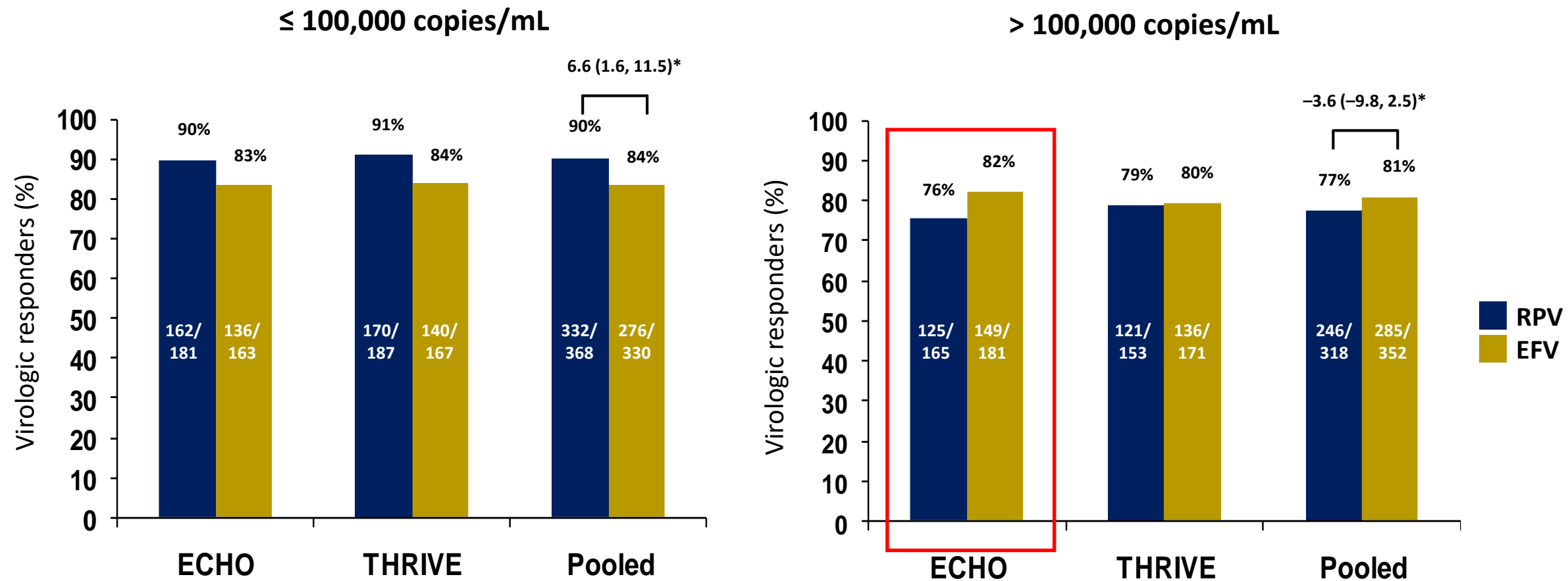
# Rilpivirine? – active against K103N

- 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	<b>rilpivirine (RPV)</b>	Susceptible
didanosine (DDI)	Susceptible		
emtricitabine (FTC)	Susceptible		
tenofovir (TDF)	Susceptible		
<b>RT Comments</b>			
<b>NNRTI</b>			
• K103N causes high-level resistance to NVP, and EFV. it has no effect on ETR or RPV susceptibility.			

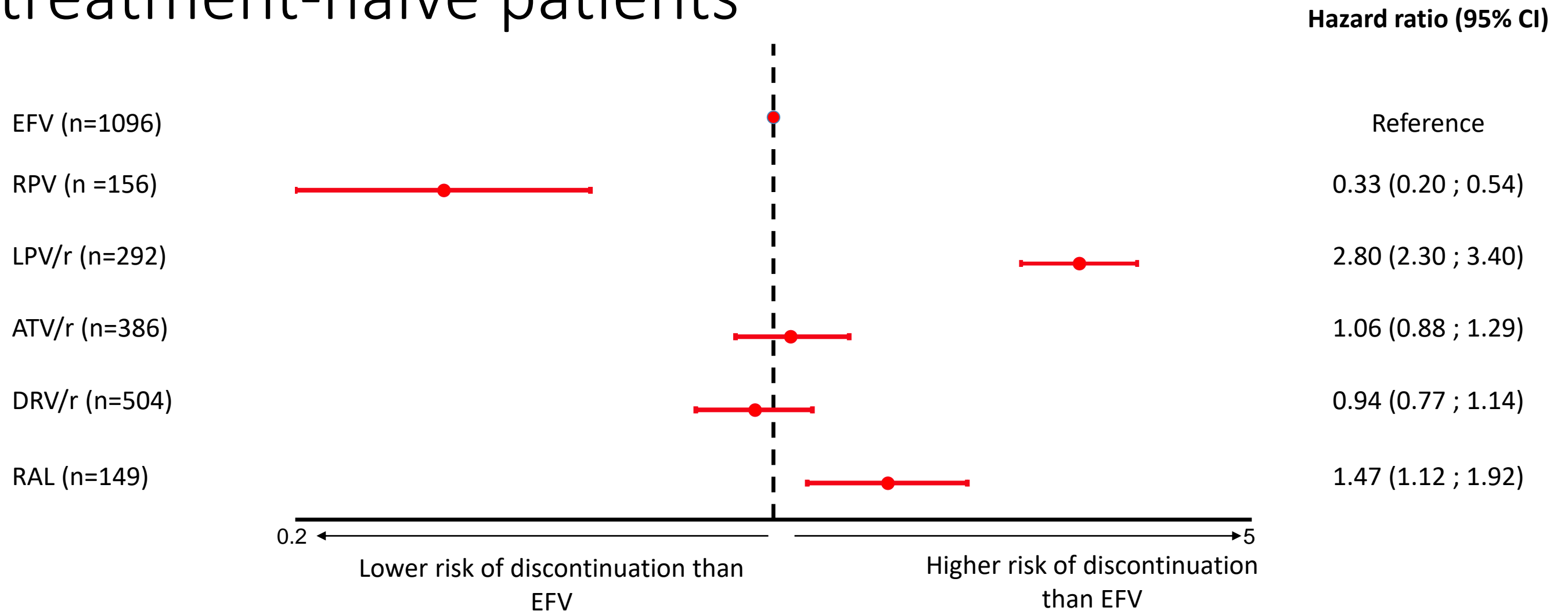
# ECHO/THRIVE study results: TDF/FTC/RPV vs TDF/FTC/EFV

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

# 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

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



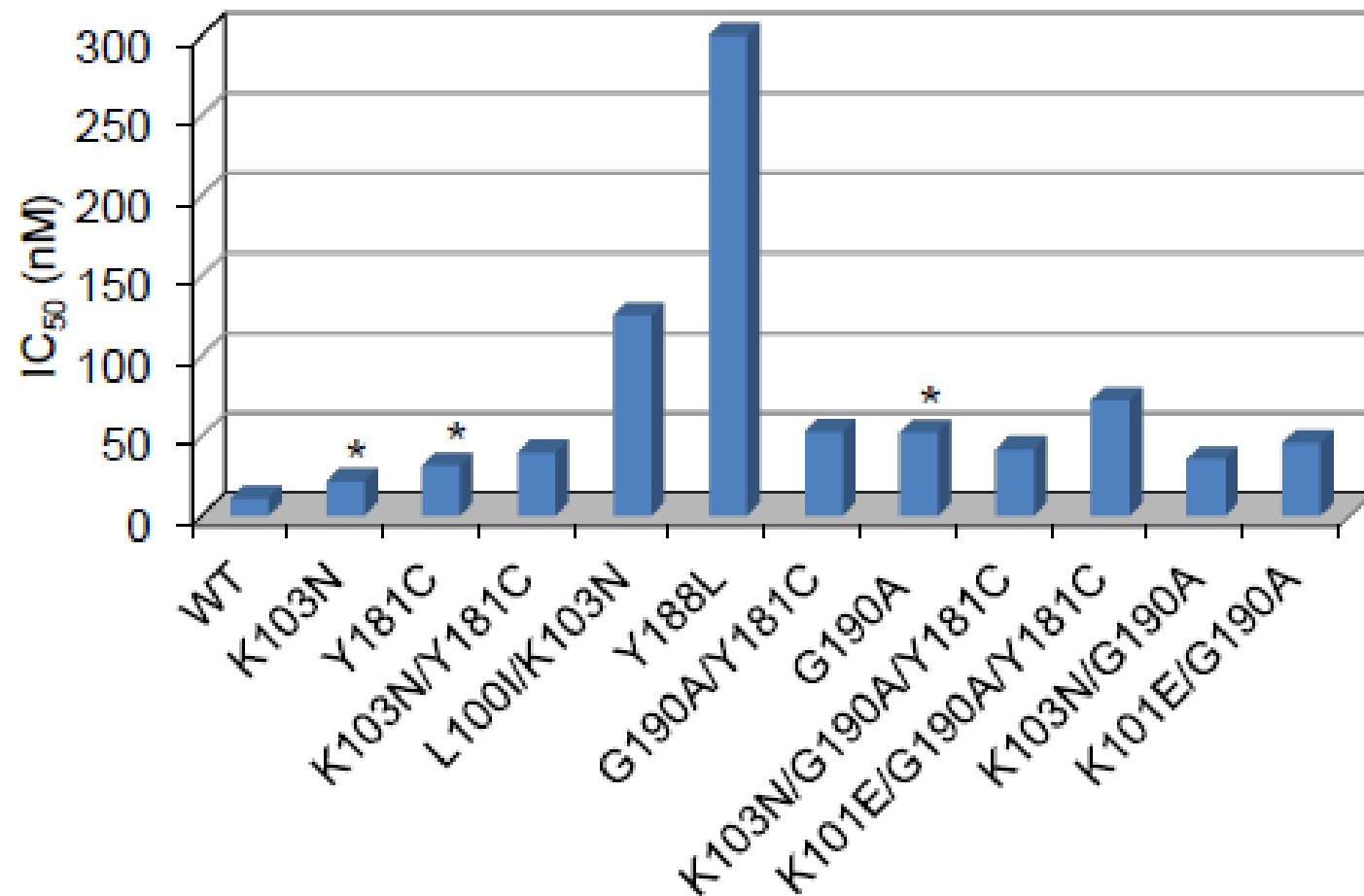
	EFV with TDF/FTC	RPV with TDF/FTC	P value
Discontinue ≥ 1 drug in regimen	<b>26%</b>	<b>13%</b>	P < 0.0001

- 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**



# Other future options?

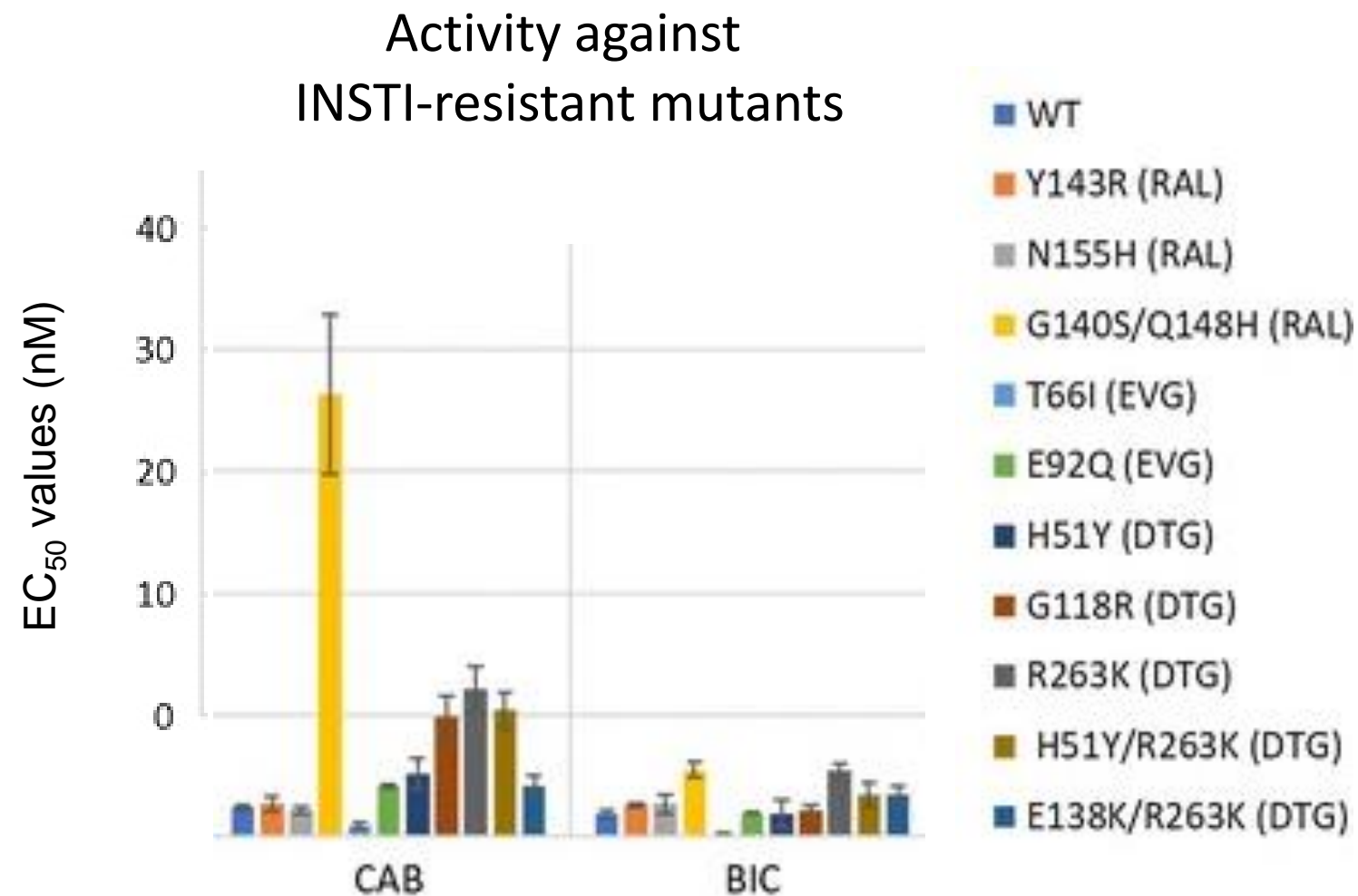
Doravirine retains antiviral potency against the most prevalent NNRTI-associated resistant viruses



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

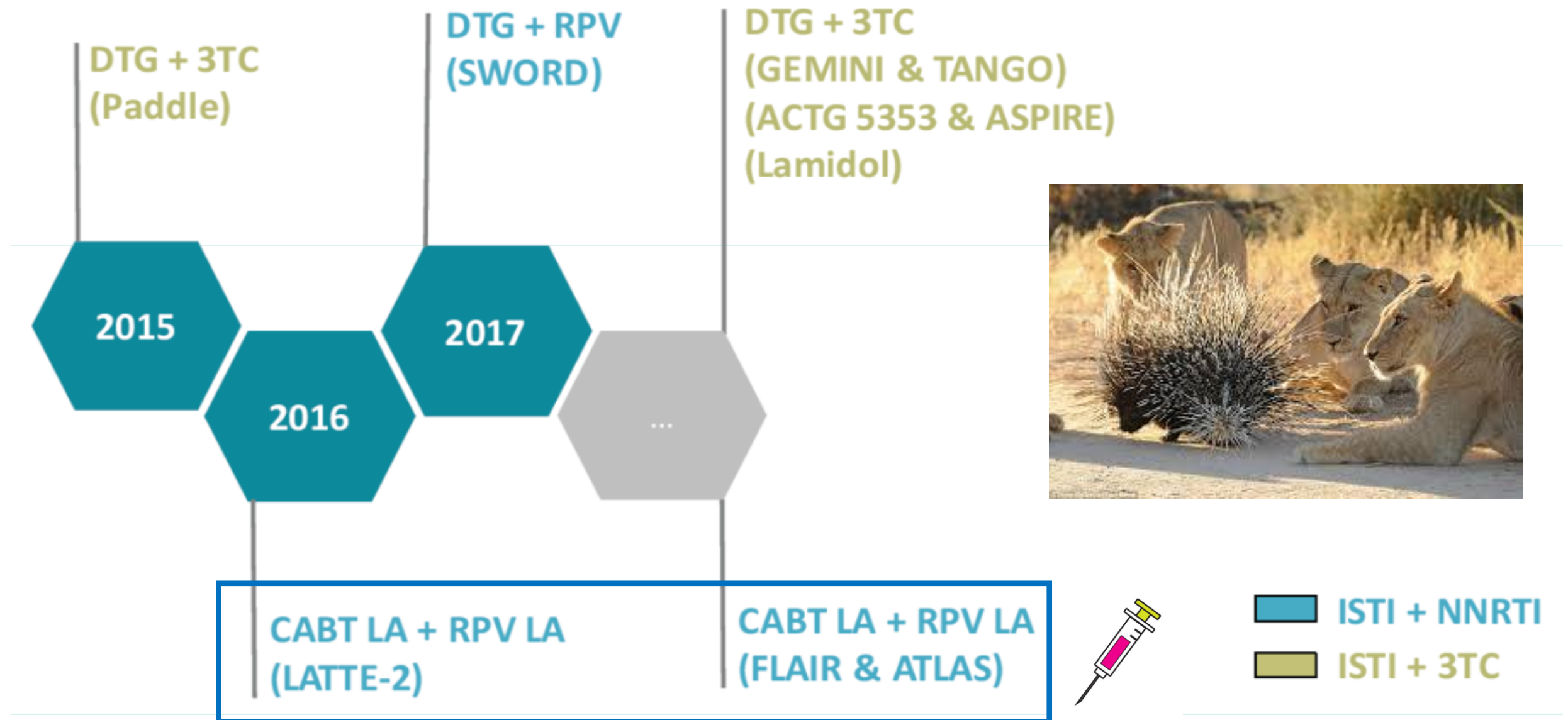
# Other future options?

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)

# Reduced drug regimens in ARV-naïve patients

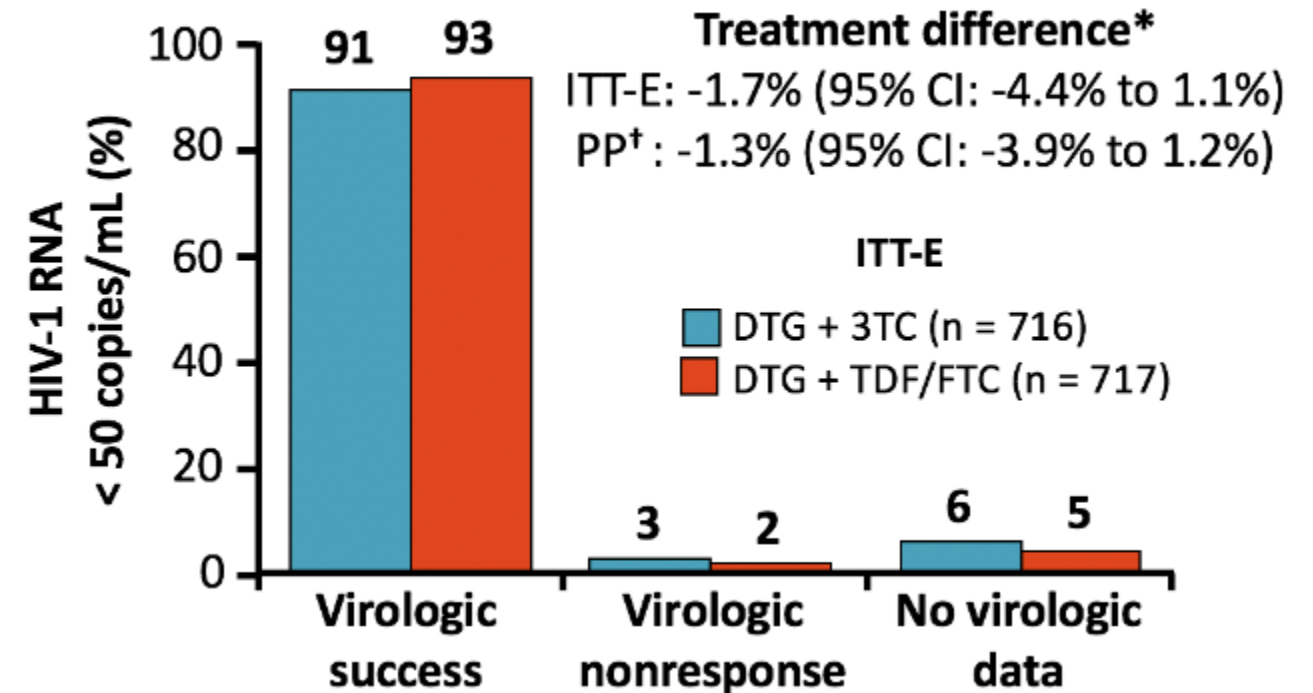
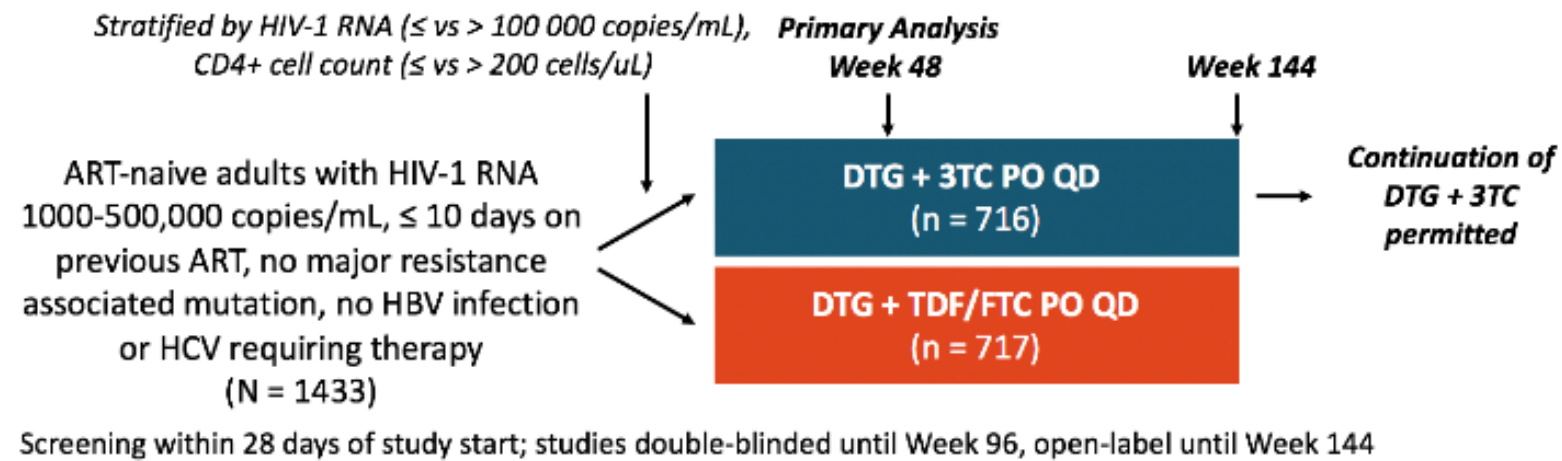


# DTG-based dual therapy regimens

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



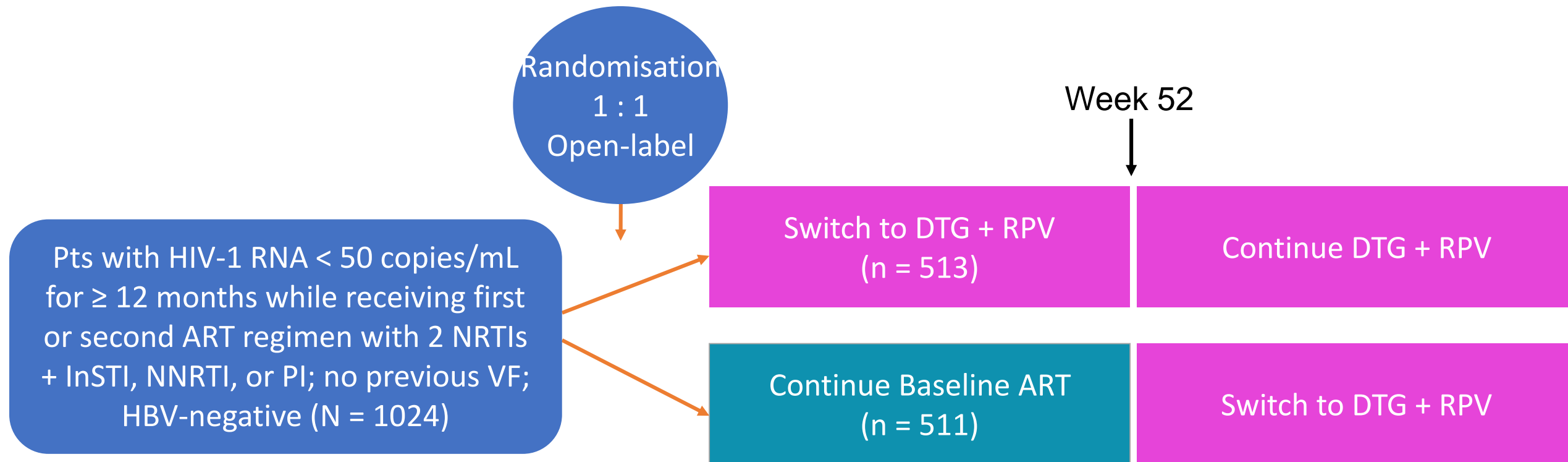
- No treatment-emergent InSTI or NRTI mutations in patients with VF in either arm
- Confirmed VF with DTG + 3TC: n = 6; Confirmed VF with DTG + TDF/FTC: n = 4
- Bone and kidney safety markers more favourable with DTG + 3TC vs DTG + TDF/FTC

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

\*Adjusted for HIV-1 RNA ( $\leq$  vs  $>$  100 000 copies/mL), CD4+ cell count ( $\leq$  vs  $>$  200 cells/uL), and study (GEMINI-1 vs GEMINI-2).

<sup>†</sup>PP = the ITT-E population excluding significant protocol violations

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



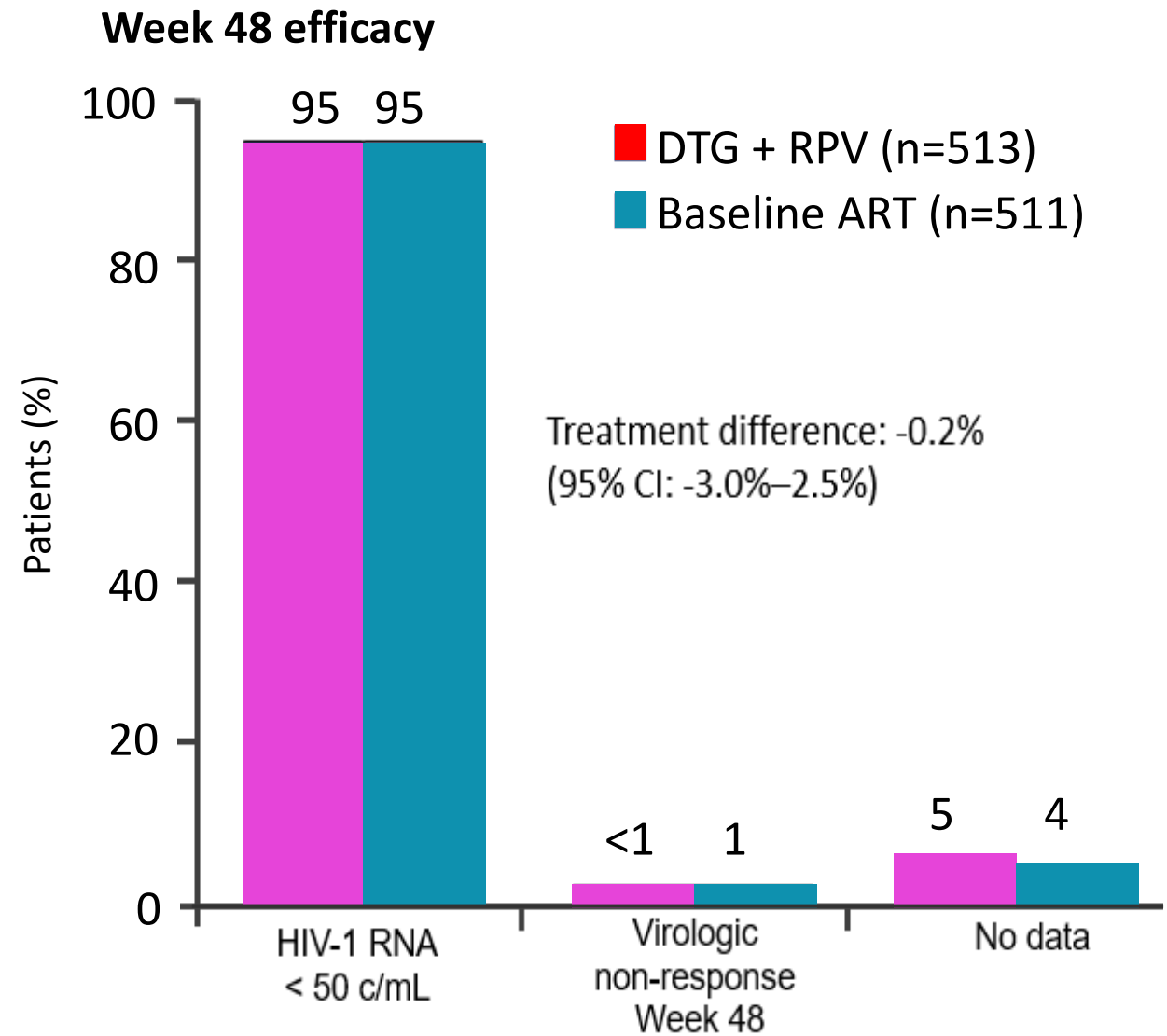
**Objectives:** To evaluate the efficacy and safety of DTG + RPV compared with continuation of current ART regimen (CAR) for 48 weeks in a large randomised population with suppressed viral load

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

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



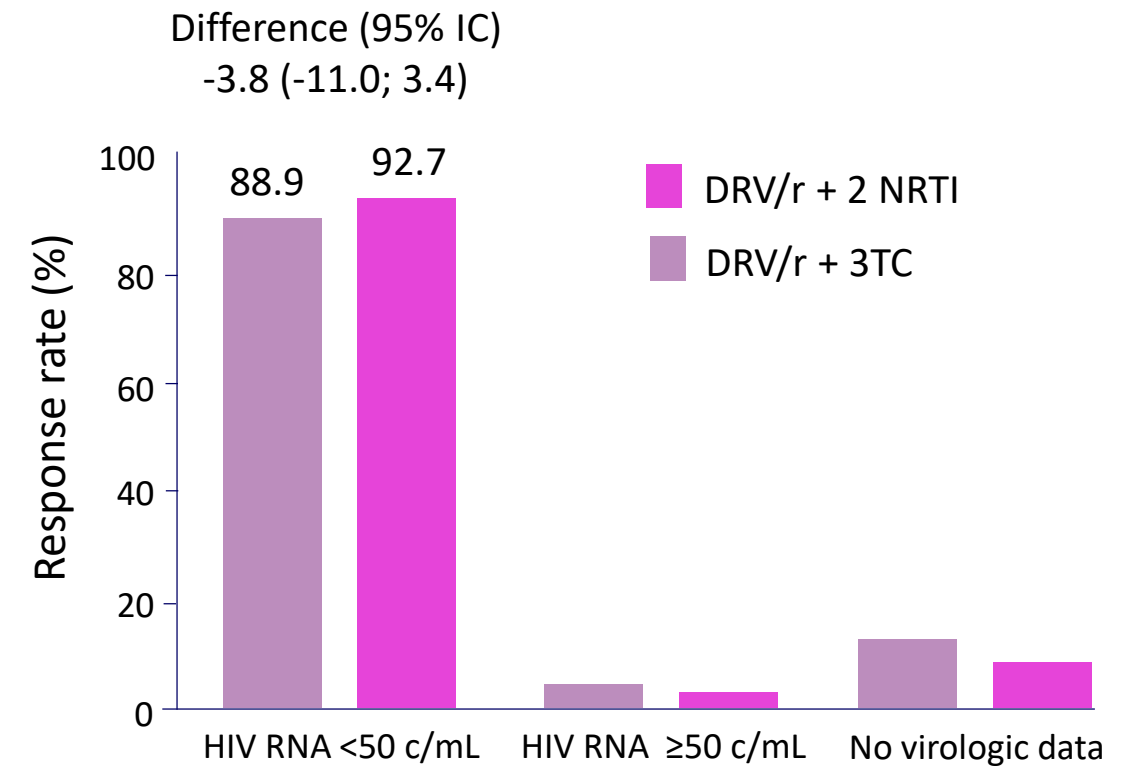
DTG + RPV was non-inferior to CAR (current ART regimen) over 48 weeks in participants with HIV suppression  
Results support the use of this two-drug regimen to maintain HIV suppression

# 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	76	74
ABC/3TC	24	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

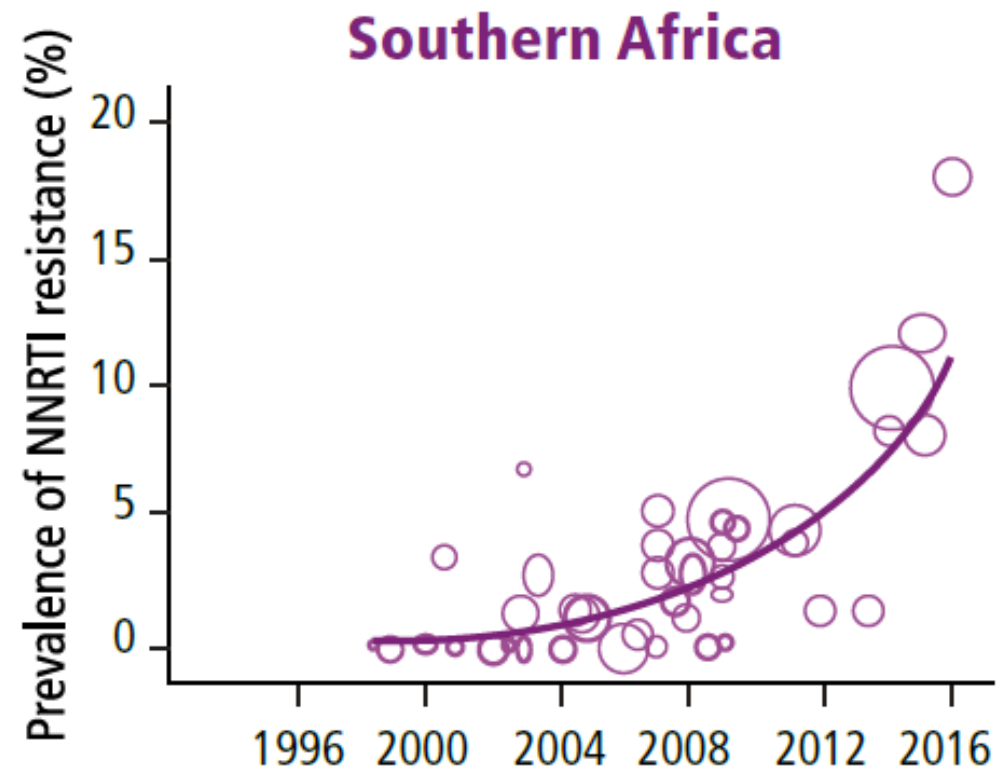


- Dual therapy with **DRV/r plus 3TC** was **non-inferior** regarding maintenance of viral suppression and **equally well tolerated** as DRV/r plus TDF/FTC (or ABC/3TC)
- Persistent virological suppression was maintained after switching to dual therapy with DRV/r plus 3TC

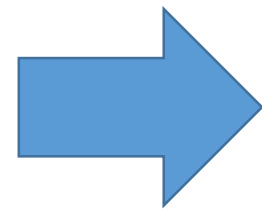


# Prevalence of NNRTI pretreatment resistance by calendar year across studies

Increasing trends in levels of DR observed



Studies: 60 Patients: 11 855  
P-value for association: 0.0000



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<sup>1</sup>

# Addressing PDR

## ↓ chance of transmitting resistant virus

### Improve adherence

- Strengthen adherence support

### Potent fixed-dose combination regimens

- Suppress HIV-RNA
- High adherence

### VL monitoring

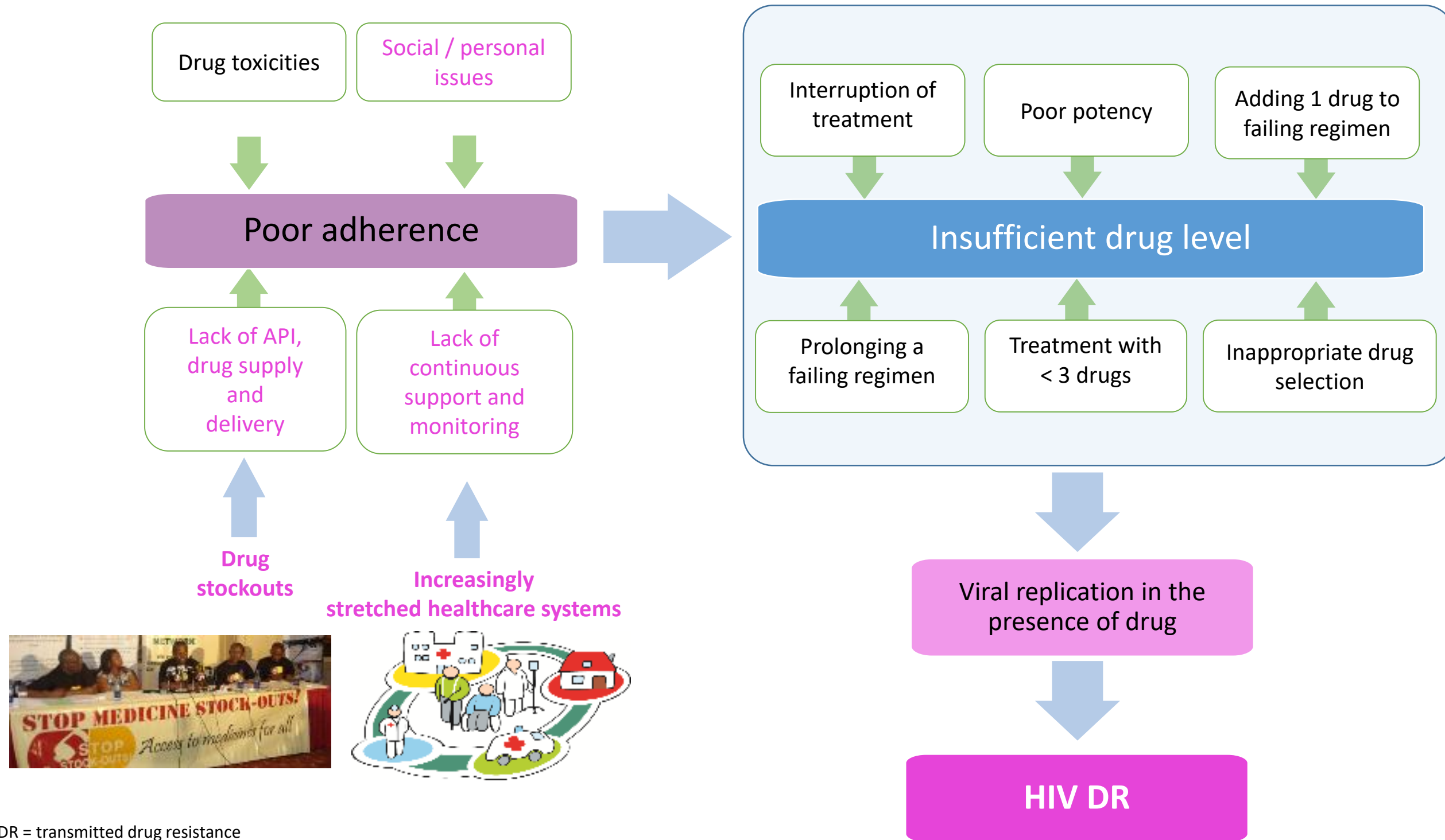
- Promptly switch individuals with confirmed VF to second-line treatment
- Minimise time spent on a failing regimen with resistant virus
- Perform viral load monitoring
- HIV-DR testing with failure

### Use agents with high genetic barrier

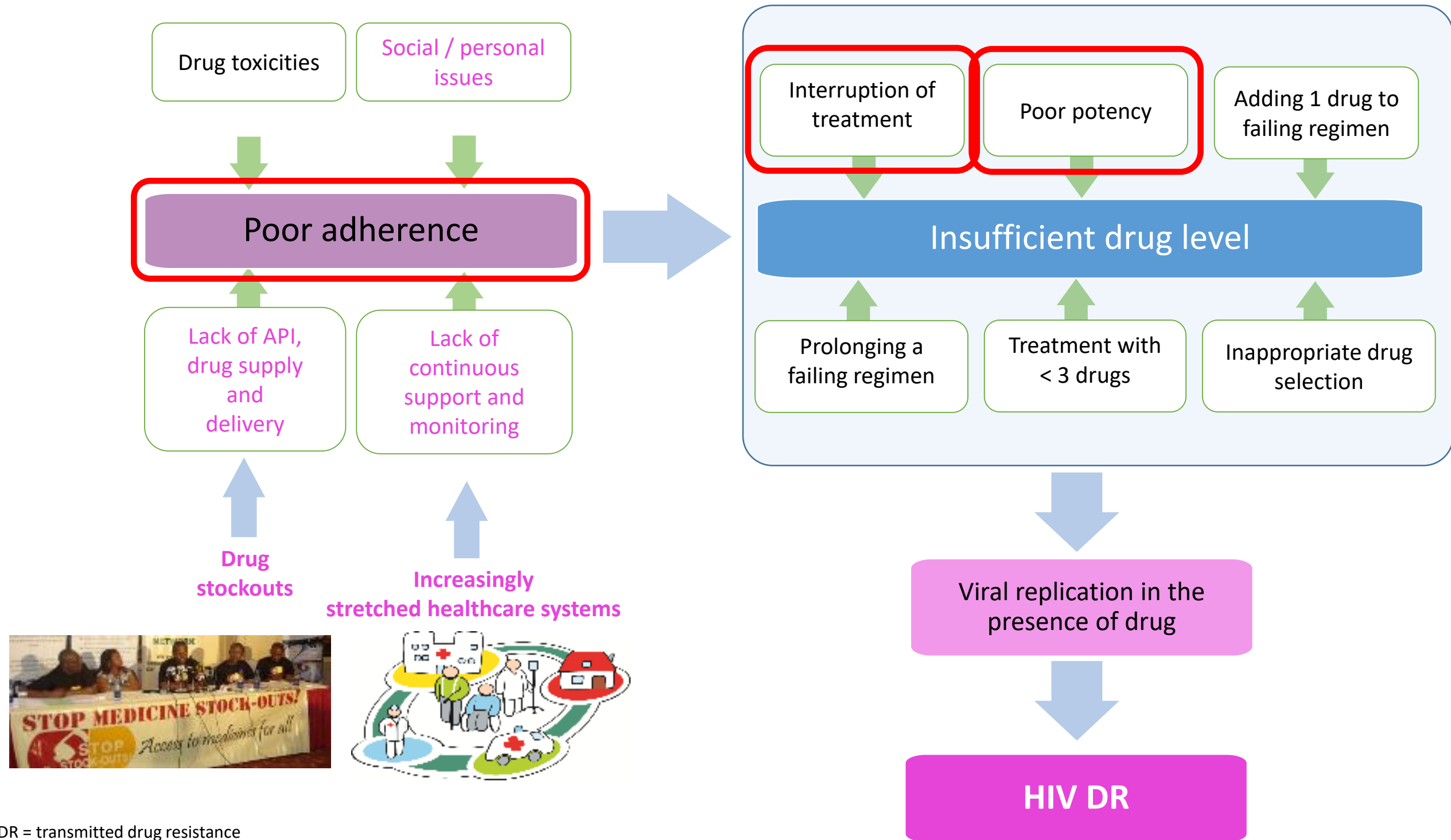
- Change first-line regimen at a national level, from an NNRTI-based regimen to DTG- or PI/r-based regimen

Which is the more cost-effective strategy?

# Factors influencing drug resistance



# Factors influencing drug resistance



# Acknowledgements



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

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

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October 2018

27<sup>th</sup> International  
Workshop on HIV Drug  
Resistance and Treatment  
Strategies



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