NNRTIs: an update

Michelle Moorhouse

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SAHCS Conference

University of the Witwatersrand
WITS RHI

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

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- 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

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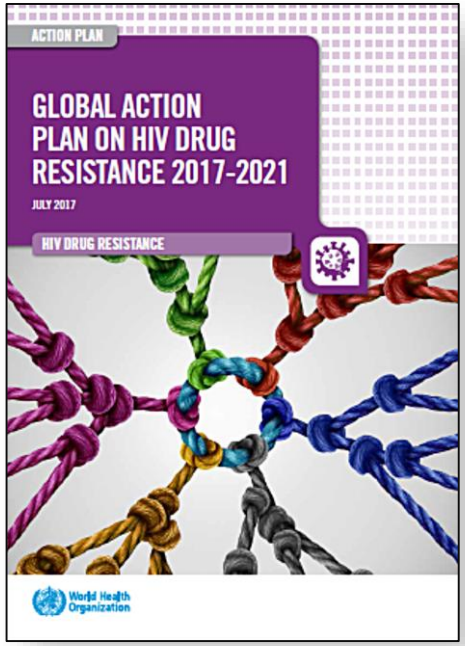
Flashback to 2016: Safest NNRTI

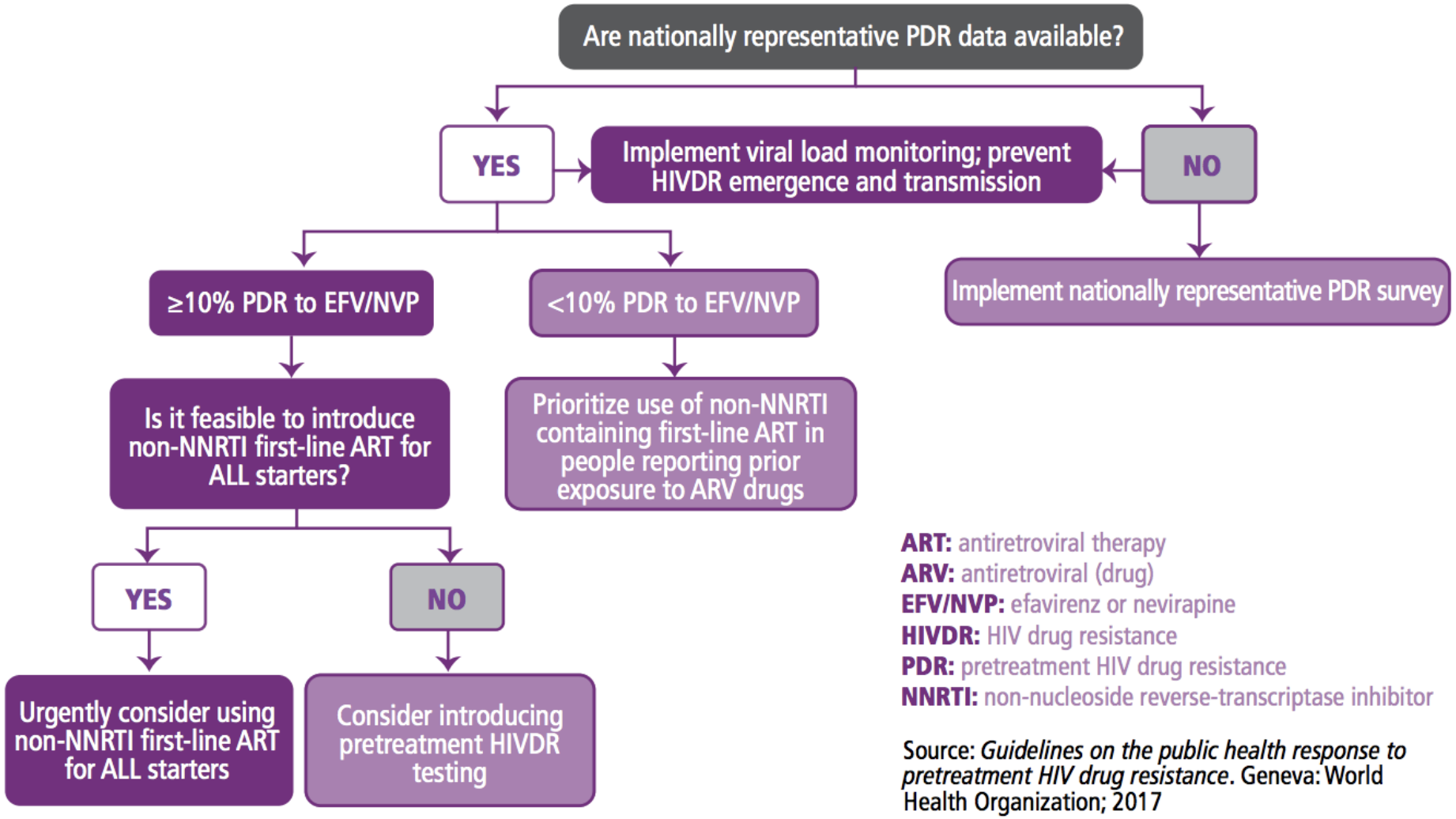
Rilpivirine

Safest NNRTI:

- Rilpivirine is the safest NNRTI for first-line
- EFV is more effective, so this should remain first choice
- Rilpivirine could replace nevirapine as the second choice NNRTI in first-line and could be used in third-line

WHO's recommendations on country response to NNRTI PDR

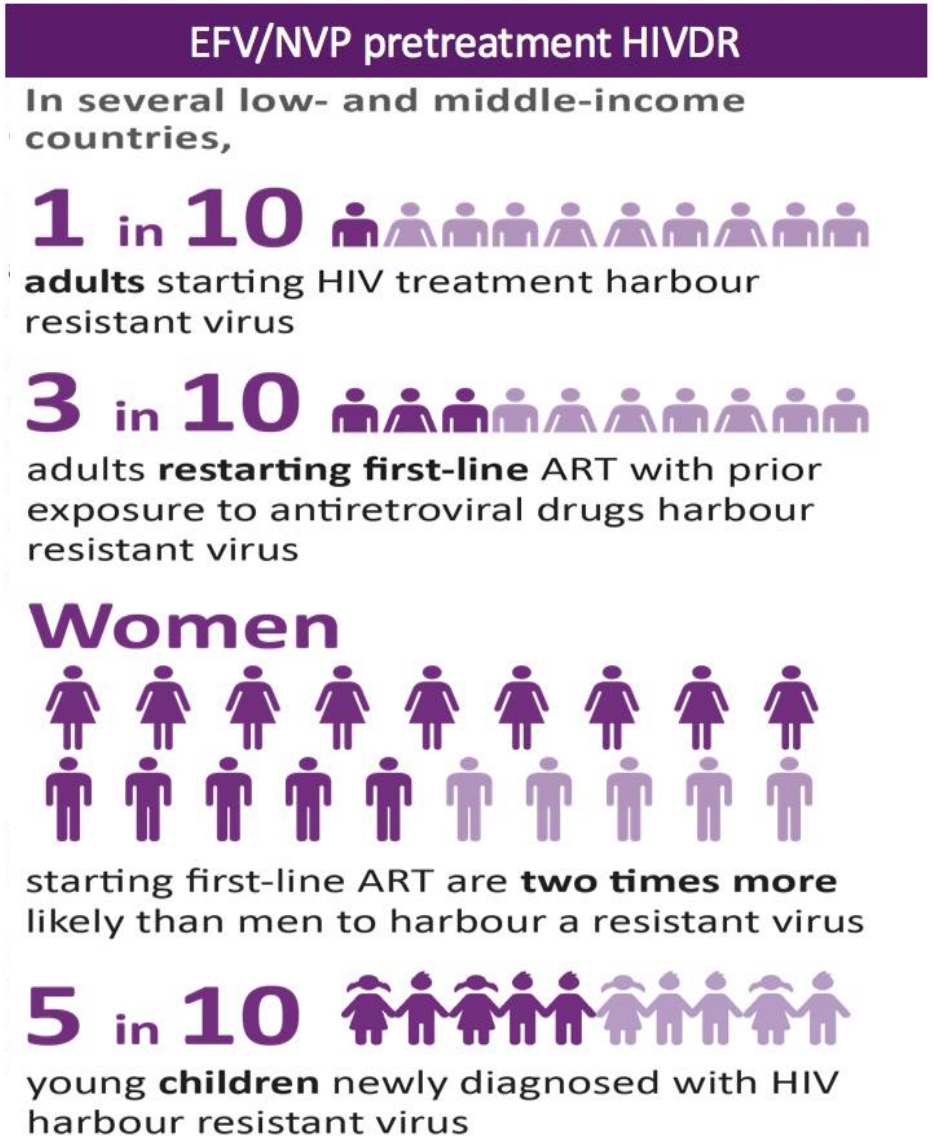


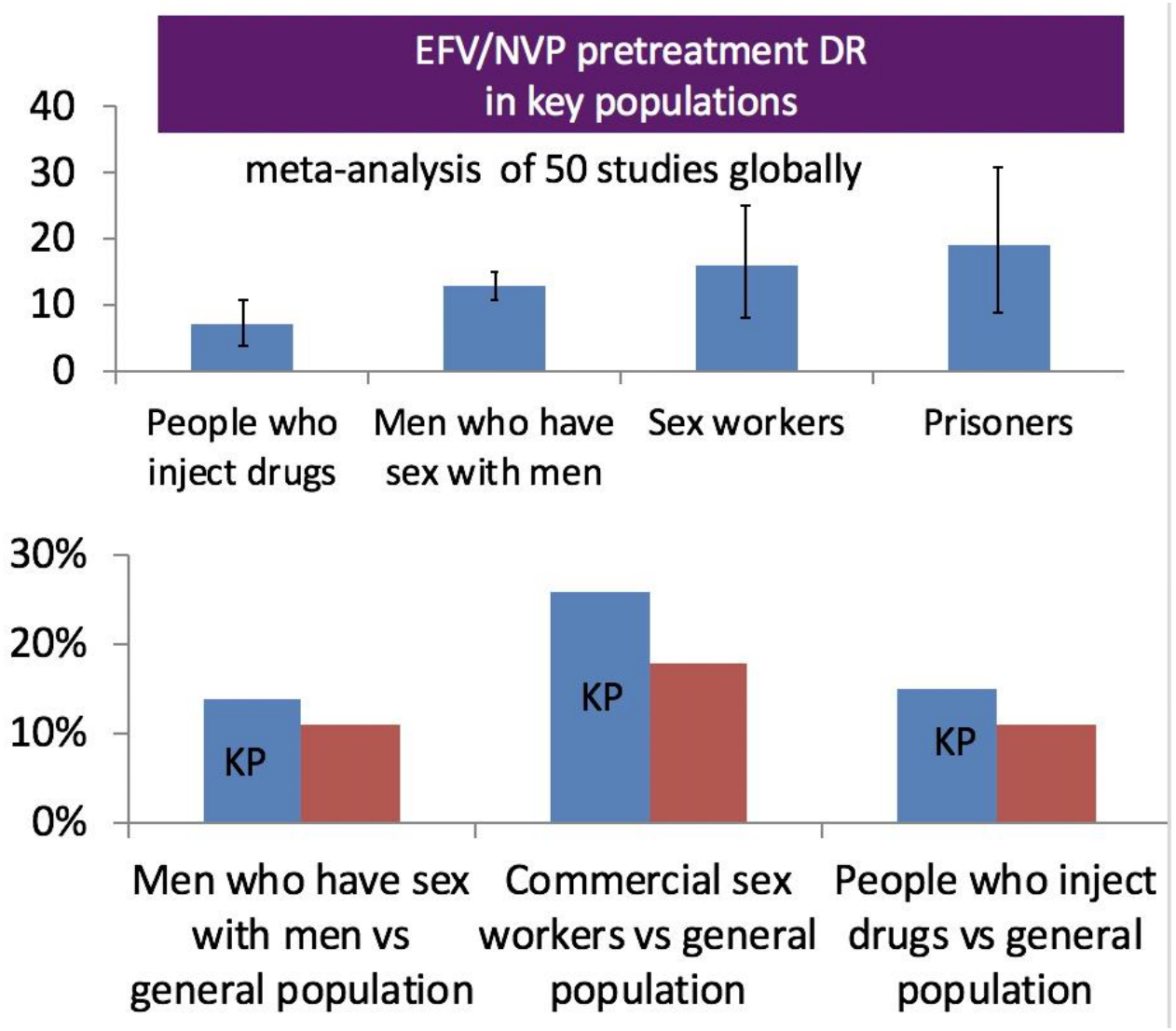


ART: antiretroviral therapy
ARV: antiretroviral (drug)
EFV/NVP: efavirenz or nevirapine
HIVDR: HIV drug resistance
PDR: pretreatment HIV drug resistance
NNRTI: non-nucleoside reverse-transcriptase inhibitor

Source: *Guidelines on the public health response to pretreatment HIV drug resistance*. Geneva: World Health Organization; 2017

Levels of pretreatment HIVDR (PDR): NNRTI





Thanks: Silvia B (WHO)

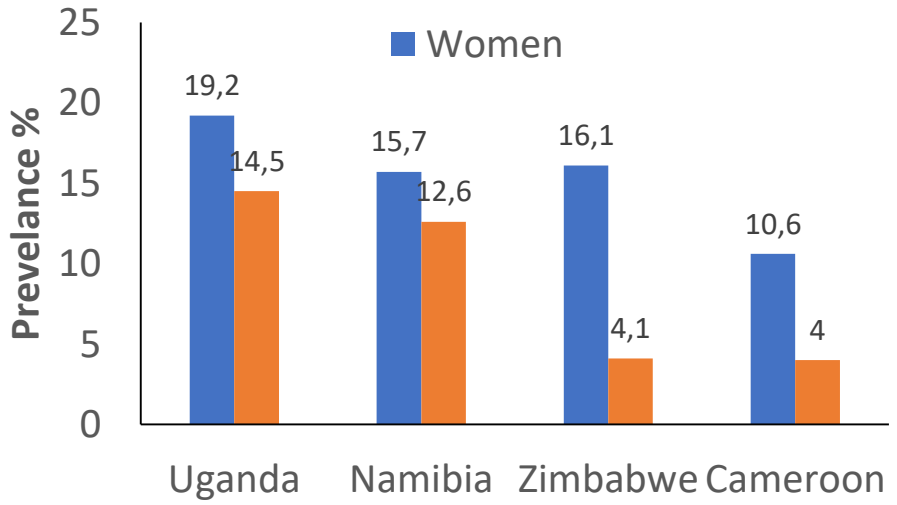
Pretreatment NNRTI drug resistance in special populations

- 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

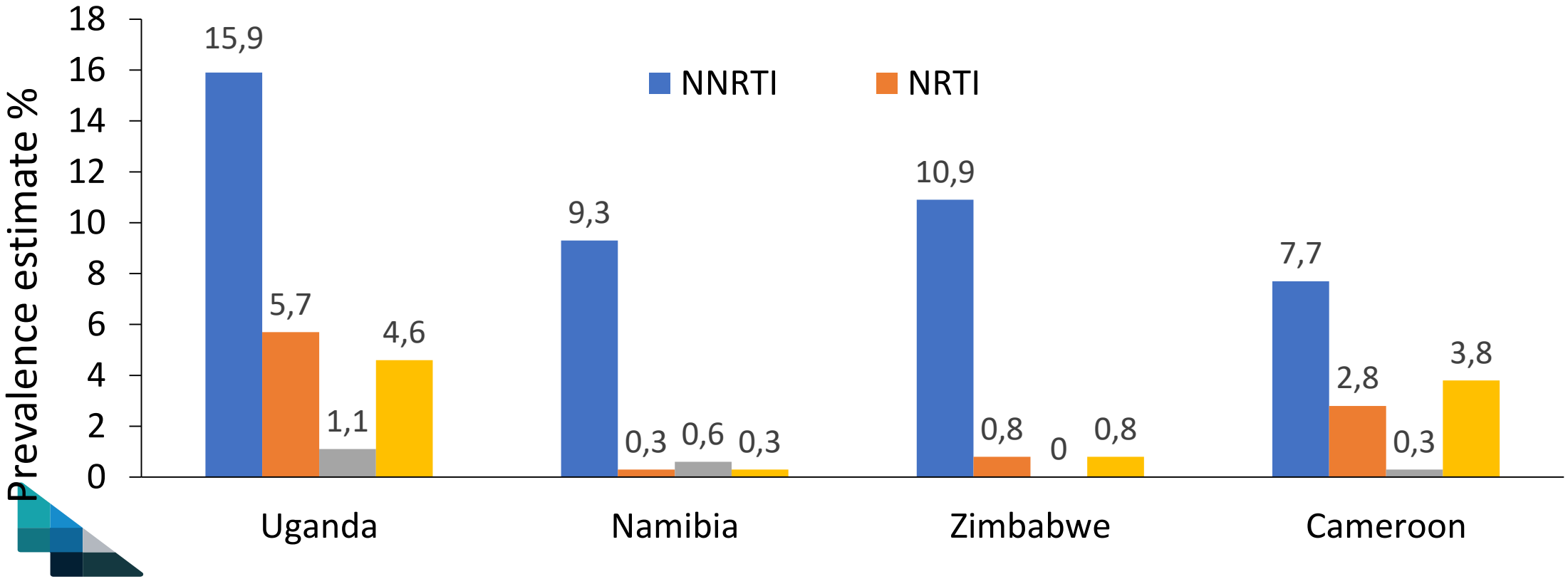
Prevalence estimates of pretreatment HIV DR



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**



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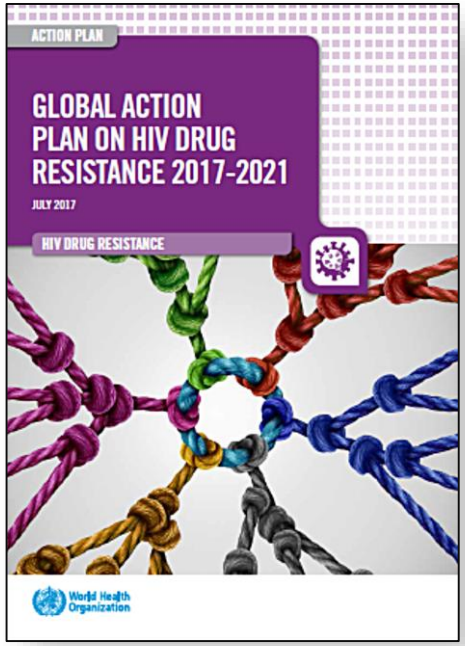
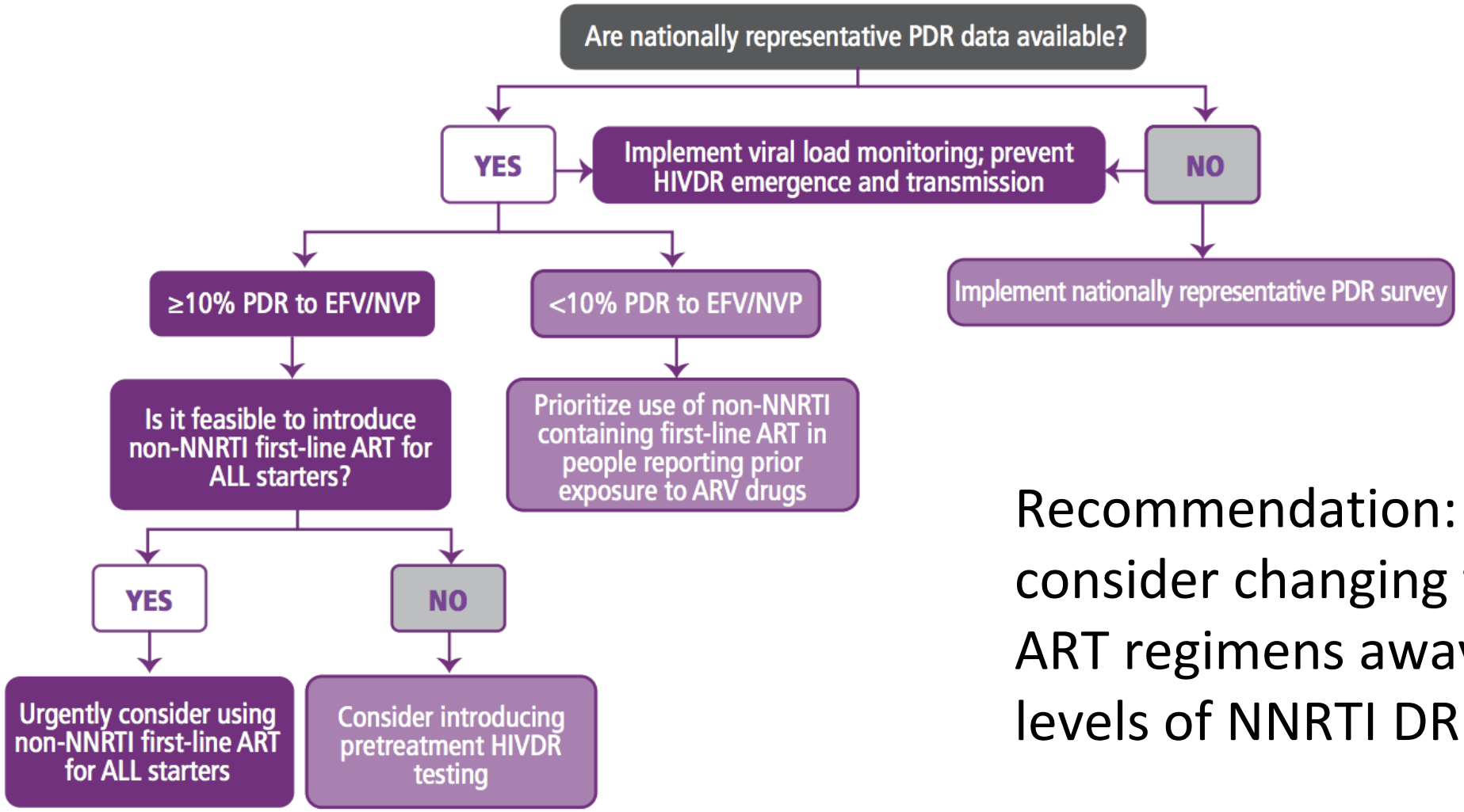
WHO's recommendations on country response to NNRTI PDR

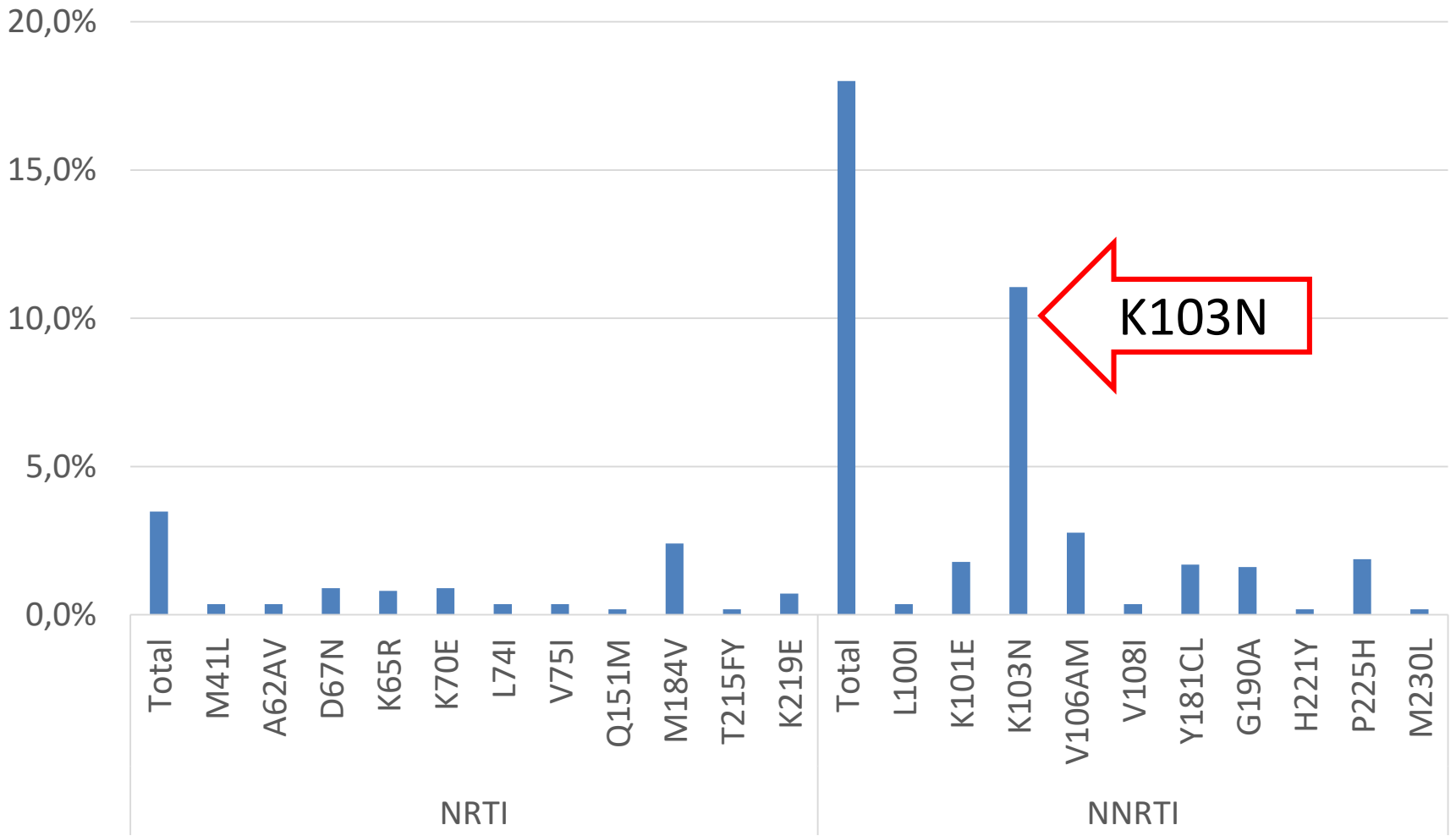




Recommendation: Countries should consider changing their first-line ART regimens away from NNRTIs if levels of NNRTI DR reach 10%

Most prevalent HIVDR mutations contributing to PDR in South Africa

- PDR: 17.5%
  - NNRTI: 13.9%
  - NNRTI and NRTI: 3.1%
  - NRTI: 0.5%
- Three participants harboured single major PI mutations (I54V, I84V)

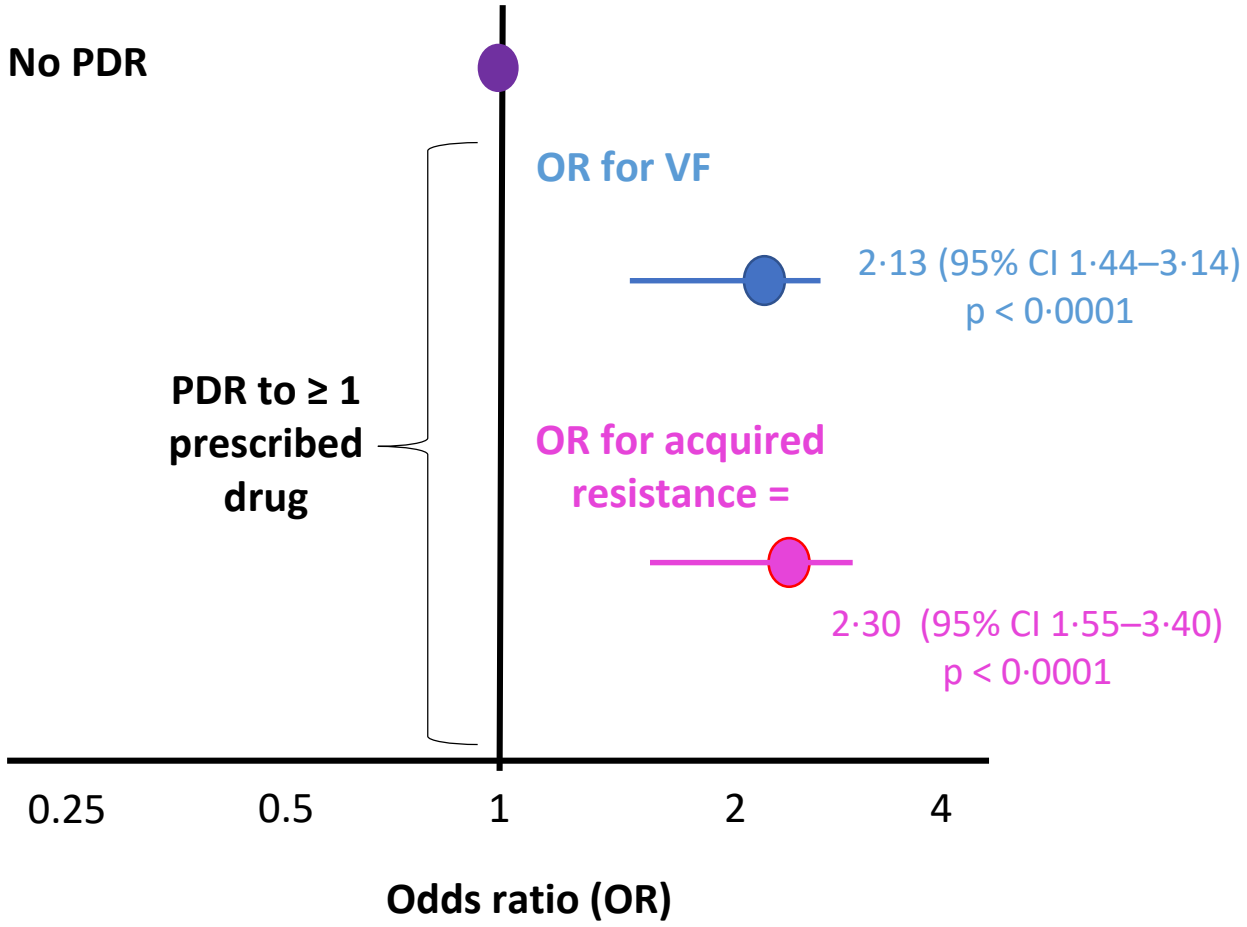


Hunt et al 2017

Magnitude of effect of PDR on long-term virological outcomes

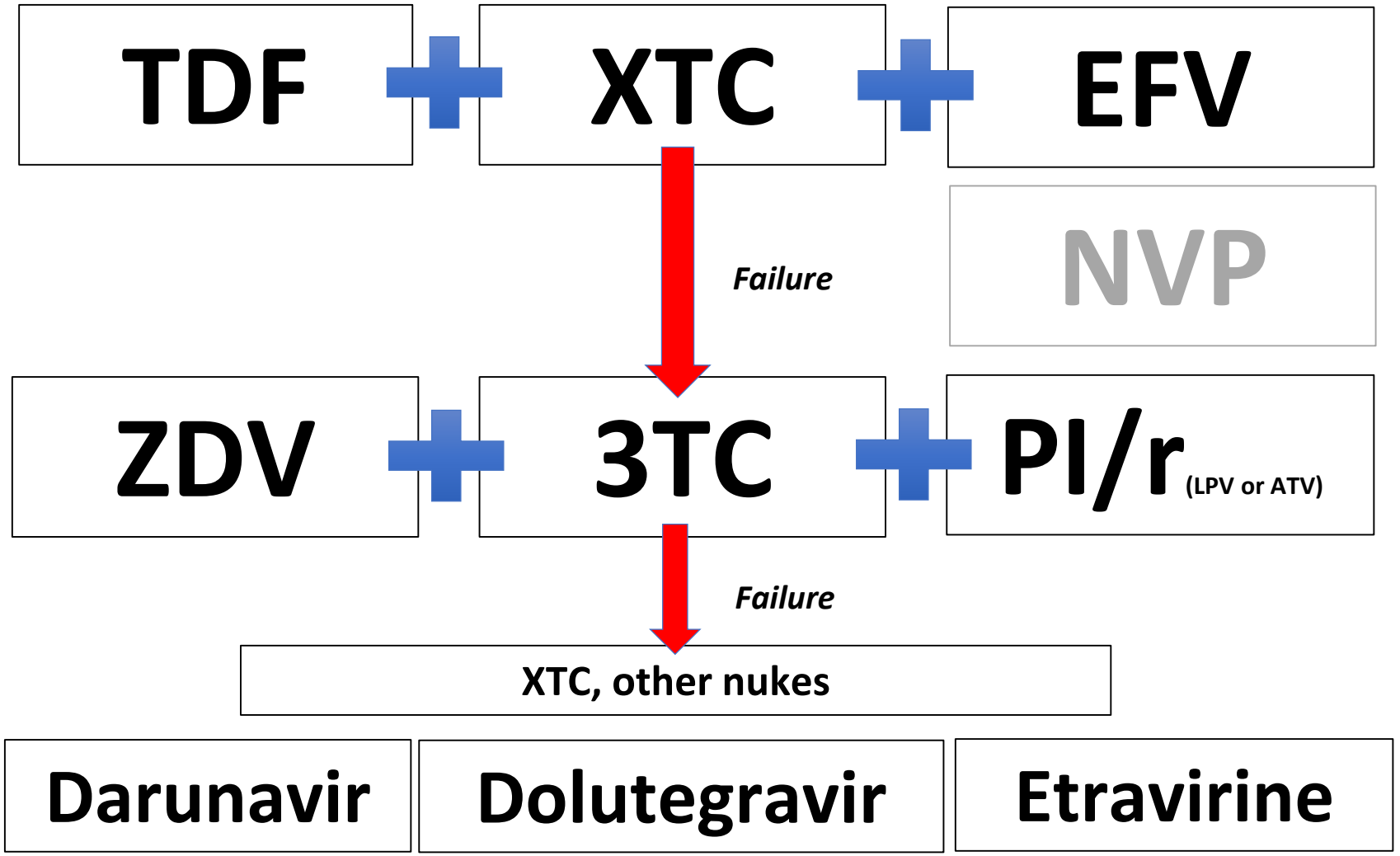
- Cohort data 2007–09; 6 countries in sub-Saharan Africa[1] with PDR results for 2579 patients
  - 2404 (93%) had no pretreatment DR
  - 123 (5%) had PDR to ≥ 1 prescribed drug
  - 52 (2%) had PDR and received fully active ART
- A separate retrospective study of 801 HIV-infected ARV-naive patients from 2001–09
  - Presence of transmitted NNRTI resistance → **1.5-fold** increased risk for treatment failure in the first 48 weeks after ART initiation[2]
- People with PDR NNRTI are **4.5 times** more likely to have unsuppressed VL

(systematic review, GDG WHO meeting, 2017)

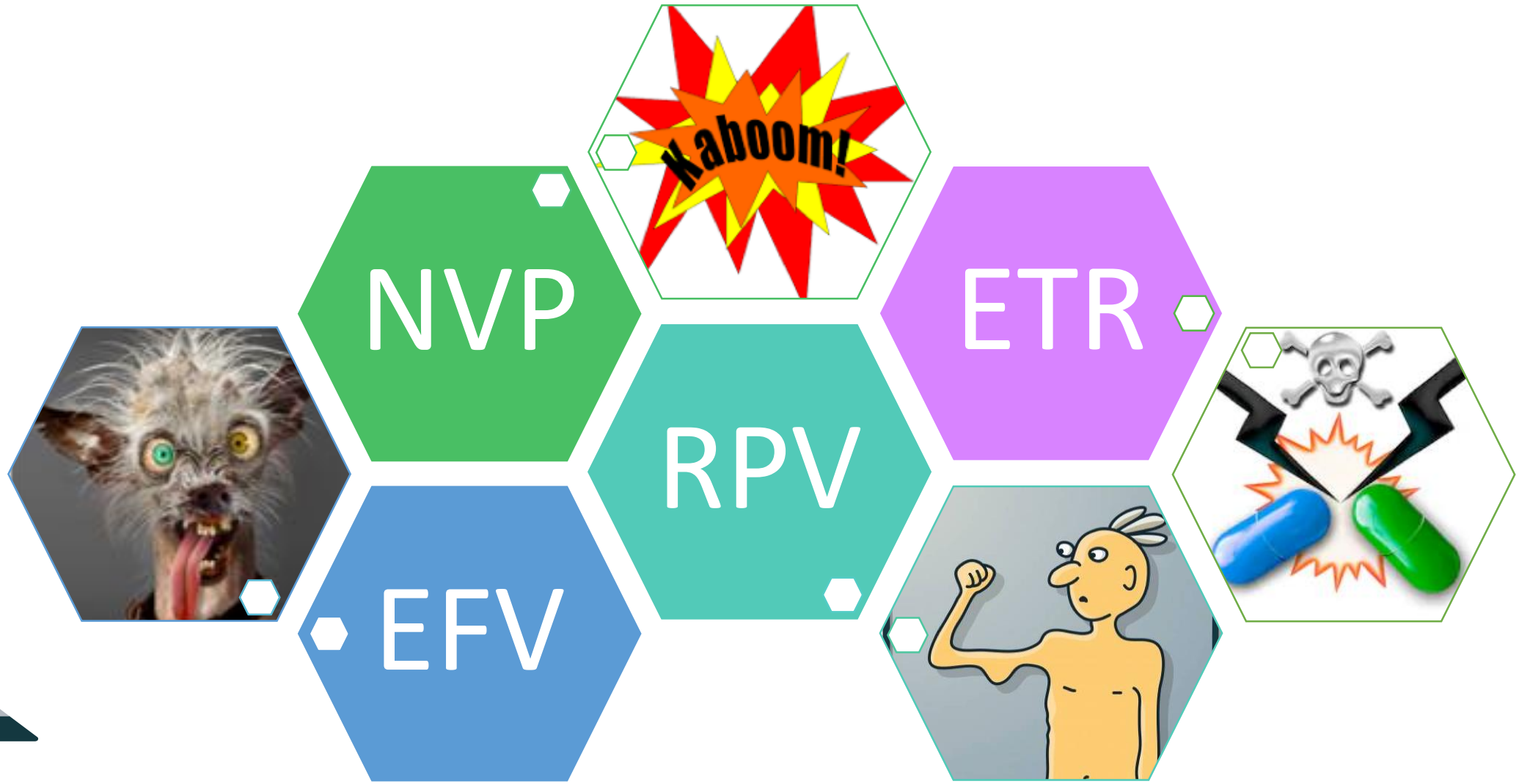


1. Hamers RL et al, Lancet Infect Dis. 2012;12:307–17 2. Taniguchi T et al. AIDS Res Hum Retroviruses 2012; 28:259-264
VF = virologic failure

SA has largest ARV programme: > 5 million



So what are the options?



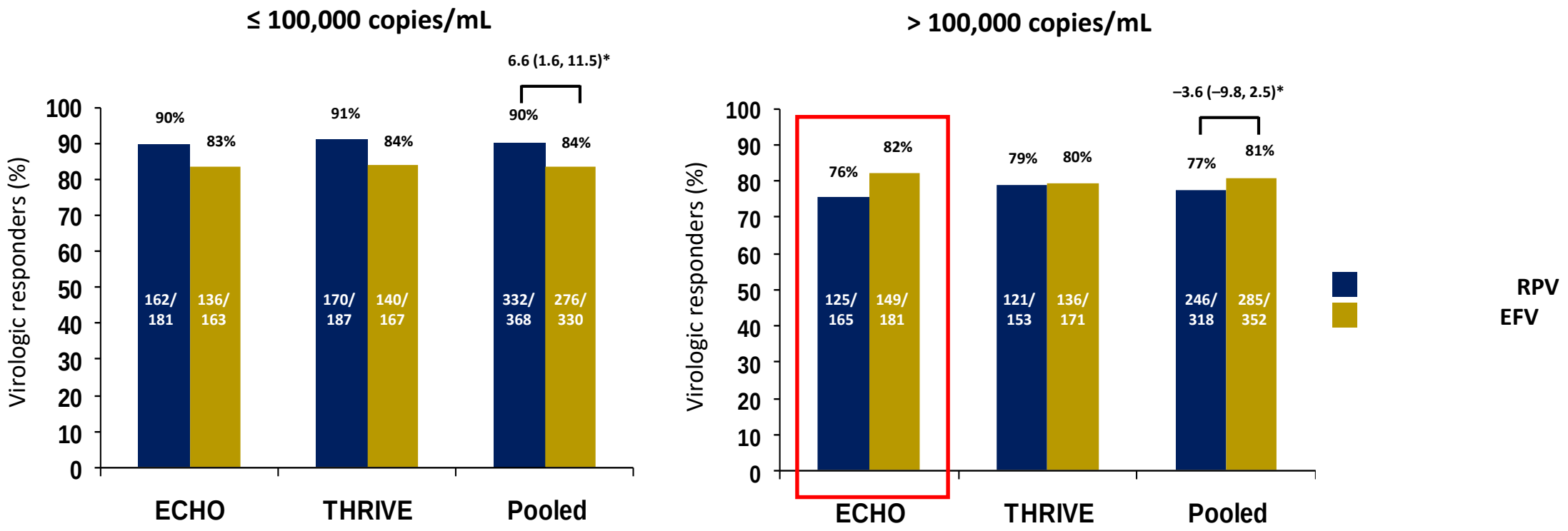
Safety and efficacy of EFV_{600} versus DTG in first-line ART (summary 2018 WHO Systematic Review and NMA)

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

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

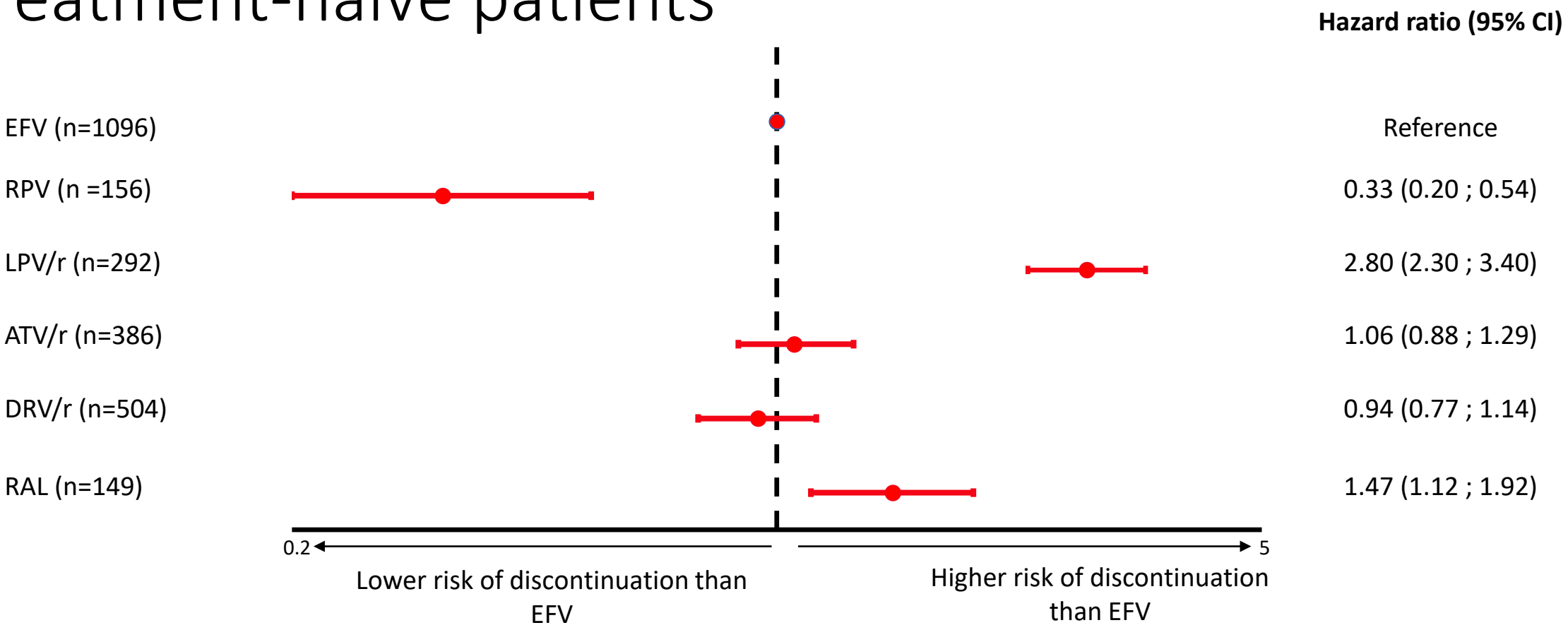
ECHO and THRIVE Week 48 analysis: VL < 50 copies/mL by baseline VL (ITT-TLOVR)



- 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

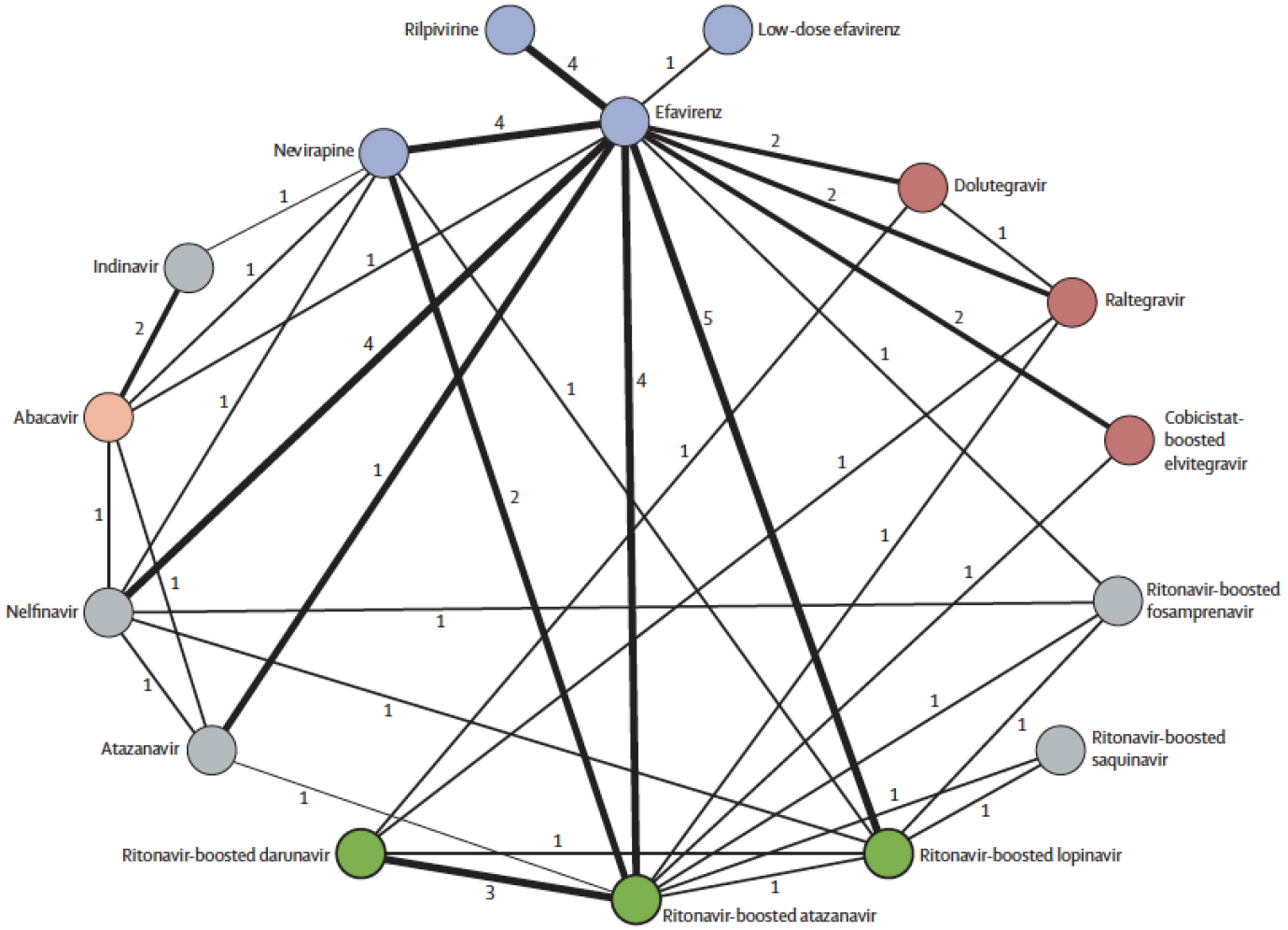
ICONA: Comparison of durability of first-line EFV and RPV with TDF/FTC

	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

Rilpivirine versus efavirenz

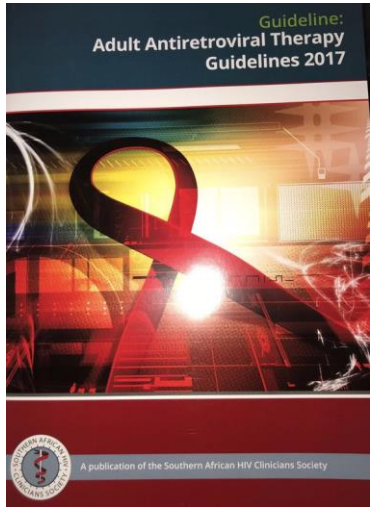


- Similar efficacy for virological suppression at 48 and 96 weeks
- Less discontinuations with rilpivirine relative to efavirenz

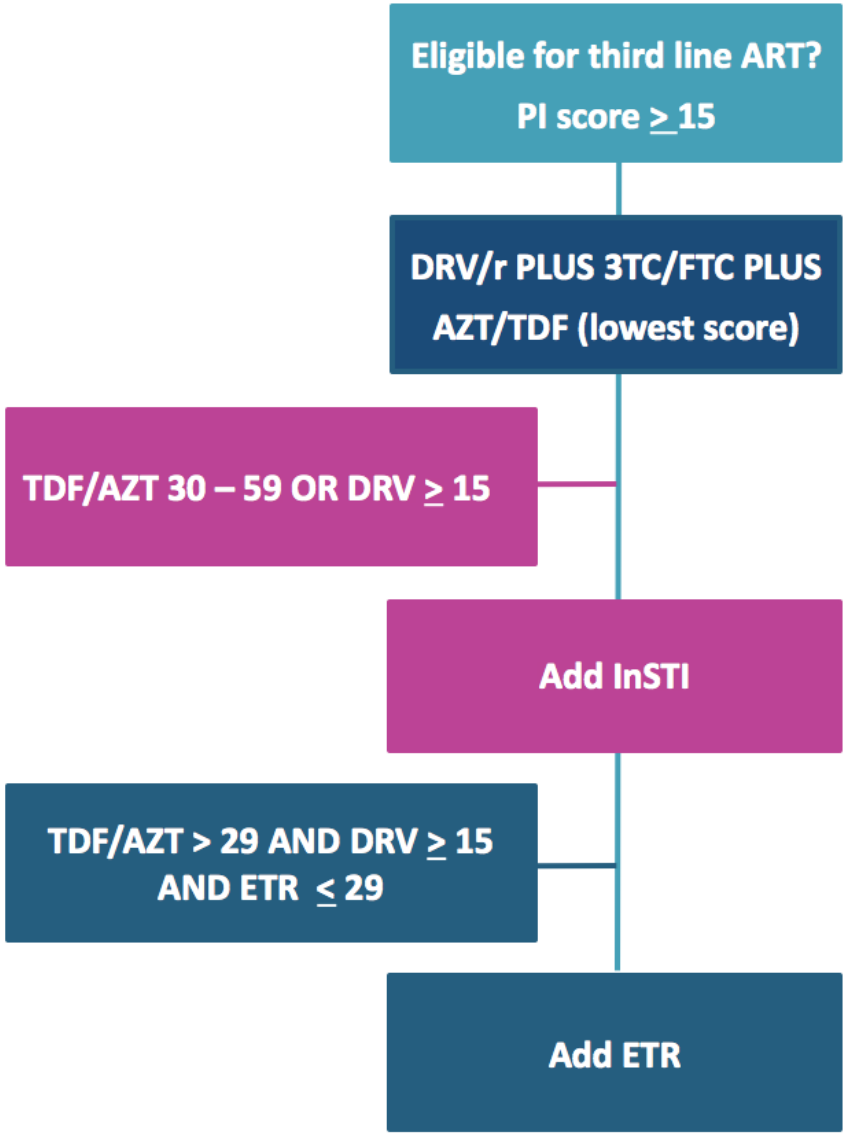
Where does rilpivirine fit in?

TABLE 4: Preferred first-line regimen options.

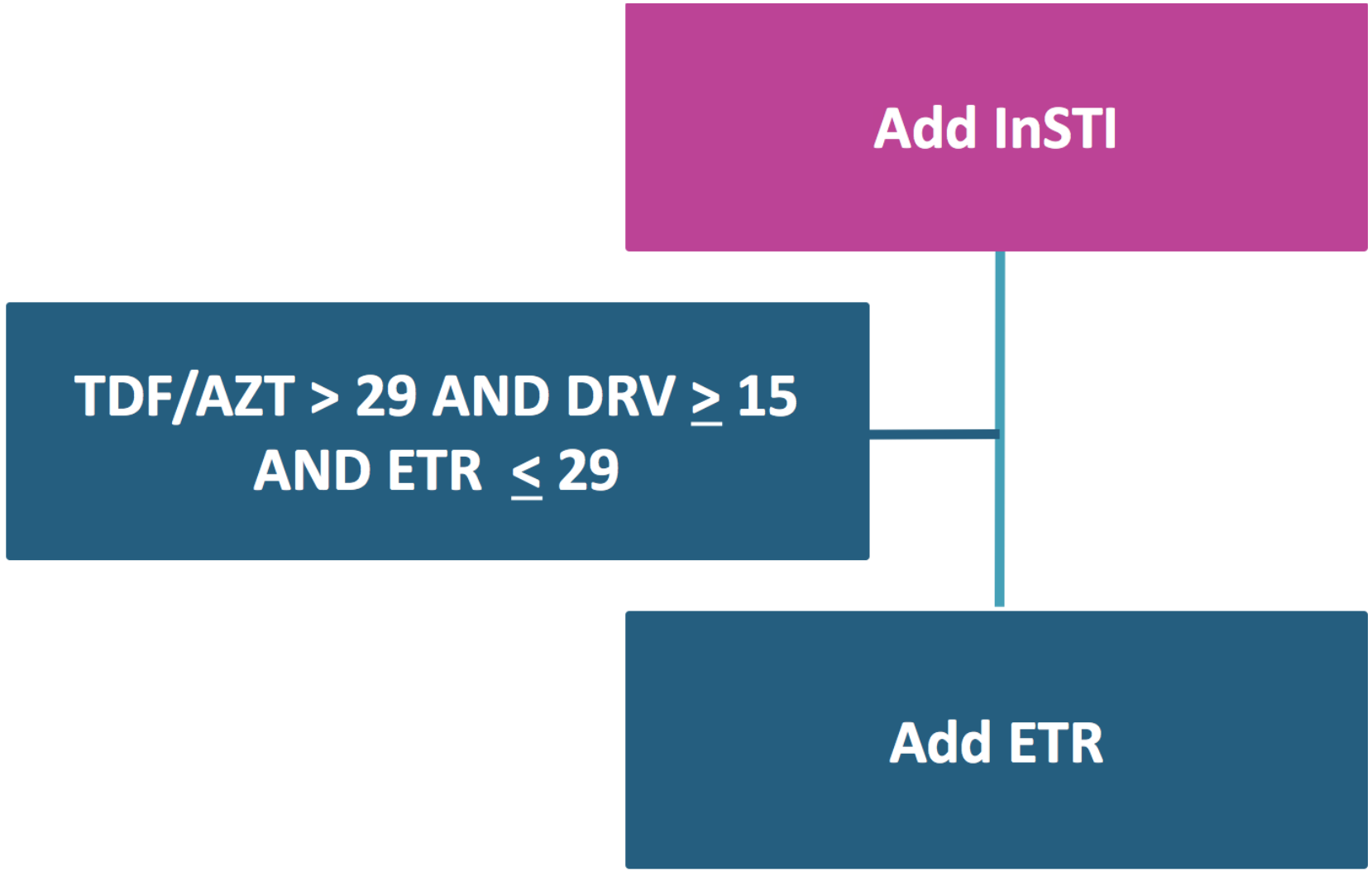
Options	Preferred	Alternative	One of
NRTI backbone	TDF + FTC/3TC	ABC† + 3TC	–
	–	AZT‡ + 3TC	–
	–	d4T§ + 3TC	–
Third drug	–	–	EFV
	–	–	DTG
	–	–	RPV¶



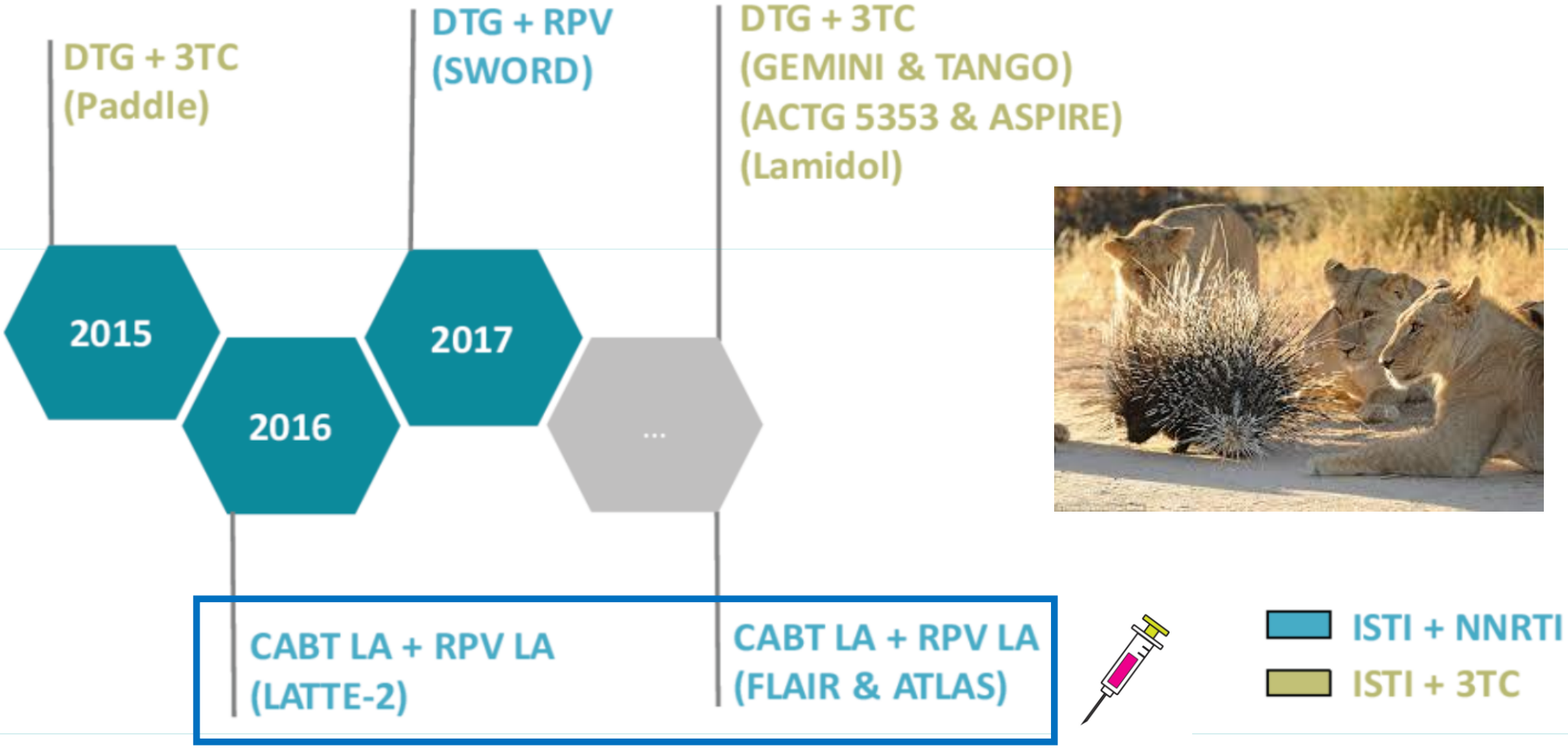
But not in WHO or SA national guidelines



And etravirine?



Reduced drug regimens in ARV-naïve patients



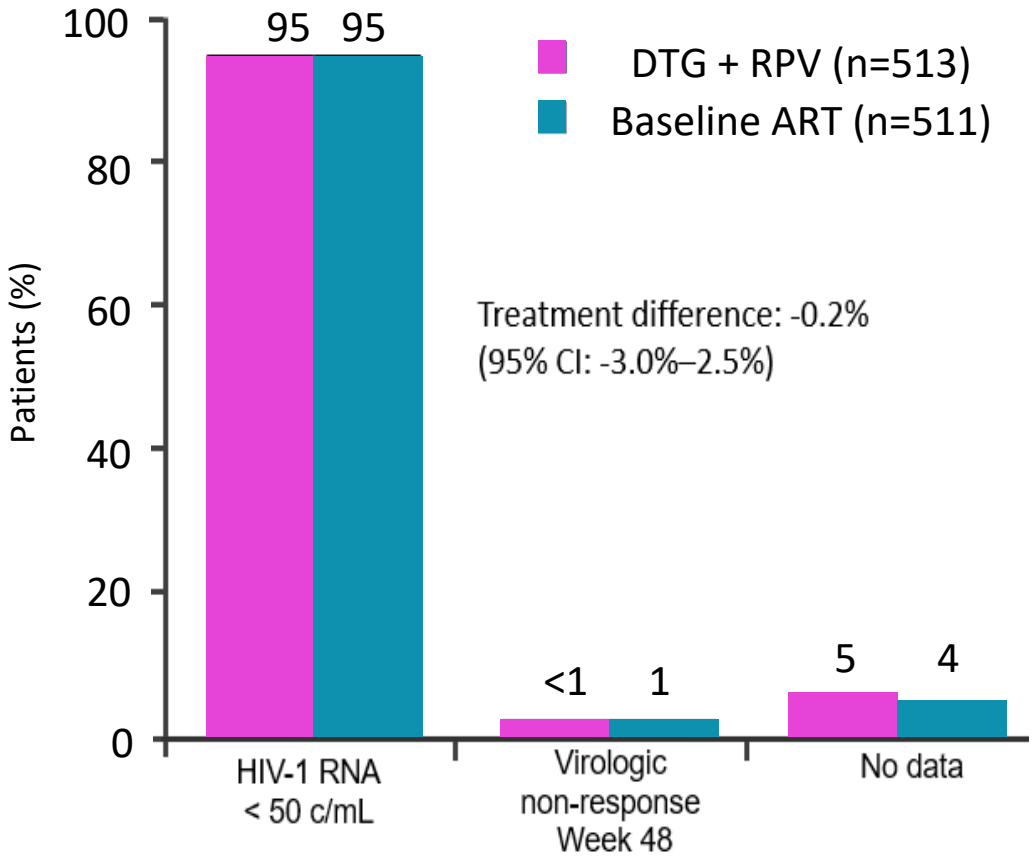
Courtesy: J Arribas

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

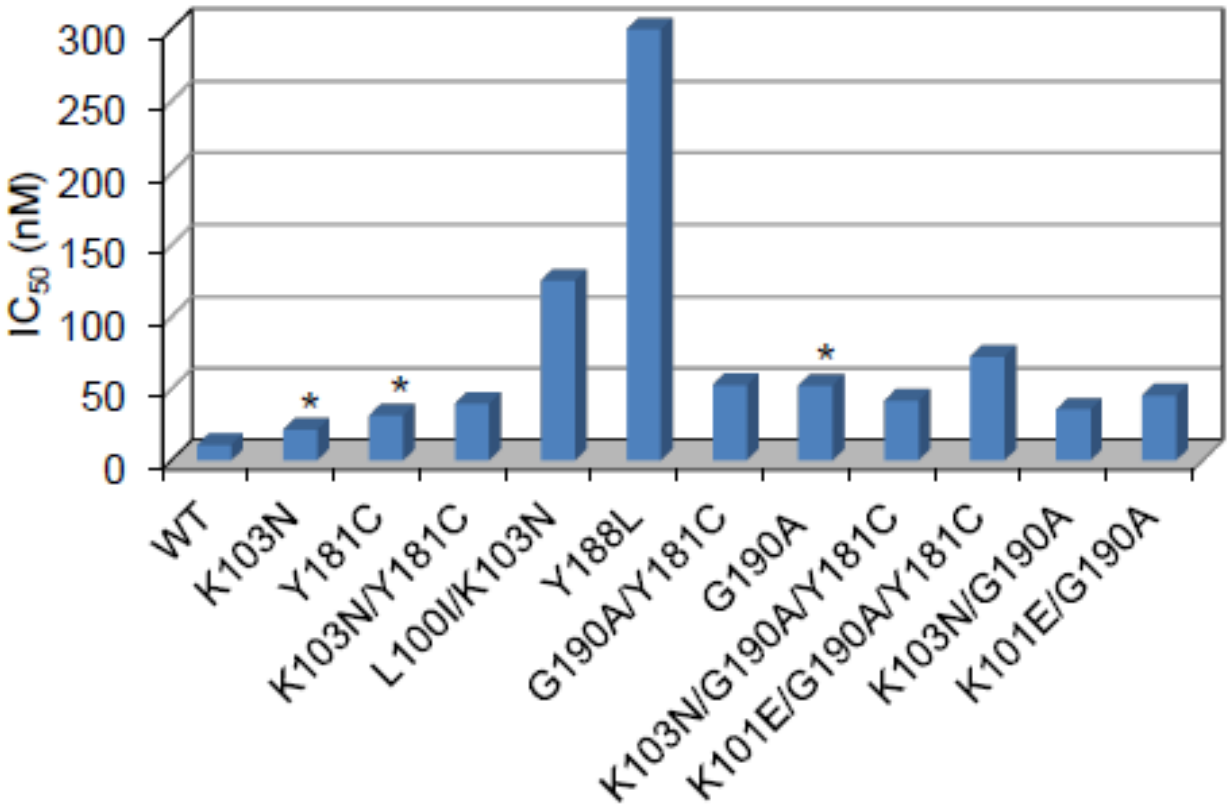
Week 48 efficacy



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

Future options?



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

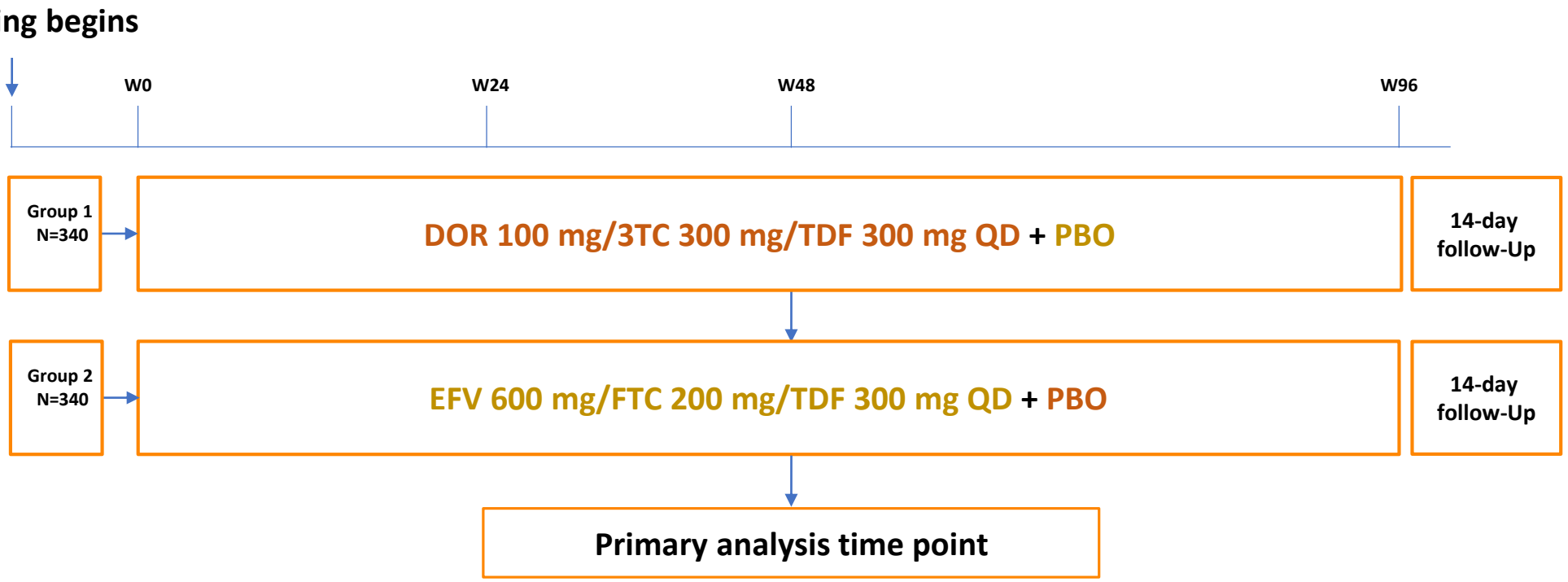
Doravirine retains antiviral potency against the most prevalent NNRTI-associated resistant viruses

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

Doravirine

Key entry criteria:

- HIV-1 RNA ≥1000 copies/mL within 45 days before Day 1
- Antiretroviral-naïve
- No genotypic resistance to any study drugs
- Stratification factors: HIV-1 RNA >100,000 copies/mL and chronic hepatitis B or C infection status



1. Molina JM, et al. AIDS 2018. Abstract LBPEB017. 2. Molina JM, et al. CROI 2017. Abstract 45LB.

Safest NNRTI

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- EFV is more effective, so this should remain first choice
- Rilpivirine could replace nevirapine as the second choice NNRTI in first-line and could be used in third-line

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- EFV is more effective, so this should remain first choice NNRTI
- Rilpivirine should replace nevirapine as the second choice NNRTI in first-line and is used in third-line
- With increasing NNRTI PDR, we are moving into the InSTI era

NNRTIs: an update

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