BHIVA
British HIV Association

2023 Spring Conference

Mon 24th – Wed 26th April
Gateshead, UK

HIV and Resistance

Chair:
Nicola Mackie

This educational event is supported by

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MSD
ViiV Healthcare

Public health approach to HIV treatment and the impact of drug resistance

Nick Paton

National University of Singapore

BHIVA
British HIV Association
2023 Spring Conference
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The public health approach to HIV treatment, and resistance issues

Prof. Nicholas Paton MD FRCP
National University of Singapore
London School of Hygiene and Tropical Medicine

Conflict of Interest

Grant support (NADIA, TRUNCATE-TB, CARES trials) from Janssen

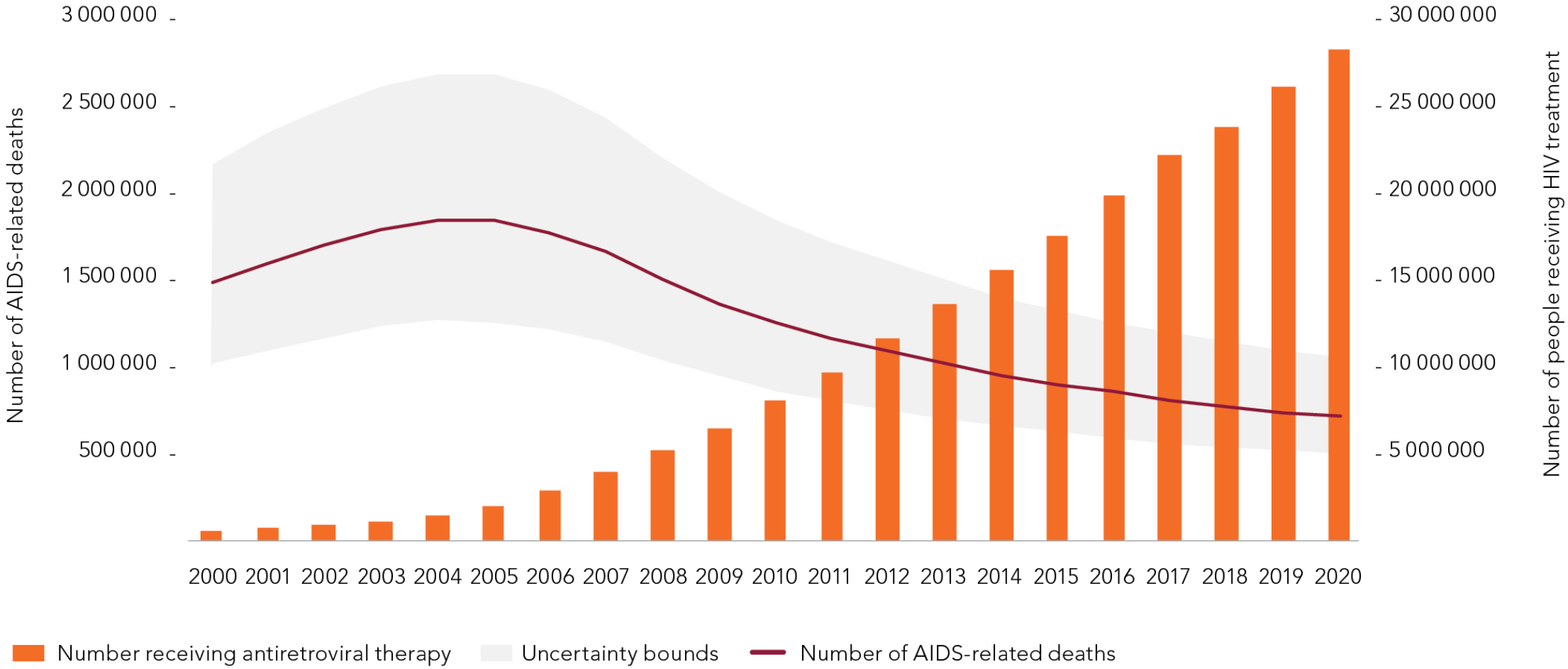
In kind support (drug donations for trials) from Sanofi and Pfizer

Speakers are required by the Federation of the Royal Colleges of Physicians to disclose conflicts of interest at the beginning of their presentation, with sufficient time for the information to be read by the audience. They should disclose financial relationships with manufacturers of any commercial product and/or providers of commercial services used on or produced for patients relating to the 36 months prior to the event. These include speaker fees, research grants, fees for other educational activities such as training of health professionals and consultation fees. Where a speaker owns shares or stocks directly in a company producing products or services for healthcare this should also be declared.

Content

- Key components of the public health approach
- Standard regimens recommended in the public health approach
- Evidence for efficacy of those regimens (especially in context of NRTI resistance – EARNEST and NADIA trials)
- Role of resistance mutations in NRTI drug activity
- Current position of drug selection in the public health approach

Numbers of AIDS-related deaths and people receiving HIV treatment, global, 2000–2020



Source: UNAIDS epidemiological estimates, 2021.

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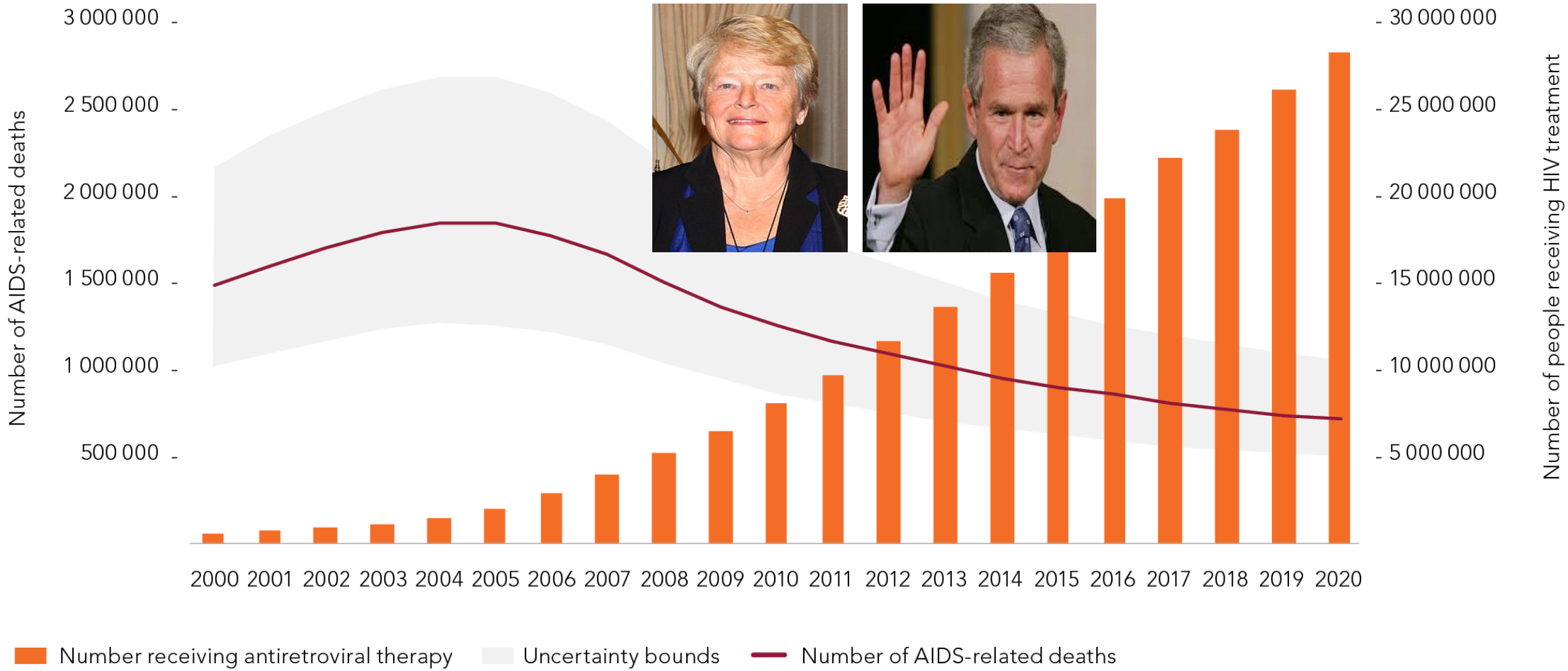


Source: UNAIDS epidemiological estimates, 2021.

WHO's public health approach

Minimal number of standard regimens

2 regimens, non-overlapping drugs (remove need for resistance testing)

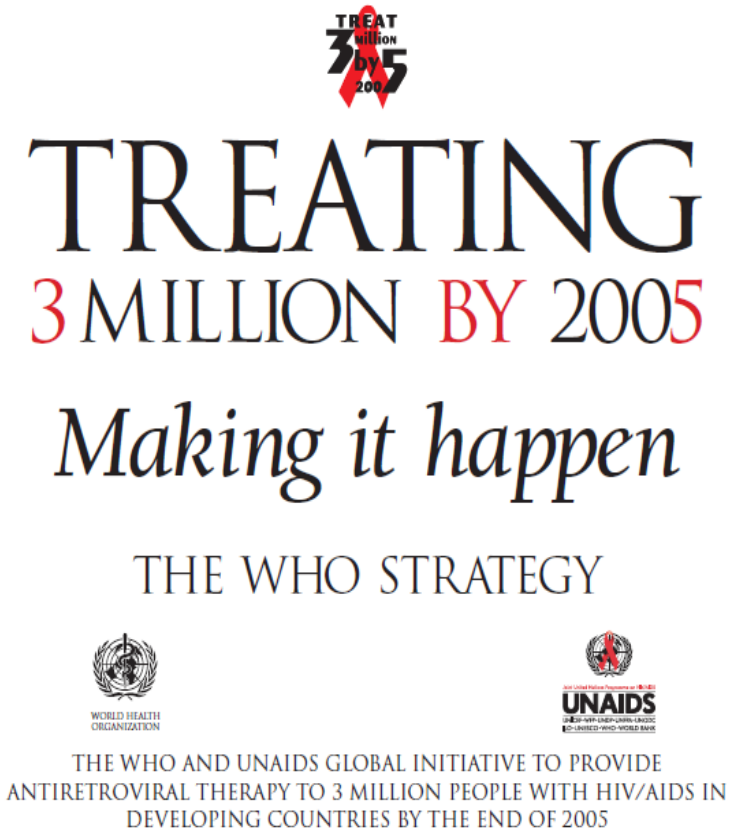
- Procure at scale – decrease cost, simplify distribution
- Simplify medical decisions – task shift away from doctors

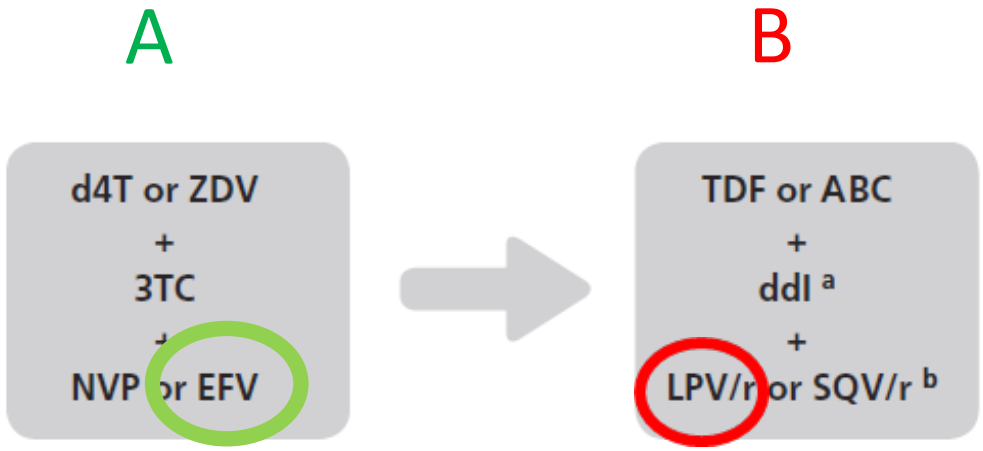
Simplified monitoring

Sparse VL (every 6-12 months) and safety monitoring; no resistance testing

- Decrease cost
- Feasiblity of implementation at scale

What to switch to: WHO ART Guidelines 2003





WHO ART guidelines 2003

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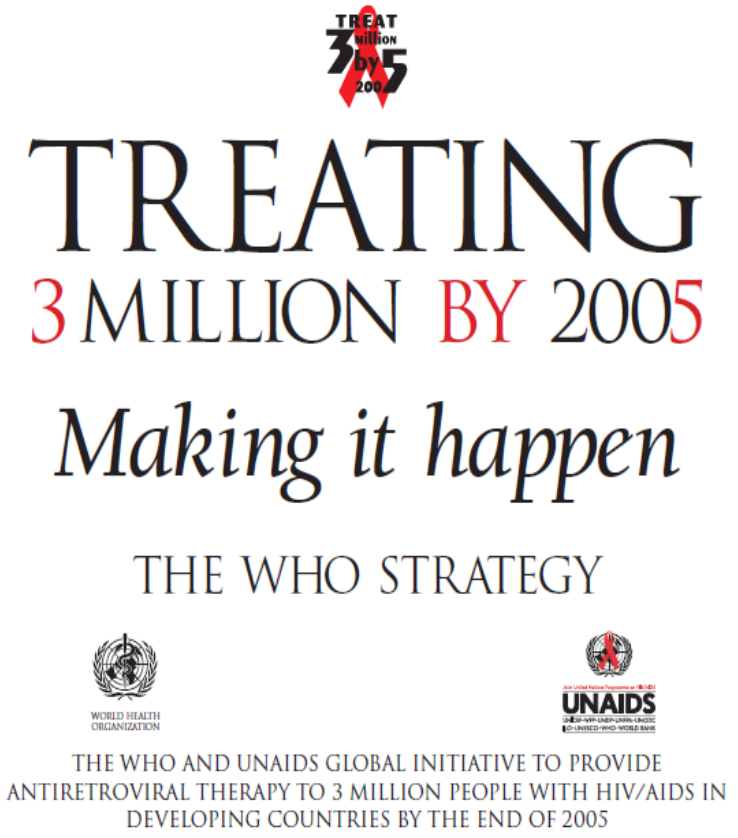
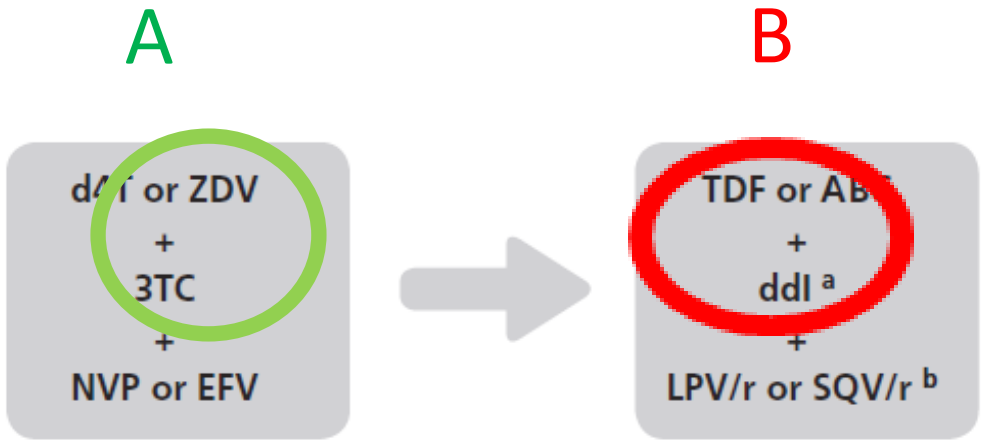




WHO ART guidelines 2003

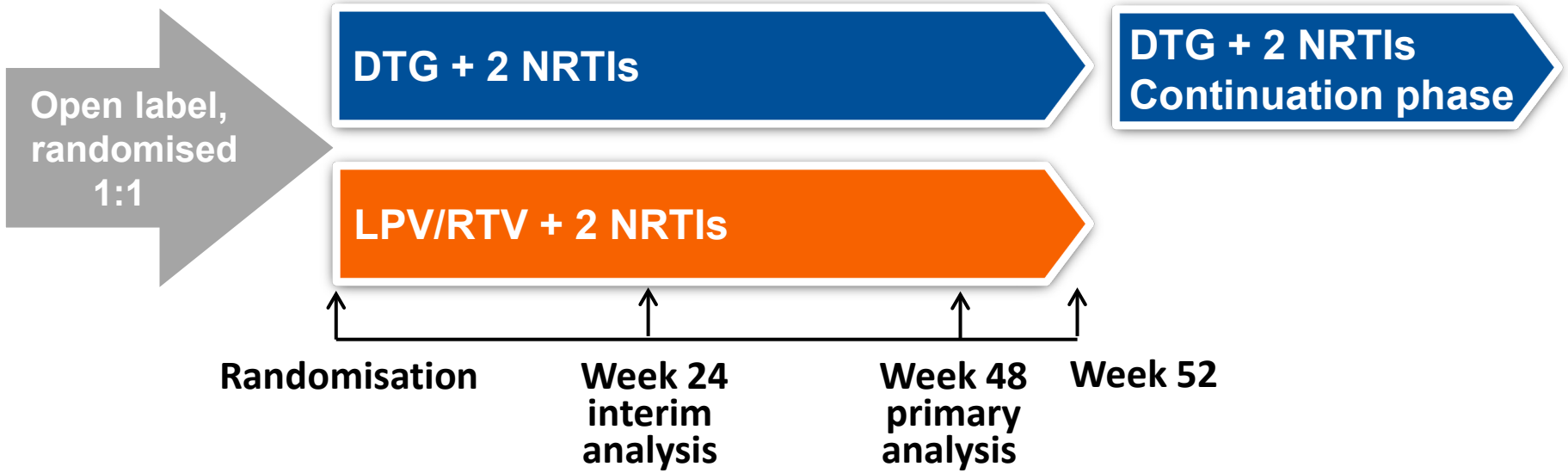
Second-line therapy: WHO 2018 Guidelines

Recommendations

NEW	DTG in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone is recommended as the preferred second-line regimen for people living with HIV[a] for whom non-DTG-based regimens are failing *(conditional recommendation, moderate-certainty evidence)*
NEW	DTG in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone is recommended as the preferred second-line regimen for children with approved DTG dosing for whom non-DTG-based regimens are failing *(conditional recommendation, low-certainty evidence)*
	[a] See Box 1 on women and adolescent girls of childbearing potential using DTG.

DAWNING Study Design

Open-label randomised noninferiority phase IIIb study



- **Key eligibility criteria:** on first-line 2 NRTIs + NNRTI regimen for ≥ 6 months, failing virologically (HIV-1 RNA ≥400 c/mL on 2 occasions); no primary viral resistance to PIs or INSTIs
- **Stratification:** by HIV-1 RNA (≤ or >100,000 copies/mL), number of fully active NRTIs in the investigator-selected study background regimen (2 or <2)
- **Primary endpoint:** proportion with HIV-1 RNA <50 c/mL at Week 48 using the FDA snapshot algorithm (12% noninferiority margin)

FDA, US Food and Drug Administration; INSTI, integrase strand transfer inhibitor.

Aboud et al. IAS 2017; Paris, France. Slides TUAB0105LB.

DAWNING Results

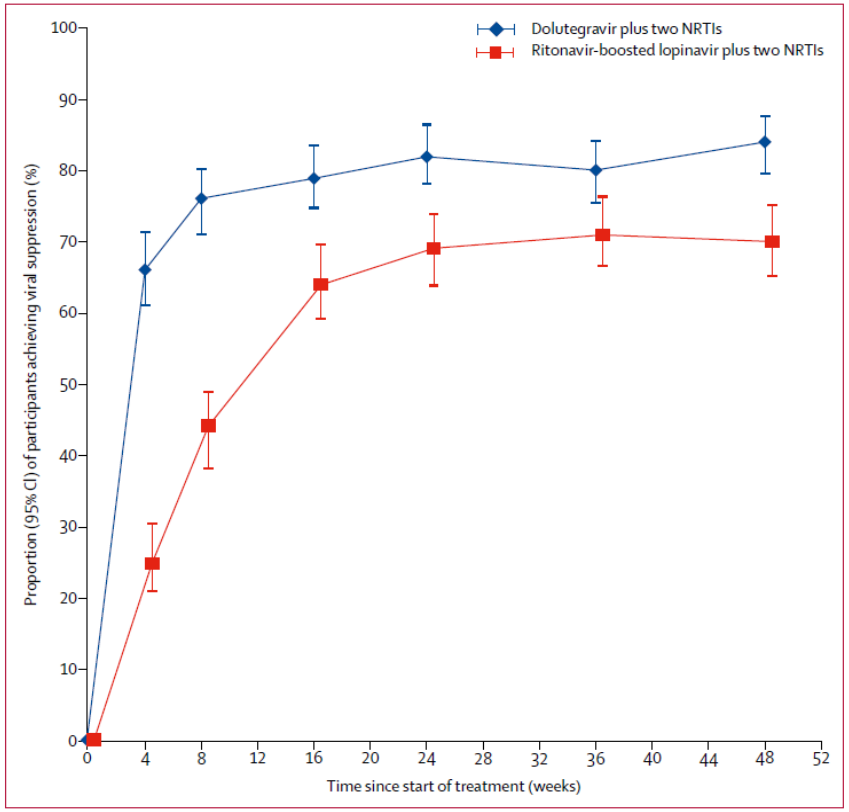


Figure 3: **Participants achieving viral suppression over the course of the study**
Analysis is in the intention-to-treat-exposed population. Viral suppression is defined as plasma HIV-1 RNA less than 50 copies per mL. NRTI=nucleoside reverse transcriptase inhibitor.

	Dolutegravir (n=312)	Ritonavir-boosted lopinavir (n=312)
Response	261 (84%)	219 (70%)
Non-response	30 (10%)	68 (22%)
Did not achieve <50 copies per mL by week 48	18 (6%)	34 (11%)
Discontinued because of no efficacy before reaching <50 copies per mL	6 (2%)	20 (6%)
Discontinued for other reason when not at <50 copies per mL	2 (1%)	7 (2%)
Change in antiretroviral therapy	4 (1%)	7 (2%)
No data available	21 (7%)	25 (8%)
Discontinued because of adverse event or death	7 (2%)	17 (5%)
Discontinued for other reasons	12 (4%)	6 (2%)
Missing data but still on study	2 (1%)	2 (1%)

Table 2: **Primary outcome results at week 48**

VL suppression Week 48 (ITT)

	DTG	LPV/r
< 50	84%	70%
< 400	88%	77%

Similar proportions in PP analysis

IDMC interim review of week 24 data: recommended stop LPV/r
Modified protocol to allow withdrawal of pts on LPV/r (9) or switch to DTG (12)

Aboud et al, Lancet ID, 2019

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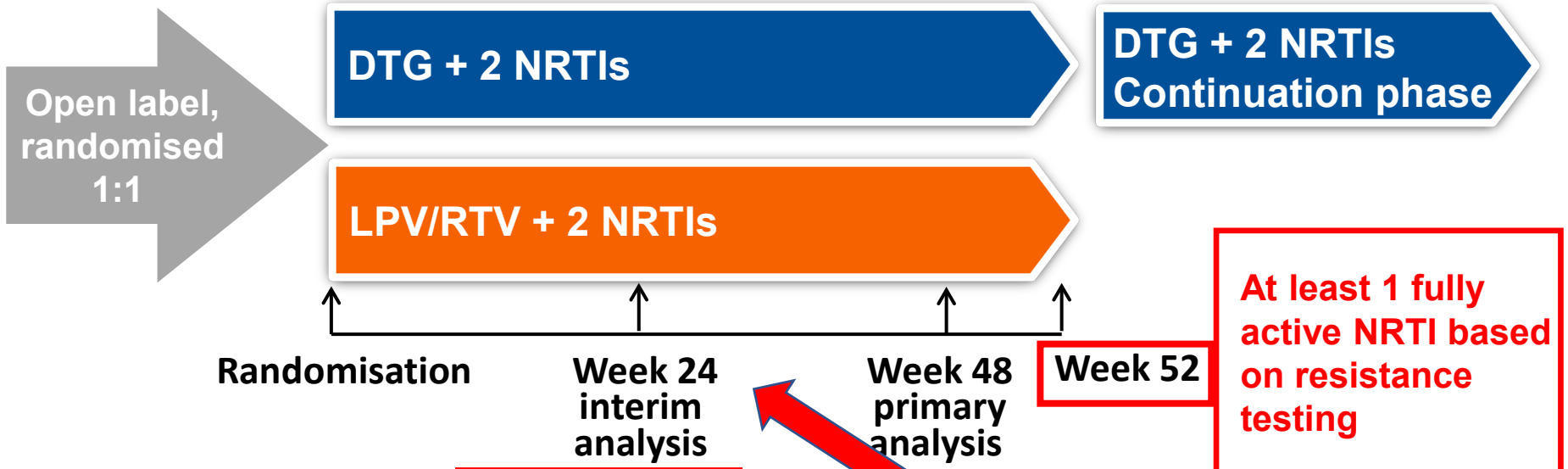

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VL testing every 1-3 months

+ stopped at IDMC review of 24 weeks' data

Second-line therapy: WHO 2018 Guidelines

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	[a] See Box 1 on women and adolescent girls of childbearing potential using DTG.

WHO was worried too……

In the DAWNING study, people were switched from NNRTI to DTG-based ART with at least one active NRTI predicted by genotypic resistance testing. Although DTG seems to be effective with at least one active NRTI for people for whom NNRTI-based ART is failing, a retrospective analysis suggests that selecting NRTI backbone sequencing according to WHO guidelines achieved modest but significantly greater suppression of viral loads *(85)*.

Further, there has been no direct evaluation of DTG with an NRTI backbone predicted to be inactive by genotypic resistance testing, but findings from DTG monotherapy studies have demonstrated the rapid accumulation of integrase inhibitor mutations *(89,90)*.

Overall, insufficient evidence supports using DTG in combination with TDF and 3TC as second-line ART for people for whom TDF + 3TC (or FTC) + EFV is failing as a first-line regimen. More data are needed on the efficacy of DTG among people with resistance to 3TC and TDF *(78)*.

WHO 2018 guidelines

NADIA Question 1

NADIA

Is DTG really non-inferior to PI/r in the public health approach (in people with extensive NRTI resistance) …. over medium to long-term follow-up?

Table 4.7 Preferred and alternative second-line ART regimens for adults, adolescents, children and infants

Population	Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimens
Adults and adolescents[a]	TDF[b] + 3TC (or FTC) + DTG[c]	AZT+ 3TC + ATV/r (or LPV/r)	AZT + 3TC + DRV/r[d]
	TDF + 3TC (or FTC) + EFV (or NVP)	AZT +3TC + DTG[c]	AZT + 3TC + ATV/r (or LPV/r or DRV/r)[d]
	AZT + 3TC +EFV (or NVP)	TDF[b] + 3TC (or FTC) + DTG[c]	TDF[b] + 3TC (or FTC) + ATV/r (or LPV/r or DRV/r)[d]
Children and infants	ABC + 3TC + DTG[e]	AZT+ 3TC + LPV/r (or ATV/rf)	AZT +3TC + DRV/r[g]
	ABC (or AZT) +3TC + LPV/r	AZT (or ABC) + 3TC + DTG[e]	AZT (or ABC) +3TC + RAL
	ABC (or AZT) + 3TC + EFV	AZT (or ABC) + 3TC + DTG[e]	AZT (or ABC) +3TC + LPV/r (or ATV/r[f])
	AZT + 3TC + NVP	ABC + 3TC + DTG[e]	ABC + 3TC + LPV/r (or ATV/r[f])

WHO Guidelines July 2021

Which PI?

Darunavir / r

Best for:
Tolerability
Potency
Genetic barrier to resistance

Main limitations (in the past):
Lack of FDC
High cost

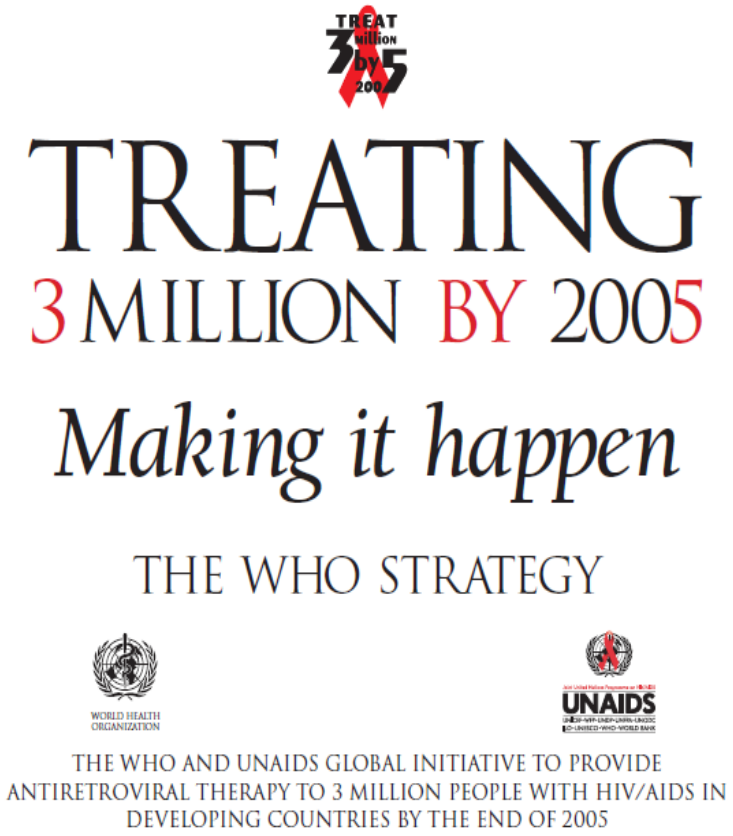
NADIA Question 1

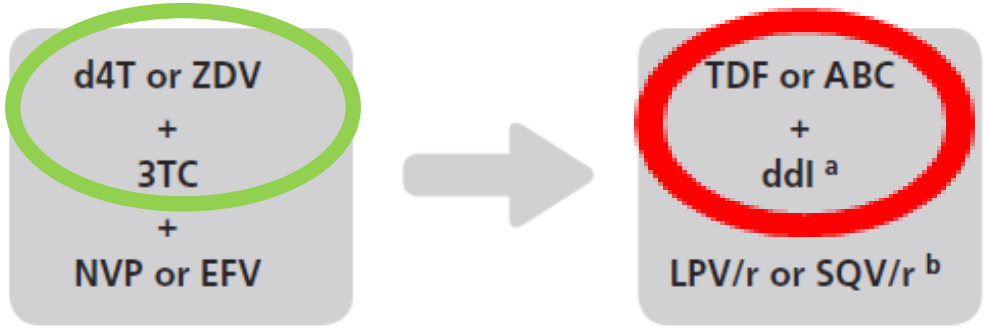
NADIA

best in class PI/r (DRV/r)

Is DTG really non-inferior to ~~PI/r~~ in the public health approach (in people with extensive NRTI resistance) …. over medium to long-term follow-up?

What to switch to: WHO ART Guidelines 2003





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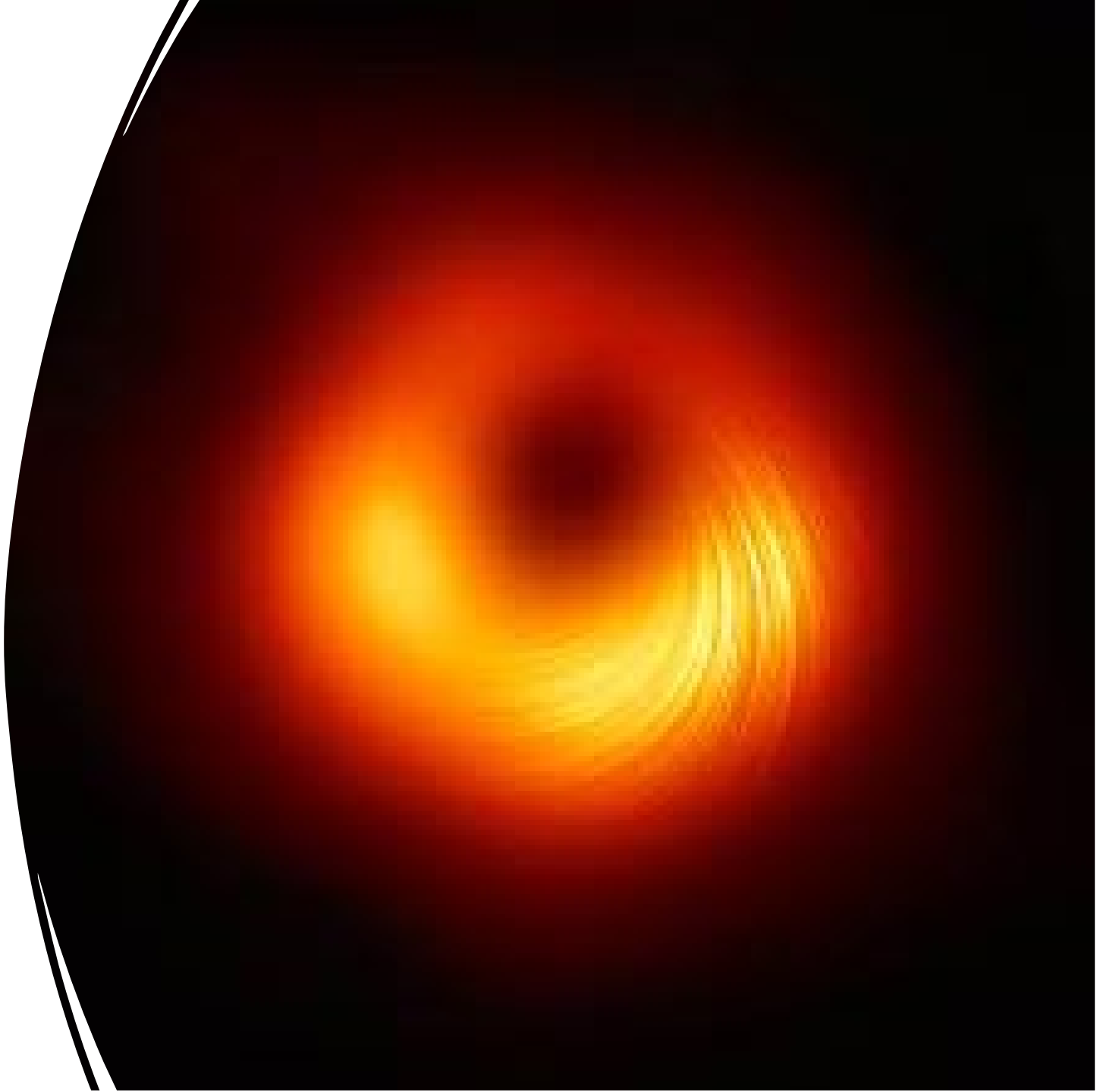
	ABC (or AZT) +3TC + LPV/r	AZT (or ABC) + 3TC + DTG[e]	AZT (or ABC) +3TC + RAL
	ABC (or AZT) + 3TC + EFV	AZT (or ABC) + 3TC + DTG[e]	AZT (or ABC) +3TC + LPV/r (or ATV/r[f])
	AZT + 3TC + NVP	ABC + 3TC + DTG[e]	ABC + 3TC + LPV/r (or ATV/r[f])

WHO Guidelines July 2021

RCT evidence for WHO algorithmic switch of NRTIs in second-line (prior to NADIA)

RCT evidence for WHO algorithmic switch of NRTIs in second-line (prior to NADIA)



Event Horizon Telescope Collaboration, 2022

~~RCT evidence~~

….for WHO algorithmic switch of NRTIs in second-line (prior to NADIA)

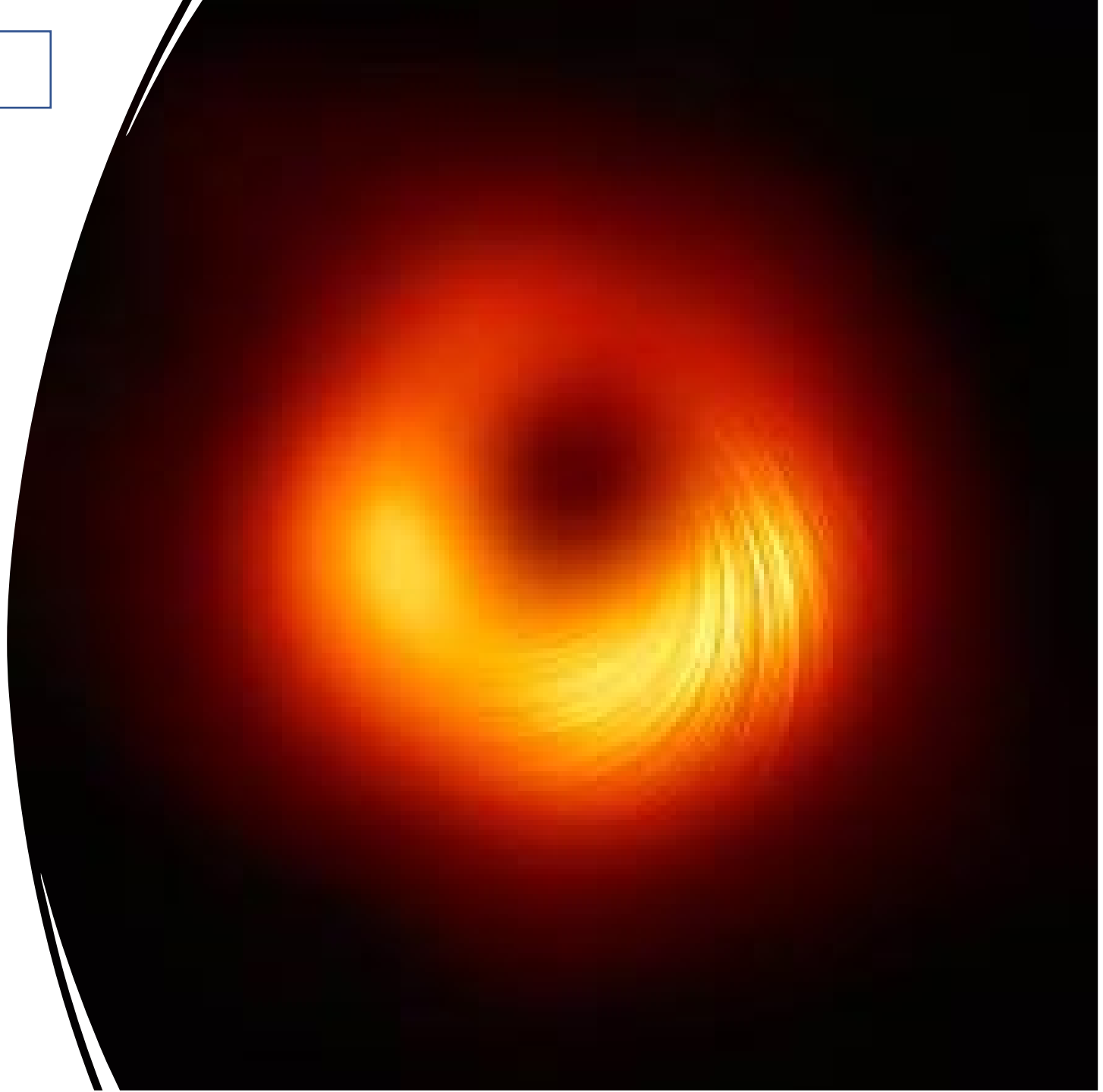
Expert opinion:

- Traditional mantra: change > 1 drug in a failing regimen
- Virological theory / *In vitro* data on effects of resistance mutations
- Relational databases (=in vitro data)

Observational

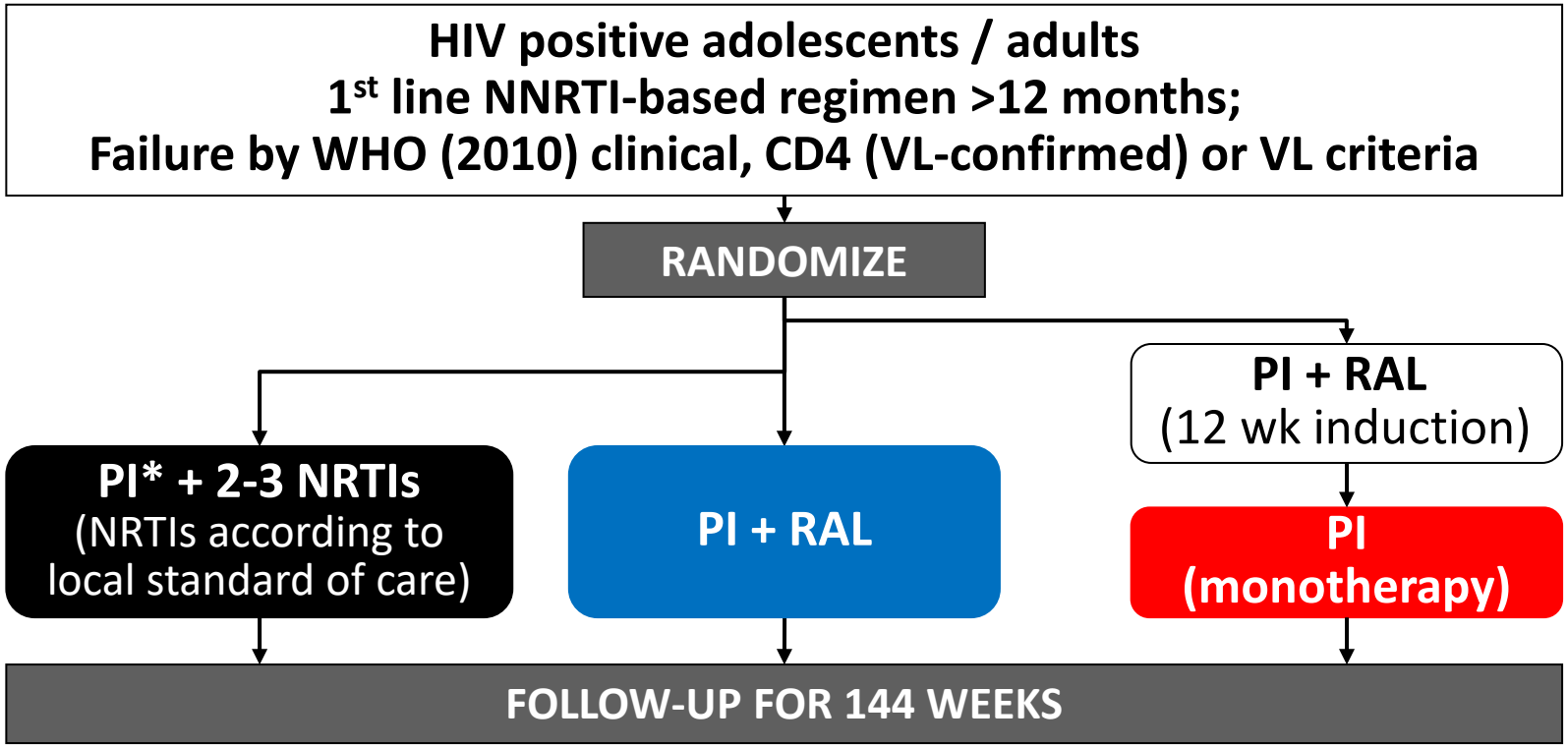
Against?

~~RCT~~ evidence ~~for~~ WHO algorithmic switch of NRTIs in second-line (prior to NADIA)



Event Horizon Telescope Collaboration, 2022

EARNEST Trial design



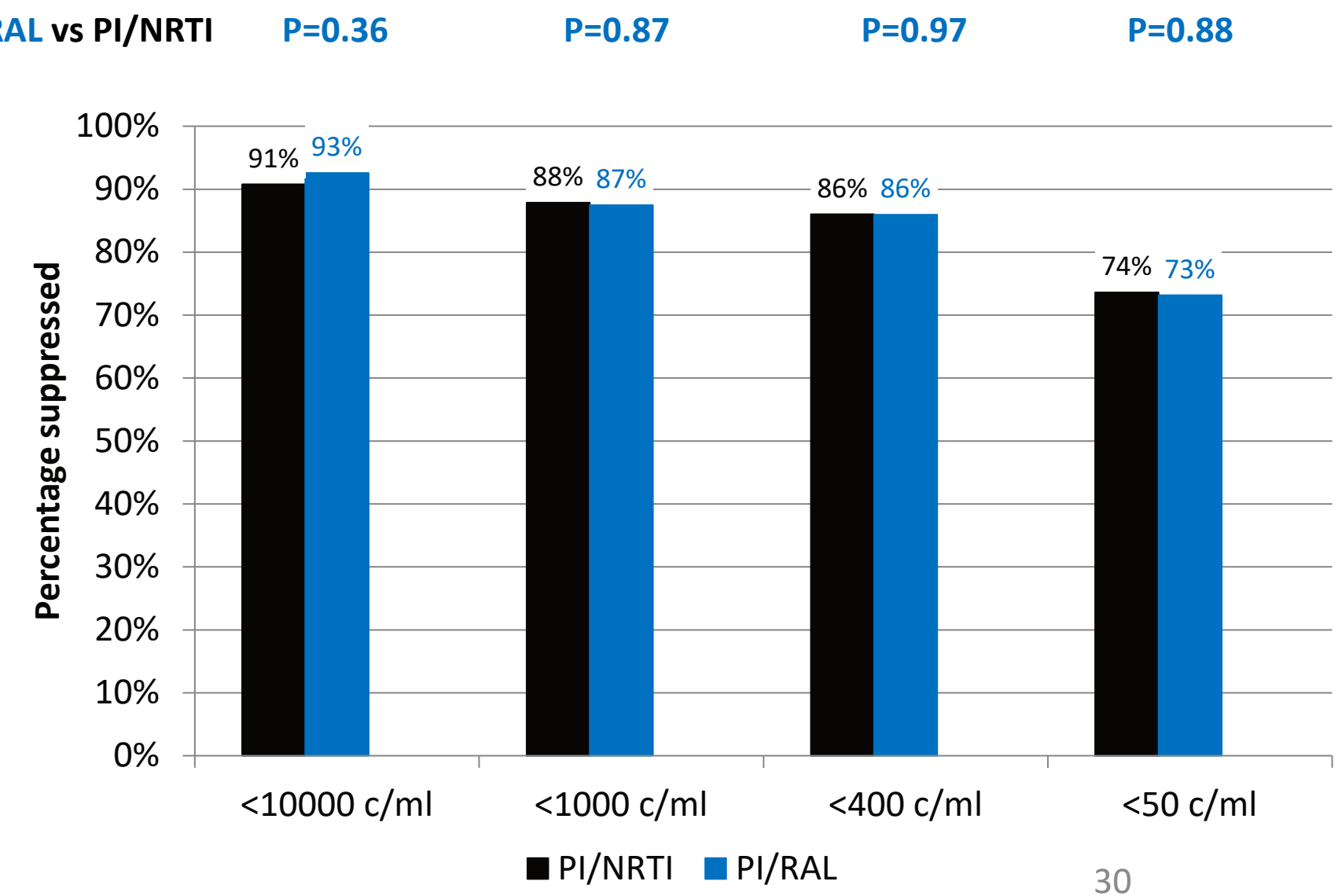
Visits: 1-2 monthly, mainly nurse-led
Adherence: assessed at all visits by structured questions; intensive counselling
Monitoring: Clinical + CD4 count every 12–16 weeks (open)
VL annually in batch – results seen only by Data Monitoring Committee

*PI standardized to LPV/r all arms

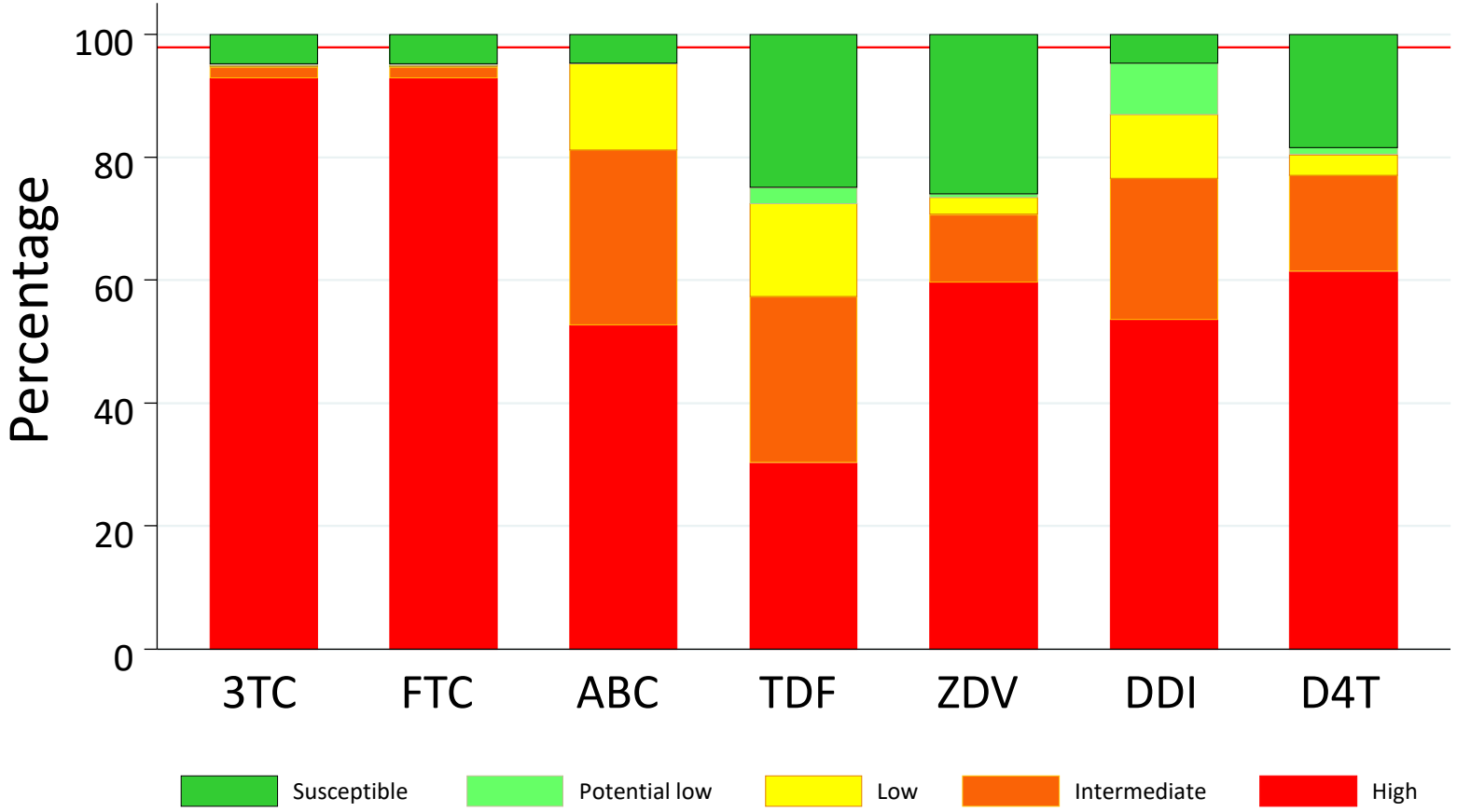
NRTIs physician-selected without resistance testing

Paton et al, NEJM 2014; 371: 234-47

EARNEST: VL suppression at 96 weeks



NRTI resistance at baseline



Baseline sequences obtained in 92% of those randomized to PI/NRTI arm
Figure shows resistance data from 792 randomized patients

Kityo et al, JAIDS 2017

Predicted activity of NRTIs in regimens

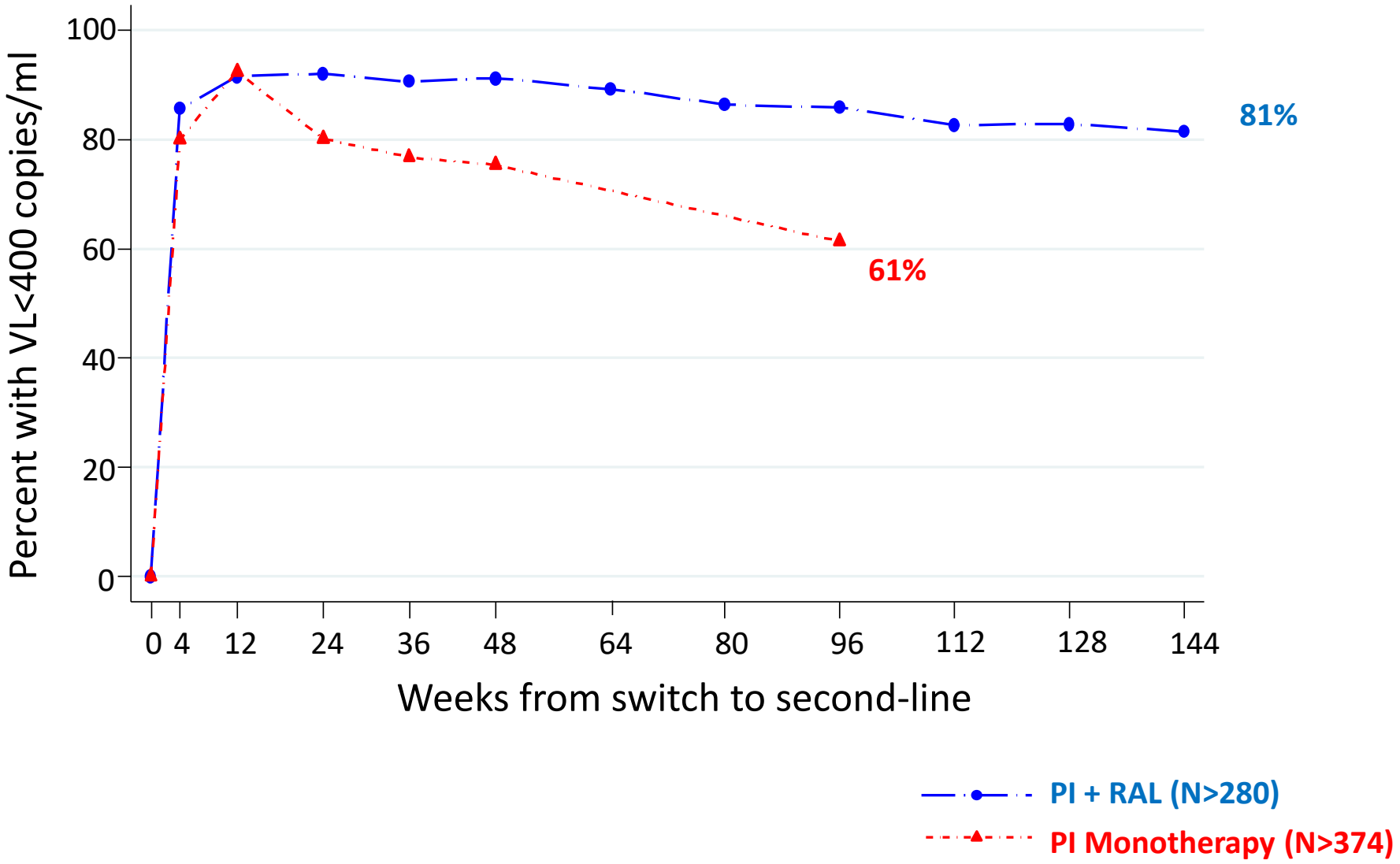
- **Number of predicted "active" NRTIs in prescribed second-line Rx*:**

0	230 (59%)
1	128 (33%)
≥2	33 (8%)

*NRTI predicted "active" if no int./high level resistance by Stanford

Paton et al, Lancet HIV 2017

VL response by number of active NRTIs in the regimen



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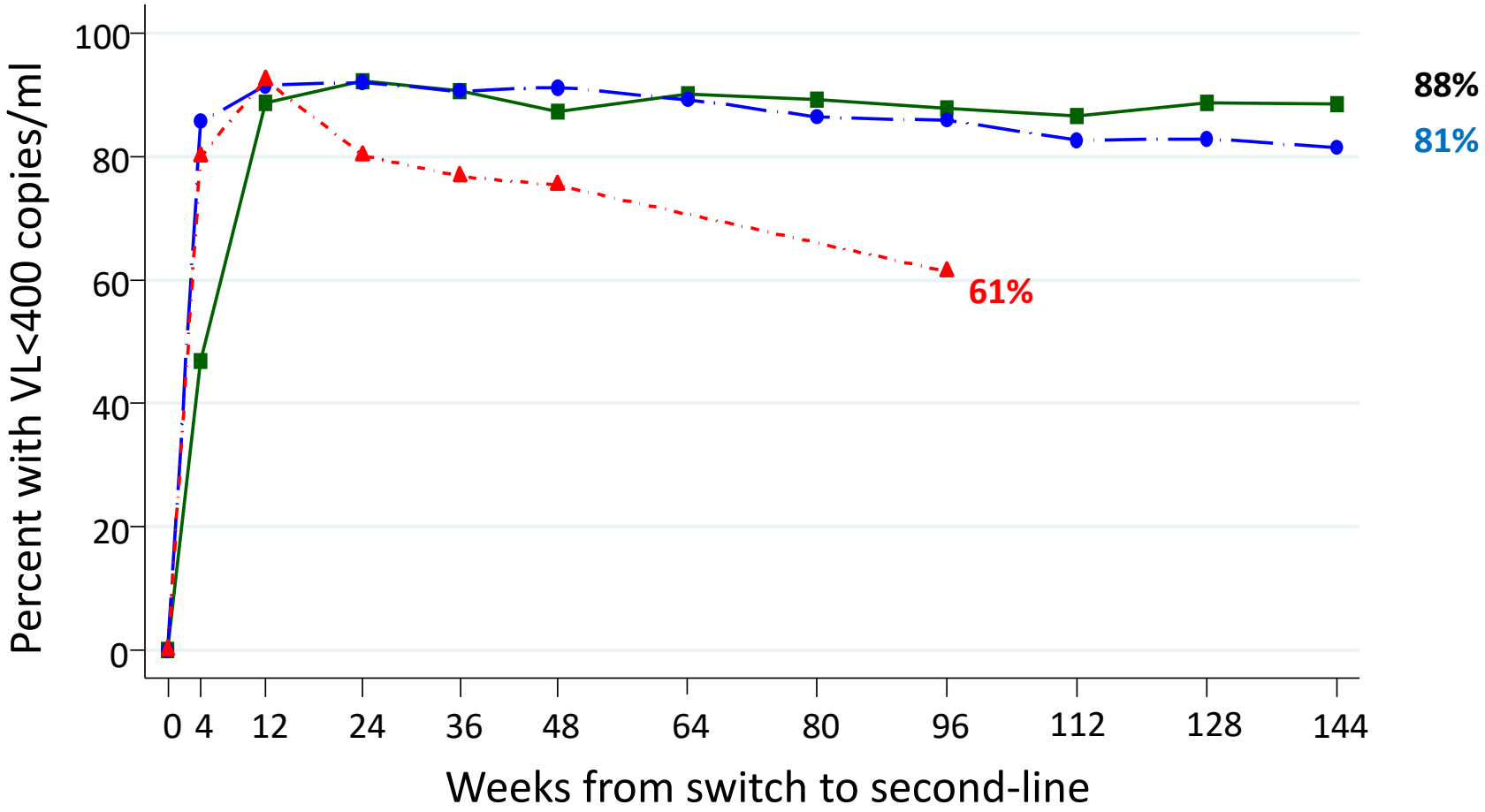
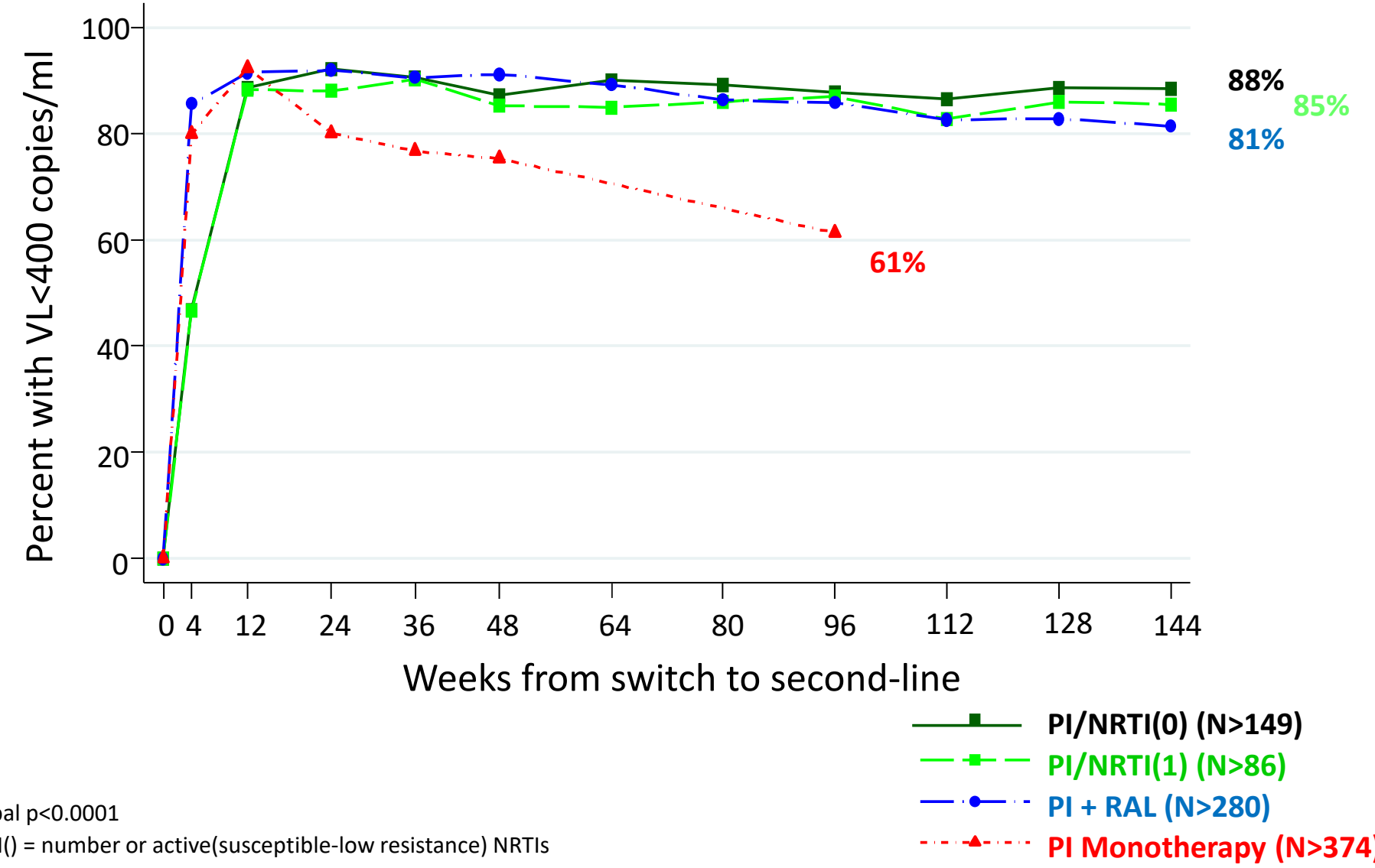


Global p<0.0001

NRTI() = number or active(susceptible-low resistance) NRTIs

VL response by number of active NRTIs in the regimen



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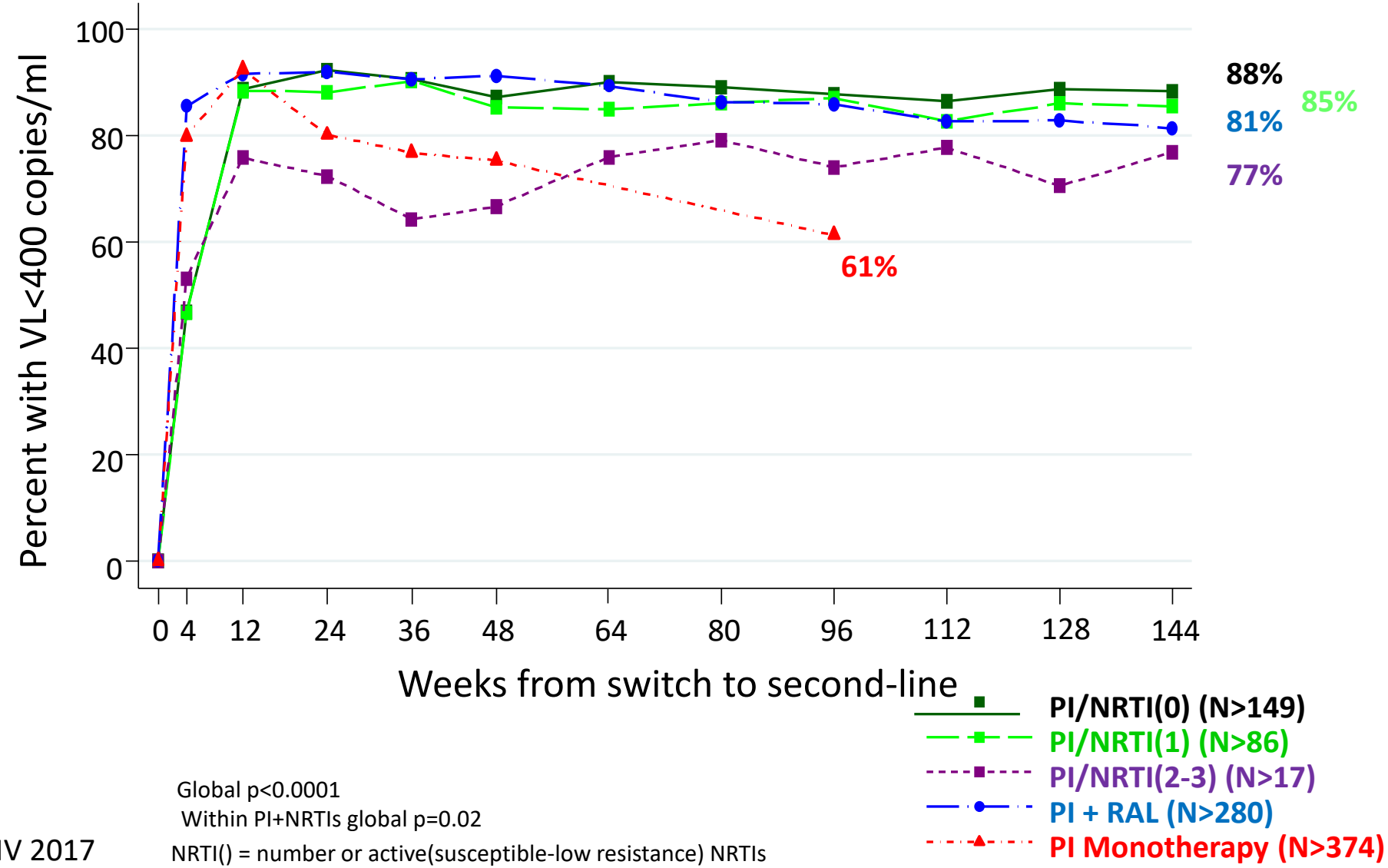
VL response by number of active NRTIs in the regimen



Global p<0.0001
Within PI+NRTIs global p=0.02
NRTI() = number or active(susceptible-low resistance) NRTIs

Paton et al, Lancet HIV 2017

Conclusions from EARNEST (about NRTI switch)

- Contribution of NRTIs is independent of NRTI resistance and predicted activity from resistance testing (paradoxical relationship)
- May not matter what NRTIs you use (as long as have NRTIs)
  - May do better to base decisions on tolerability / toxicity
  - May not need to switch at all

NADIA Questions

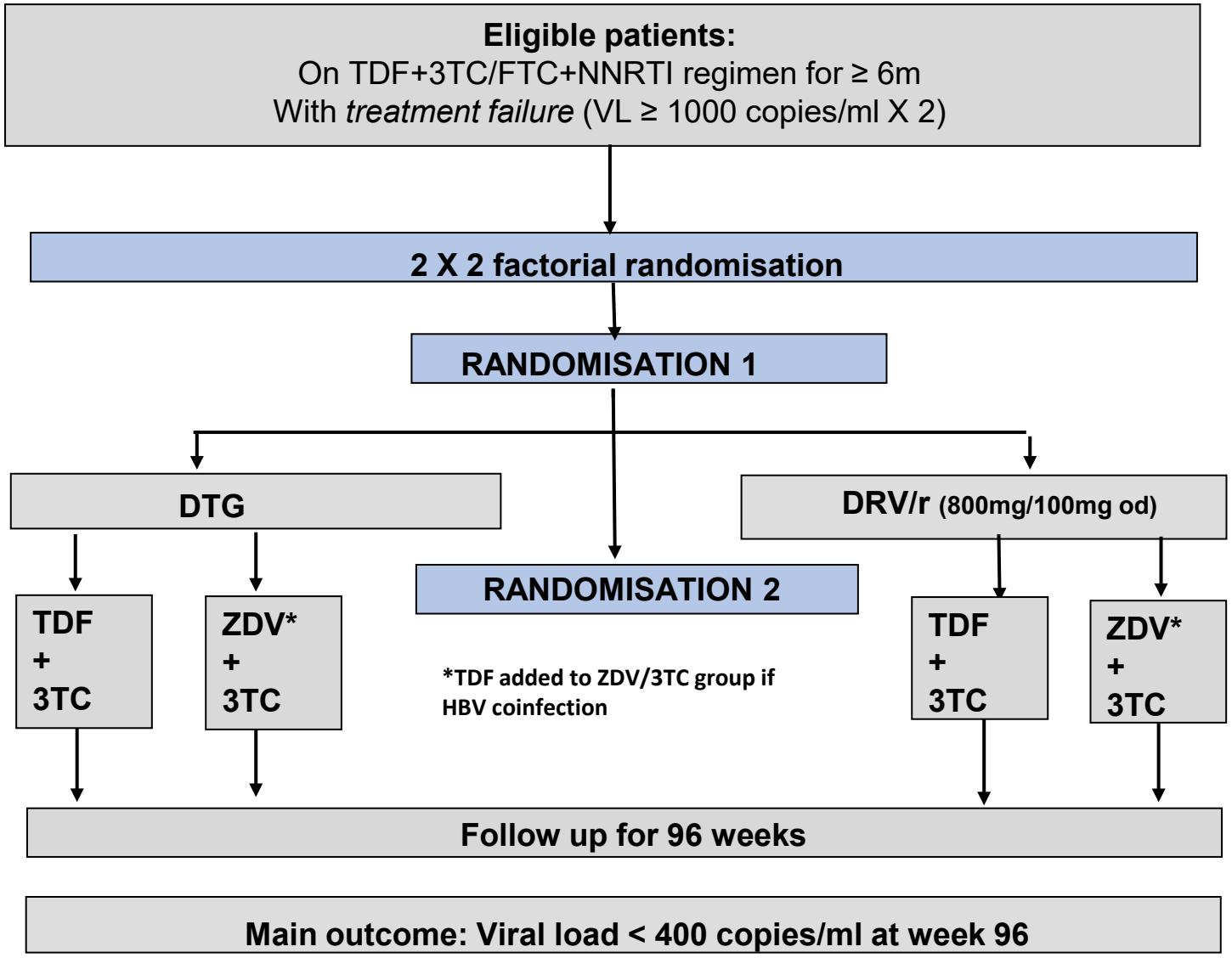
QUESTION 1: Companion drug

Is DTG non-inferior to DRV/r in the public health approach (used with NRTIs with extensive NRTI resistance and no resistance testing to select NRTI drugs)

QUESTION 2: NRTI switch

Is maintaining TDF non-inferior to switching to ZDV in second-line therapy in the public health approach (with either PI or DTG regimen; and with no resistance testing)

NADIA Trial Design



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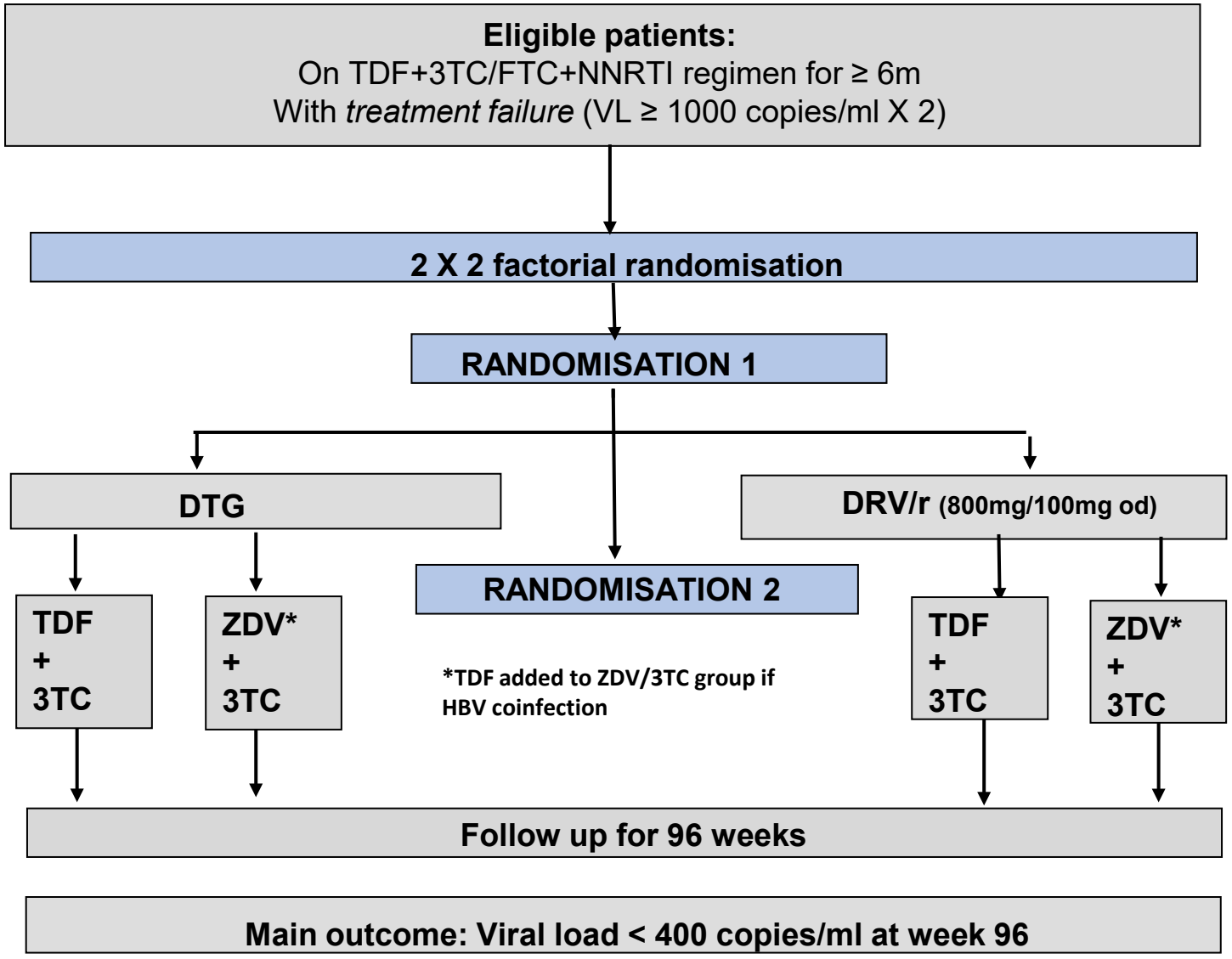


Viral load monitoring

Open, scheduled

- W24, W48, W96

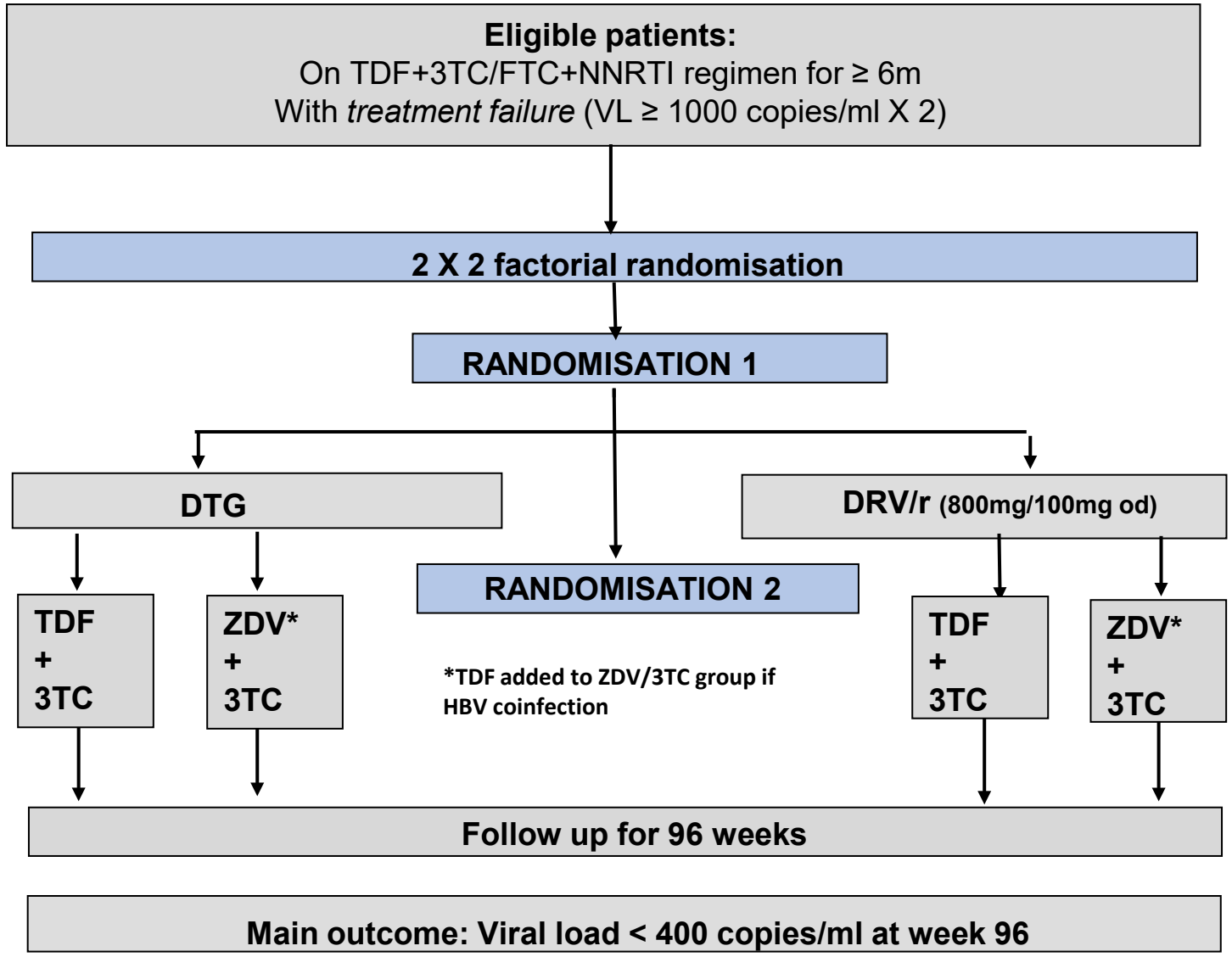
Open, additional

- W72 (if not stable at W48)
- 12 weeks after VL≥1000c/ml

Closed (batched; results to IDMC only)

- W12, W72 (all)

NADIA Trial Design



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Closed (batched; results to IDMC only)

- W12, W72 (all)

Resistance testing

Open

- Confirmed VL rebound ≥1,000 c/ml

Closed (batched; results to IDMC only)

- Baseline
- Confirmed VL rebound ≥ 400 c/ml
- VL ≥ 400 at week 96

All resistance testing done at WHO-accredited central lab (JCRC Kampala); susceptibility predictions used Stanford algorithm

Enrollment, retention, adherence

Enrolment

464 participants from 7 sites in Uganda, Kenya, Zimbabwe

Baseline characteristics*

Female: 61%, CD4 < 200 cells/mm^3: 51%, VL ≥ 100,000c/ml: 28%

Baseline intermediate-high level resistance

TDF: 59%, ZDV: 18%, 3TC: 92%

Retention and adherence to W96

3 (0.6%) withdrew or were lost-to-follow-up

8 (1.7%) died

>98% of scheduled visits were attended

>95% of follow-up time on exact assigned drug regimen

*Characteristics similar between groups; Paton, Musaazi, Kityo et al. NEJM 2021; 385: 330-41

Efficacy outcomes (W96): DTG vs DRV/r

Outcome	Dolutegravir Group (N=235)	Darunavir Group (N=229)	Difference (95% CI) %	P
HIV-1 RNA level, intention-to-treat population – no (%)				
< 400 copies/ml (ITT)	211(89.8)	199 (86.9)	2.9 (-3.0 to 8.7)	0.332
≥ 400 copies/ml	20 (8.5)	25 (10.9)	-	
No virological data - Withdrew because of AE/death - Withdrew for other reasons	4 (1.7) 3 (1.3) 1 (0.4)	5 (2.2) 5 (2.2) 0	-	
HIV-1 RNA level < 400 c/ml (sensitivity analyses) – no (%)				
< 400 copies/ml (adjusted)	90.2	86.7	3.5 (-2.9 to 9.8)	0.278
VL < 400 copies (per protocol)	201 (92.2)	192 (91.0)	1.2 (-4.0 to 6.5)	0.652
Secondary and other efficacy outcomes – no (%)				
VL < 1000 c/ml (ITT)	213 (90.6)	203 (88.6)	2.0 (-3.6 to 7.5)	0.481
VL< 50 c/ml (ITT)	189 (80.4)	172 (75.1)	5.3 (-2.2 to 12.9)	0.168
VL rebound ≥ 1000 c/ml, confirmed	20 (8.5)	26 (11.3)	-2.8 (-8.3 to 2.6)	0.306
VL rebound ≥ 1000 c/ml, confirmed with ≥1 major RM to DTG or DRV*	7	0	-	-

* ≥1 major DTG mutation: 7
  ≥1 major DRV mutation: 0

Paton, Musaazi, Kityo et al. Lancet HIV 2022

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VL < 1000 c/ml (ITT)	213 (90.6)	203 (88.6)	2.0 (-3.6 to 7.5)	0.481
VL< 50 c/ml (ITT)	189 (80.4)	172 (75.1)	5.3 (-2.2 to 12.9)	0.168
VL rebound ≥ 1000 c/ml, confirmed	20 (8.5)	26 (11.3)	-2.8 (-8.3 to 2.6)	0.306
VL rebound ≥ 1000 c/ml, confirmed with ≥1 major RM to DTG or DRV*	7	0	-	-

* ≥1 major DTG mutation: 7
≥1 major DRV mutation: 0

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Efficacy outcomes (W96): DTG vs DRV/r

Outcome	Dolutegravir Group (N=235)	Darunavir Group (N=229)	Difference (95% CI) %	P
HIV-1 RNA level, intention-to-treat population – no (%)				
< 400 copies/ml (ITT)	211(89.8)	199 (86.9)	2.9 (-3.0 to 8.7)	0.332
≥ 400 copies/ml	20 (8.5)	25 (10.9)	-	
No virological data - Withdrew because of AE/death - Withdrew for other reasons	4 (1.7) 3 (1.3) 1 (0.4)	5 (2.2) 5 (2.2) 0	-	
HIV-1 RNA level < 400 c/ml (sensitivity analyses) – no (%)				
< 400 copies/ml (adjusted)	90.2	86.7	3.5 (-2.9 to 9.8)	0.278
VL < 400 copies (per protocol)	201 (92.2)	192 (91.0)	1.2 (-4.0 to 6.5)	0.652
Secondary and other efficacy outcomes – no (%)				
VL < 1000 c/ml (ITT)	213 (90.6)	203 (88.6)	2.0 (-3.6 to 7.5)	0.481
VL< 50 c/ml (ITT)	189 (80.4)	172 (75.1)	5.3 (-2.2 to 12.9)	0.168
VL rebound ≥ 1000 c/ml, confirmed	20 (8.5)	26 (11.3)	-2.8 (-8.3 to 2.6)	0.306
VL rebound ≥ 1000 c/ml, confirmed with ≥1 major RM to DTG or DRV*	7	0	-	-

* ≥1 major DTG mutation: 7
≥1 major DRV mutation: 0

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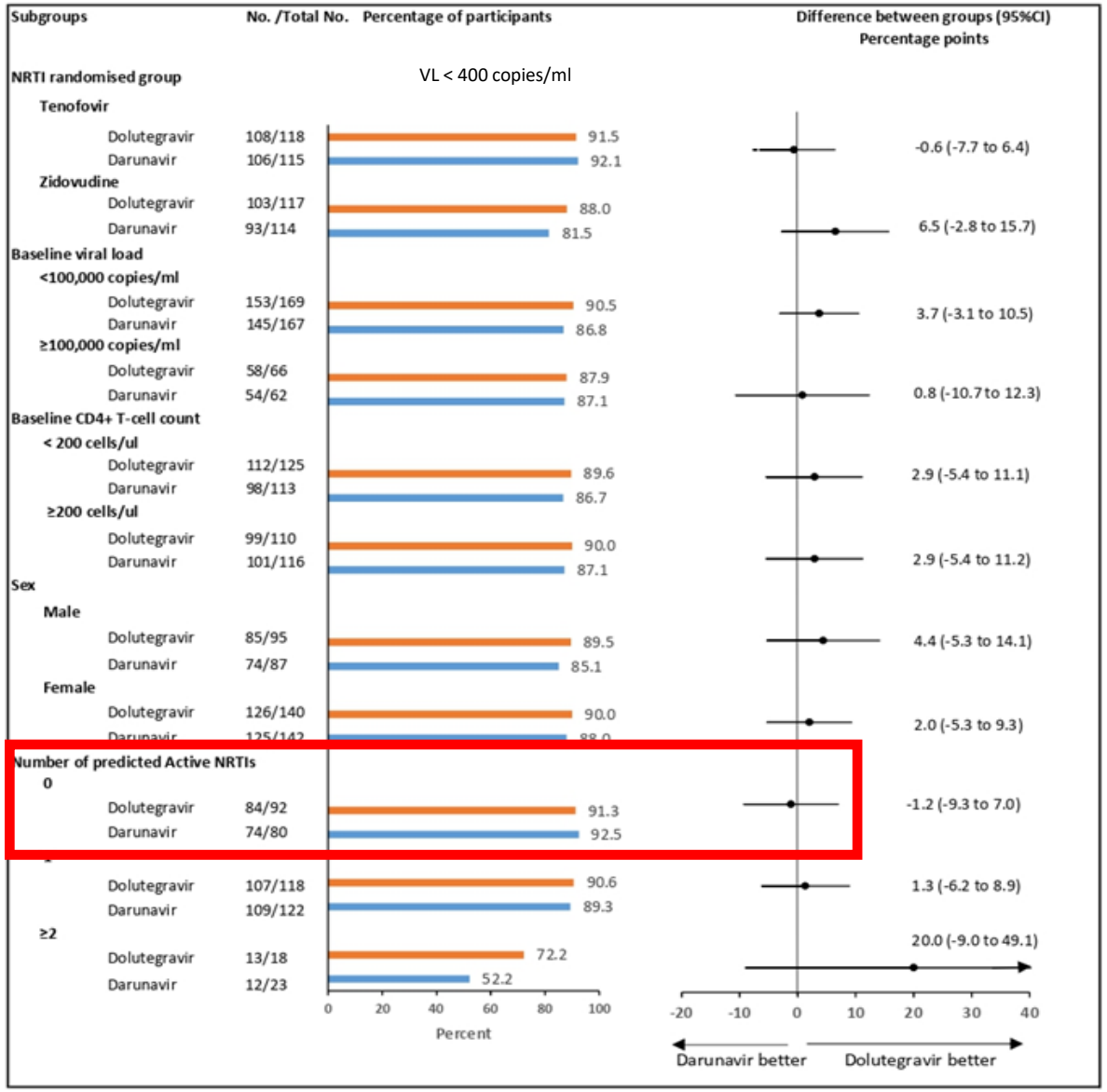
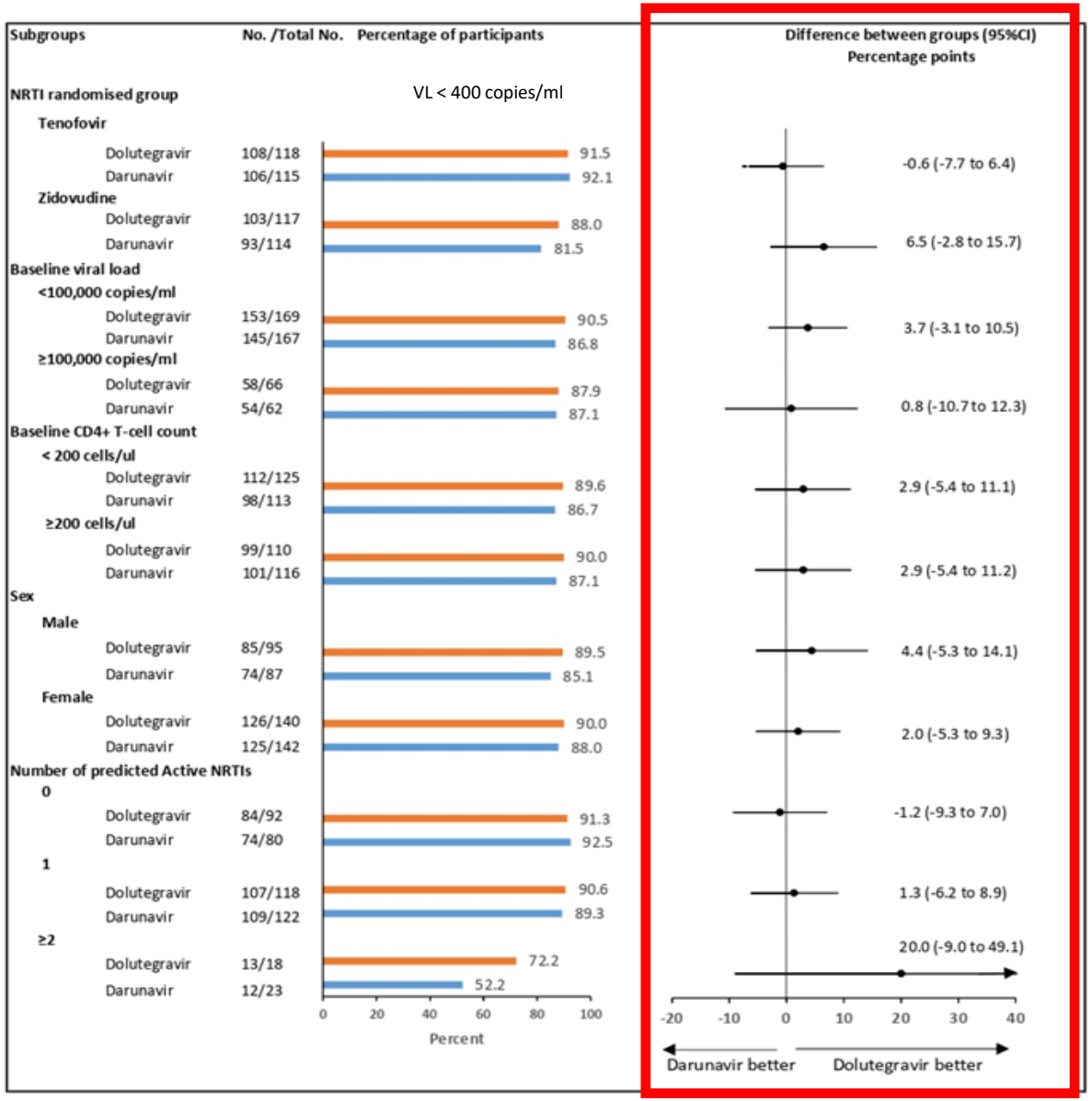
Subgroup analysis (W96): DTG vs DRV/r



Subgroup analysis (W96): DTG vs DRV/r



Efficacy Outcomes (W96): TDF vs ZDV

Outcome	Tenofovir Group (N= 233)	Zidovudine Group (N= 231)	Difference (95% CI) %	P
HIV-1 RNA level, intention-to-treat population – no (%)				
< 400 copies/ml (ITT)	214 (91.8)	196 (84.8)	7.0 (1.2 to 12.8)	0.019
≥ 400 copies/ml	13 (5.6)	32 (13.9)	-	-
No virological data - Withdrew because of AE/death - Withdrew for other reasons	6 (2.6) 6 (2.6) 0	3 (1.3) 2 (0.9) 1 (0.4)	-	-
HIV-1 RNA level < 400 c/ml (sensitivity analyses) – no (%)				
< 400 copies/ml (adjusted)	92.4	84.5	7.9 (1.9 to 14.0)	0.01
< 400 copies (per protocol)	206 (95.4)	187 (87.8)	7.6 (2.4 to 12.8)	0.005
Secondary and other efficacy outcomes – no (%)				
< 1000 c/ml	216 (92.7)	200 (86.6)	6.1 (0.6 to 11.6)	0.03
< 50 c/ml	188 (80.7)	173 (74.9)	5.8 (-1.8 to 13.3)	0.133
VL rebound ≥ 1000 c/ml, confirmed (ITT)	13 (5.6)	33 (14.3)	-8.7 (-14.4 to -3.3)	0.002
VL rebound ≥ 1000 c/ml, confirmed with ≥1 major RM to DTG or DRV*	2	5	-	-

* ≥1 major DTG mutation: 7
  ≥1 major DRV mutation: 0

Efficacy Outcomes (W96): TDF vs ZDV

Outcome	Tenofovir Group (N= 233)	Zidovudine Group (N= 231)	Difference (95% CI) %	P
HIV-1 RNA level, intention-to-treat population – no (%)				
< 400 copies/ml (ITT)	214 (91.8)	196 (84.8)	7.0 (1.2 to 12.8)	0.019
≥ 400 copies/ml	13 (5.6)	32 (13.9)	-	-
No virological data - Withdrew because of AE/death - Withdrew for other reasons	6 (2.6) 6 (2.6) 0	3 (1.3) 2 (0.9) 1 (0.4)	-	-
HIV-1 RNA level < 400 c/ml (sensitivity analyses) – no (%)				
< 400 copies/ml (adjusted)	92.4	84.5	7.9 (1.9 to 14.0)	0.01
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Efficacy Outcomes (W96): TDF vs ZDV

Outcome	Tenofovir Group (N= 233)	Zidovudine Group (N= 231)	Difference (95% CI) %	P
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< 400 copies/ml (ITT)	214 (91.8)	196 (84.8)	7.0 (1.2 to 12.8)	0.019
≥ 400 copies/ml	13 (5.6)	32 (13.9)	-	-
No virological data - Withdrew because of AE/death - Withdrew for other reasons	6 (2.6) 6 (2.6) 0	3 (1.3) 2 (0.9) 1 (0.4)	-	-
HIV-1 RNA level < 400 c/ml (sensitivity analyses) – no (%)				
< 400 copies/ml (adjusted)	92.4	84.5	7.9 (1.9 to 14.0)	0.01
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< 1000 c/ml	216 (92.7)	200 (86.6)	6.1 (0.6 to 11.6)	0.03
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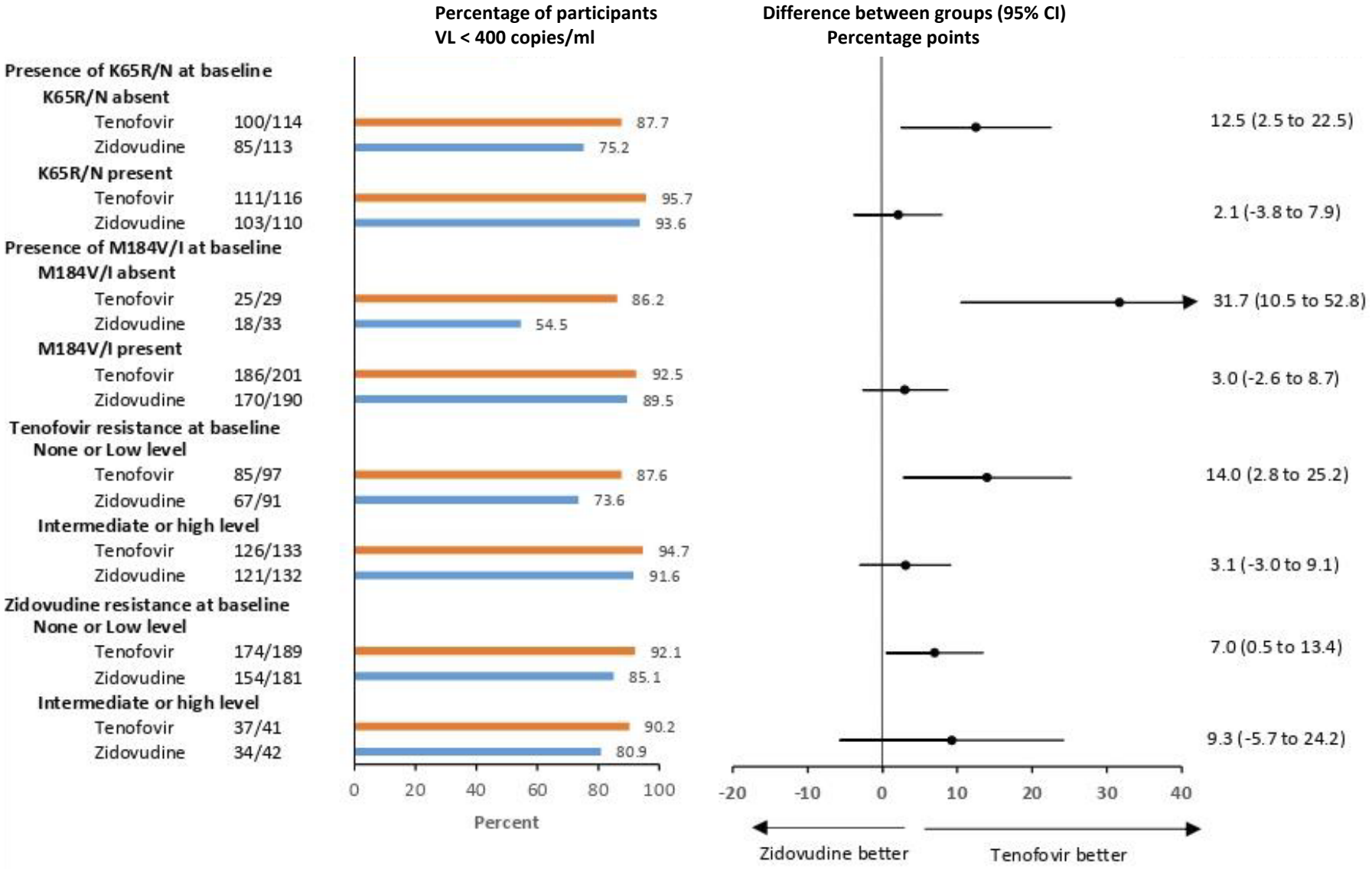
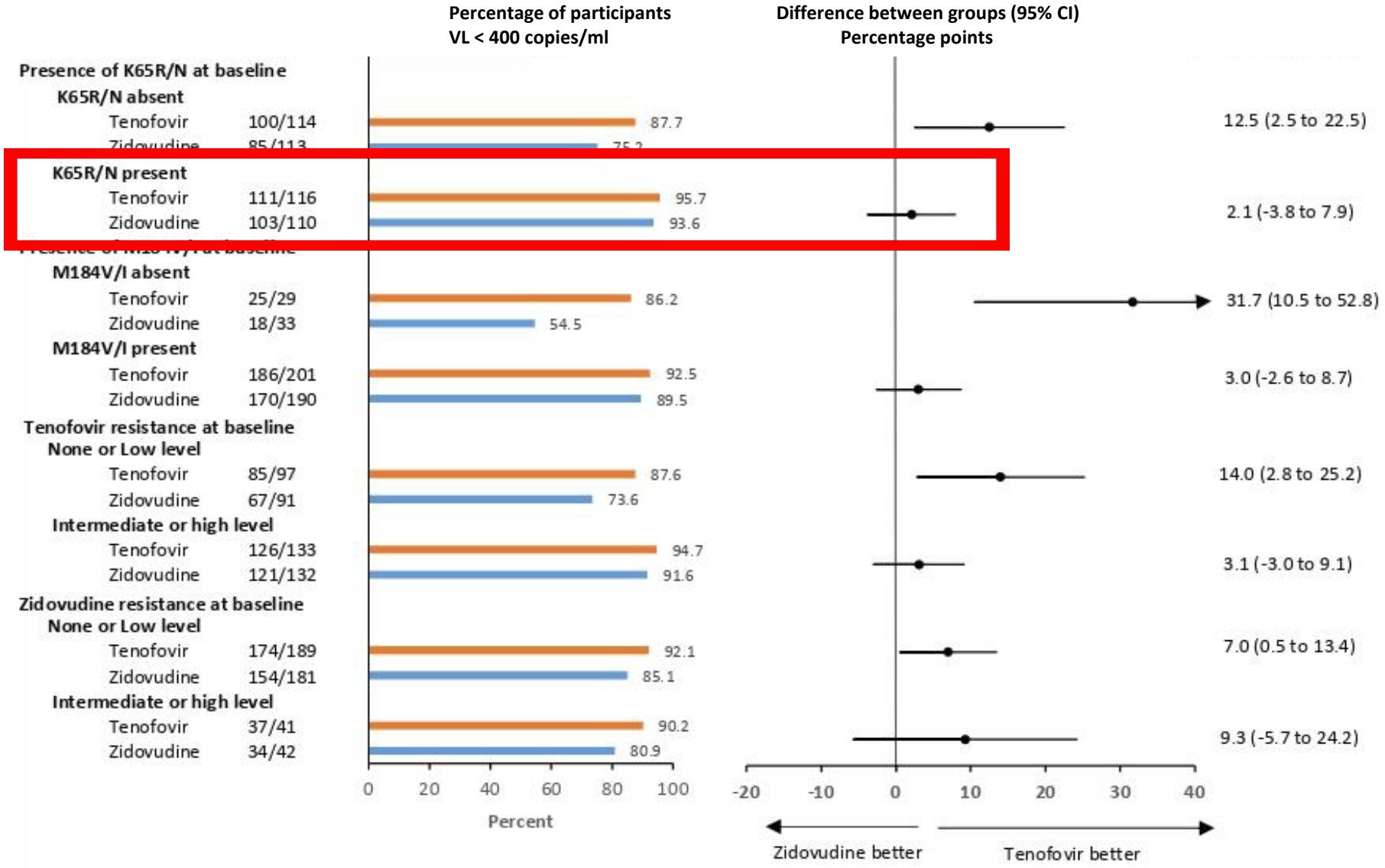
VL rebound ≥ 1000 c/ml, confirmed (ITT)	13 (5.6)	33 (14.3)	-8.7 (-14.4 to -3.3)	0.002
VL rebound ≥ 1000 c/ml, confirmed with ≥1 major RM to DTG or DRV*	2	5	-	-

* ≥1 major DTG mutation: 7
  ≥1 major DRV mutation: 0

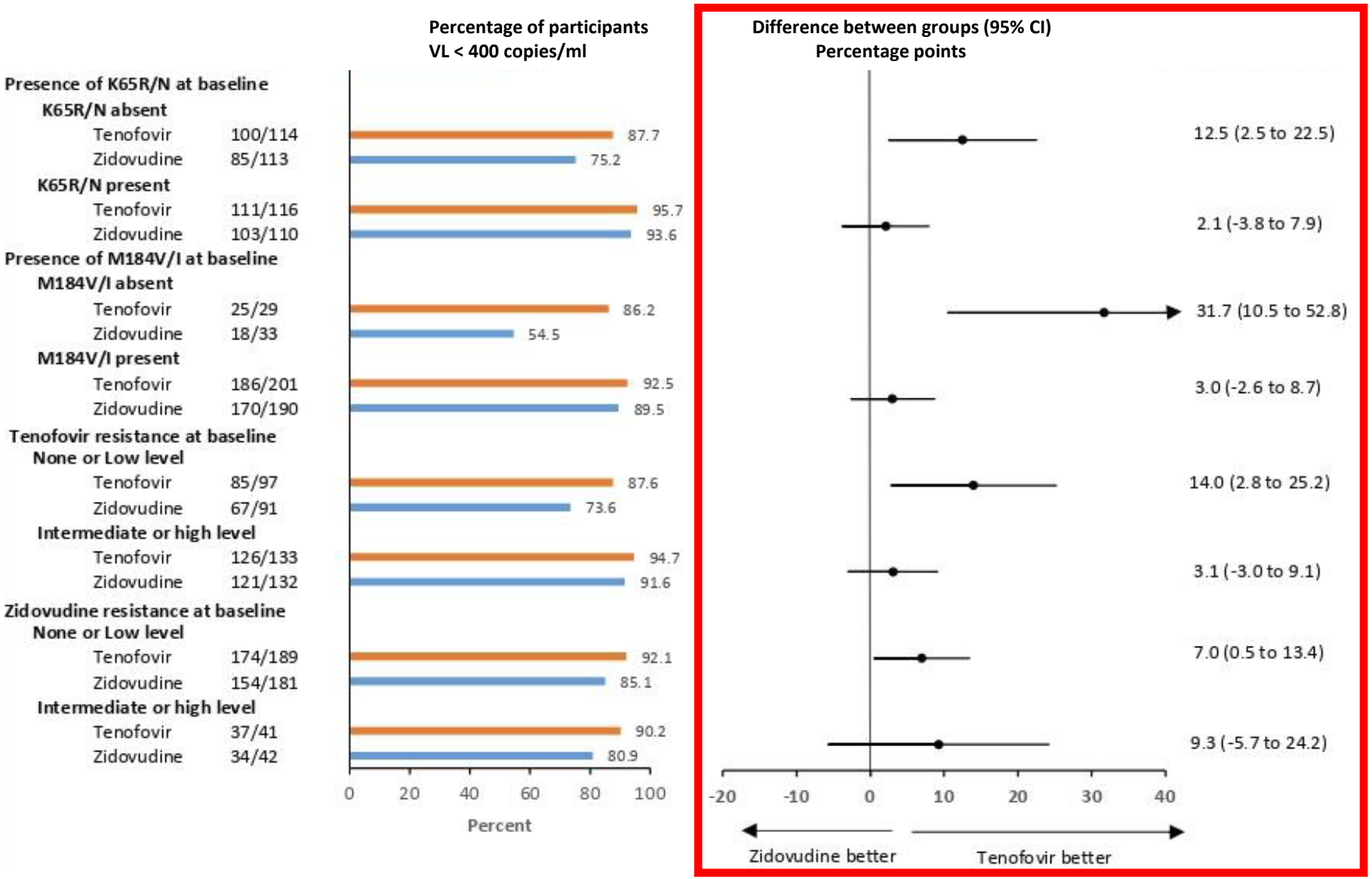
Subgroup analysis (W96): TDF vs ZDV



Subgroup analysis (W96): TDF vs ZDV



Subgroup analysis (W96): TDF vs ZDV



Dolutegravir resistance mutations

Regimen in trial	VL rebound (c/ml)	DTG resistance level (Stanford)	DTG mutations
ZDV, 3TC, DTG	≥1000	High	T66TA, G118R, E138K, G149GA, G163GR
ZDV, 3TC, DTG	≥400	High	T66TAIV, T97A, G118R, E138K
ZDV, 3TC, DTG	≥1000	High	T66I, G118R, E138K, G149GA
ZDV, 3TC, DTG	≥1000	High	T66A, G118R, E138K
ZDV, 3TC, DTG	≥1000	High	E138K, G140A, Q148R
ZDV, 3TC, DTG	≥1000	Intermediate	R263RK
TDF, 3TC, DTG	≥1000	Intermediate	M50I, R263K
TDF, 3TC, DTG	≥1000	Intermediate	M50I, R263RK
TDF, 3TC, DTG	≥400	Intermediate	M50I, R263RK

Sequences obtained from 48/55 participants

Safety

Event category	Dolutegravir Group (N=235)	Darunavir Group (N=229)	Tenofovir Group (N= 233)	Zidovudine Group (N= 231)
Any grade 3 or 4 event	26 (11.1)	28 (12.2)	22 (9.4)	32 (13.8)
Grade 3 or 4 event related to a study drug	3 (1.3)	3 (1.3)	1 (0.4)	5 (2.2)
Event (any grade) leading to discontinuation of study drug (s)	4 (1.7)	1 (0.4)	2 (0.9)	3 (1.3)
Serious adverse event (any)	18 (7.7)	16 (7.0)	17 (7.3)	17 (7.4)
Serious adverse event (death)	3 (1.3)	5 (2.2)	6 (2.6)	2 (0.9)
Haemoglobin < 9g/dl	6 (2.6)	7 (3.1)	6 (2.6)	7 (3.0)
eGFR < 60ml/min/1.73m^2	1 (0.4)	3 (1.3)	3 (1.3)	1 (0.4)

Safety

Event category	Dolutegravir Group (N=235)	Darunavir Group (N=229)	Tenofovir Group (N= 233)	Zidovudine Group (N= 231)
Any grade 3 or 4 event	26 (11.1)	28 (12.2)	22 (9.4)	32 (13.8)
Grade 3 or 4 event related to a study drug	3 (1.3)	3 (1.3)	1 (0.4)	5 (2.2)
Event (any grade) leading to discontinuation of study drug (s) †	4 (1.7)	1 (0.4)	2 (0.9)	3 (1.3)
Serious adverse event (any)	18 (7.7)	16 (7.0)	17 (7.3)	17 (7.4)
Serious adverse event (death) ‡	3 (1.3)	5 (2.2)	6 (2.6)	2 (0.9)
Haemoglobin < 9g/dl	6 (2.6)	7 (3.1)	6 (2.6)	7 (3.0)
eGFR < 60ml/min/1.73m^2 **	1 (0.4)	3 (1.3)	3 (1.3)	1 (0.4)

NADIA Conclusions (week 96)

DTG +2NRTIs vs DRV/r + 2NRTIs

- DTG + 2NRTIs gives durable suppression in second line, even if NRTIs have no predicted activity
  - Supports WHO recommendation for DTG use in second-line
  - Supports safety of programmatic switch to DTG where pre-switch VL (and resistance testing) not available

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- DTG resistance remains a concern
  - Using TDF/3TC (not AZT/3TC) may decrease risk
  - Need more data on the significance of the mutations for outcome (esp. R263K)

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- DRV/r + 2NRTIs has equivalent efficacy to DTG + 2NRTIs, without risk of resistance
  - Alternative to DTG in second-line

NADIA Conclusions (week 96)

DTG +2NRTIs vs DRV/r + 2NRTIs

- DTG + 2NRTIs gives durable suppression in second line, even if NRTIs have no predicted activity
  - Supports WHO recommendation for DTG use in second-line
  - Supports safety of programmatic switch to DTG where pre-switch VL (and resistance testing) not available

- DTG resistance remains a concern
  - Using TDF/3TC (not AZT/3TC) may decrease risk
  - Enhanced VL monitoring/adherence for initial 12m after switch if suspect/know pre-existing NRTI resistance?
  - Need more data on the significance of the mutations for outcome (esp. R263K)

- DRV/r + 2NRTIs has equivalent efficacy to DTG + 2NRTIs, without risk of resistance
  - Alternative to DTG in second-line

TDF/3TC vs ZDV/3TC

- Maintaining TDF/3TC is superior to switching to ZDV/3TC: VL suppression, rebound (& resistance?)
  - Clinical evidence adds to practical advantages (standard fixed dose combination TDF/3TC/DTG already in wide use)
  - Guidelines recommending switch from TDF/3TC to ZDV/3TC in the Public Health Approach should be reconsidered

Other RCTs confirming efficacy of TDF/3TC/DTG in setting of NRTI resistance (following TDF/3TC/EFV failure)

RCTs (but not pure randomised comparison with ZDV/3TC)

VISEND

TDF/3TC (with DTG) superior to ZDV/3TC (with ATV/r or LPV/r) at week 48

(VL < 1000 copies/ml; VL < 50 copies/ml)

D2EFT

TDF/3TC (with DTG) non-inferior to 2 NRTIs (≈80% ZDV/3TC; ≈20% TDF/3TC; GT or clinician selected; with DRV/r) at week 48

(VL <50, 200, 400 copies/ml)

VISEND: Mulenga. CROI 2022. Abstr 135
D2EFT: Matthews. CROI 2023. Abstr 198

	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)*	p value
Dolutegravir or darunavir randomised treatment group				
Darunavir	1 (ref)	..	1 (ref)	..
Dolutegravir	1·31 (0·70–2·43)	0·40	0·99 (0·49–2·01)	0·99
NRTI randomised treatment group				
Zidovudine	1 (ref)	..	1 (ref)	..
Tenofovir	2·76 (1·41 – 5·42)	0·0031	2·92 (1·39–6·13)	0·0046
Adherence (visits with missed antiretroviral therapy)				
0	1 (ref)	..	1 (ref)	..
1	0·97 (0·28–3·41)	0·96	0·88 (0·24–3·26)	0·84
2	0·22 (0·08–0·61)	0·0032	0·29 (0·10–0·85)	0·024
≥3	0·17 (0·07–0·41)	<0·0001	0·23 (0·09–0·58)	0·0021
HIV-1 RNA concentration at baseline				
<100 000 copies per mL	1 (ref)	..	..	..
≥100 000 copies per mL	1·06 (0·53–2·13)	0·87	..	..
Presence of Lys65Arg or Lys65Asn at baseline				
No	1 (ref)	..	1 (ref)	..
Yes	7·52 (3·11–18·16)	<0·0001	5·93 (2·33–15·06)	0·0002
Presence of Met184Val or Met184Ile at baseline				
No	1 (ref)	..	1 (ref)	..
Yes	5·03 (2·54–9·93)	<0·0001	4·99 (2·23–11·18)	<0·0001
Presence of thymidine analogue mutations† at baseline				
No	1 (ref)	..	1 (ref)	..
Yes	0·88 (0·44–1·74)	0·71	0·89 (0·40–1·97)	0·78

OR for suppression <400 copies/ml – drugs and mutations individually

Paton, Musaazi, Kityo et al. Lancet HIV 2022. https://doi.org/10.1016/S2352-3018(22)00092-3

Drug efficacy in presence of mutations

- No M184V (or K65R): adjusted OR for suppression 8.97 (TDF:ZDV)

TDF is more potent drug

- M184V alone: adjusted OR 1.83 for suppression (TDF:ZDV)

M184V enhances susceptibility to both ZDV and TDF; decreases difference but not sufficient to abolish difference between TDF and ZDV

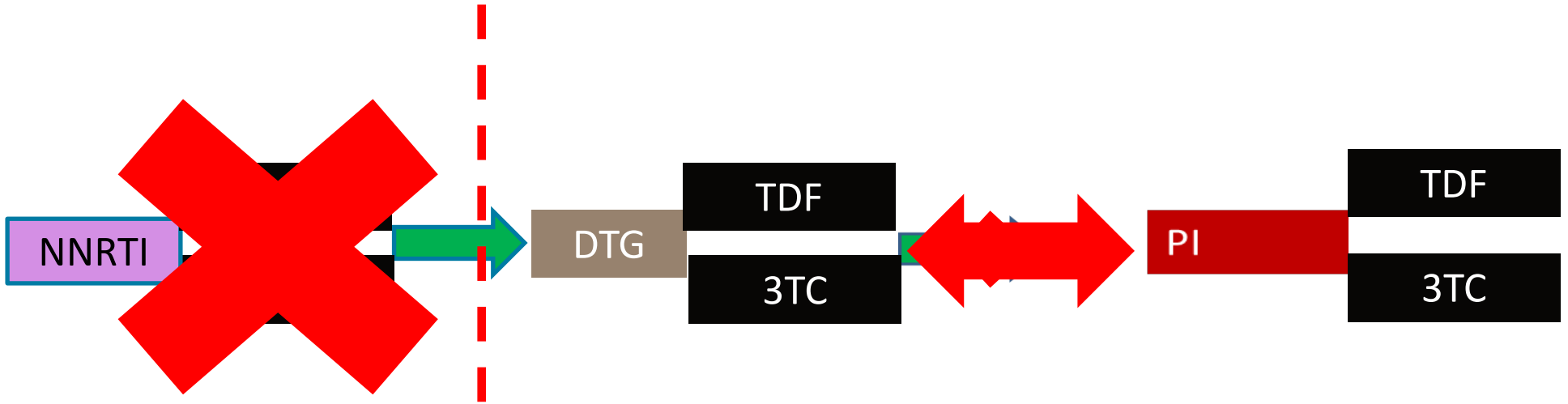
- K65R (and M184V): adjusted OR 2.07 for suppression (TDF:ZDV)

K65R further enhances susceptibility to ZDV; adverse impact of K65R on TDF susceptibility is blunted by effect M184V

Sequencing regimens for the WHO public health approach

Standardised first line ~3% fail/year Standardised second line Standardised third line

Regimens for the WHO public health approach



Potentially 2 fully interchangeable regimens

TDF/3TC DTG ⟷ TDF/3TC DRV/r

Summary

- The WHO public health approach is essential for global delivery of ART in resource-limited settings
- DTG (with TDF/3TC) is robust irrespective of NRTI resistance; preferred second-line regimen after EFV failure; programmatic switching from EFV without VL testing will likely be robust
- DRV/r (with TDF/3TC) is a good alternative (B regimen), irrespective of NRTI resistance
- Maintaining TDF/3TC is a better choice than switching to ZDV/3TC, irrespective of NRTI resistance

Acknowledgements

Clinical Sites:

Infectious Diseases Institute (IDI), Kampala (79): Andrew Kambugu, Arvind Kaimal, Barbara Castelnouvo, Daniel Kiiza, Jesca Asienzo, John Kisembo, John Nsubuga, Max Okwero, Rhona Muyise

Joint Clinical Research Centre (JCRC) Kampala (59): Cissy Kityo, Claire Nasaazi, Dridah L. Nakiboneka, Henry Mugerwa, Josephine Namusanje, Theresa Najjuuko, Timothy Masaba, Timothy Serumaga

JCRC Fort Portal (68): Adolf Alinaitwe, Allan Arinda, Angela Rweyora, Cissy Kityo, Gilbert Ategeka, Mary Goretti Kangah

JCRC Mbarara (72): Abbas Lugemwa, Cissy Kityo, Mariam Kasozi, Phionah Tukamushabe, Rogers Ankunda, Shafic Makumbi, Sharif Musumba, Sula Myalo, John Ahuura

Makerere University Walter Reed Project, Kampala (76): Annet Mary Namusisi, Daniel Kibirige, Francis Kiweewa, Grace Mirembe, Habert Mabonga, Joseph Wandege, Josephine Nakakeeto, Sharon Namubiru, Winfred Nansalire

Moi University Clinical Research Center (51): Abraham Mosigisi Siika, Charles Meja Kwobah, Chris Sande Mboya, Martha Mokeira Bisieri Mokaya, Mercy Jelagat Karoney, Priscilla Chepkorir Cheruiyot, Salinah Cherutich, Simon Wachira Njuguna, Viola Cherotich Kirui

University of Zimbabwe Clinical Research Centre (60): Ennie Chidziva, Godfrey Musoro, James Hakim, Joyline Bhiri, Misheck Phiri, Shepherd Mudzingwa, Tadios Manyanga, Margaret Borok

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IDI Coordinating Centre: Agnes Kiragga, Anchilla Mary Banegura, Andrew Kambugu, Anne Hoppe, Apolo Balyegisawa, Betty Agwang, Brian Isaaya, Constantine Tumwine, Eva Laker, Jesca Asienzo, Joseph Musaazi, Nicholas Paton, Peter Senkungu, Stephen Walimbwa, Yvonne Kamara. External statistical consultants: Elizabeth Allen, Charles Opondo

Janssen Pharmaceutica: Perry Mohammed, Willemijn van Rein-van der Horst, Yvon van Delft, Fafa Addo Boateng

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Independent Data Monitoring Committee: Francois Venter (Chair), Sam Phiri, Sarah Walker

Funding: Janssen and the TRIAL PARTICIPANTS