Recent Trials of Second-Line ART: Lessons Learned & Applications to Clinical Practice

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Disclaimer

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AETC AIDS Education & Training Center Program Mountain West

Case

- 52-year-old cisgender man with longstanding HIV
- Viral load suppressed on rilpivirine/TAF/FTC for several years
- Prior ART: efavirenz/TDF/FTC
- Lapse in adherence following onset of COVID-19 pandemic
- Viral load rebound to 1,250 copies/mL
- Genotype: new E138K and M184V mutations
- *Which new ART regimen would you recommend?*

Background

- Following virologic failure of first-line ART, traditional practice was to aim for 3 fully active drugs in new regimen
- In areas without access to resistance testing, new regimen often included a boosted PI plus switch from TDF to AZT
- With widespread availability of dolutegravir, is this still the optimal strategy?
- As many countries roll out tenofovir DF-lamivudine-dolutegravir ("TLD") as first-line ART, can it also be offered as empiric second-line ART?

DAWNING

Dolutegravir (DTG) vs. ritonavir-boosted lopinavir (LPV/r), each with two NRTIs, following virologic failure of first-line ART

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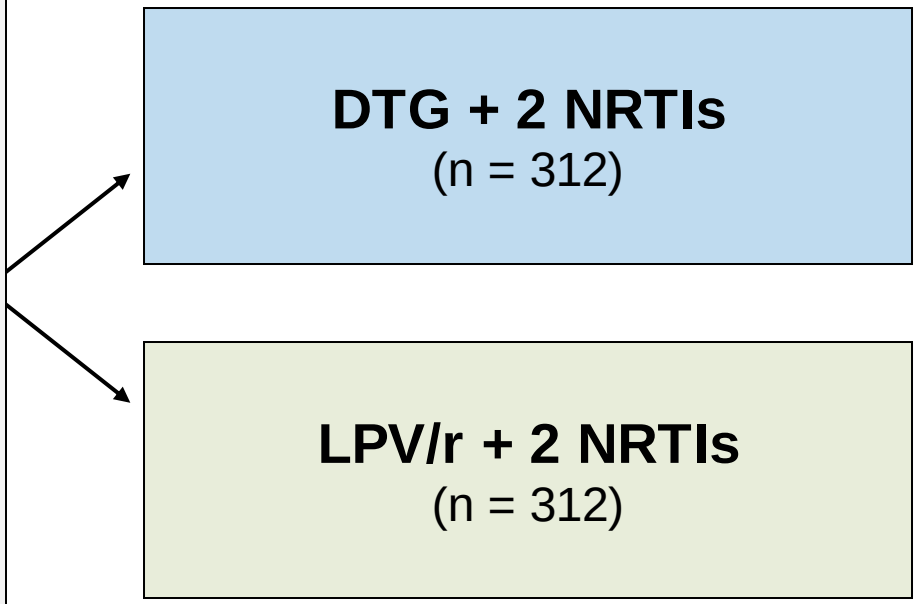
DTG vs LPV/r, each with two NRTIs, after first-line ART virologic failure
DAWNING: Design

- **Design**
  - Open-label, randomized, phase 3b study performed in multiple countries in sub-Saharan Africa, South America, Central America, Asia, and Eastern Europe
- **Including Criteria**
  - Age ≥18 with HIV-1
  - Virologic failure after at least 6 months taking NNRTI plus 2 NRTIs (HIV RNA ≥400 copies/mL x 2)
  - No history of taking a boosted PI or INSTI
  - All had genotype resistance test at baseline
  - All received investigator-selected NRTIs (at least one fully active based on genotype)



Source: Aboud M, et al. Lancet Infectious Dis. 2019;19:253-64.

DTG vs LPV/r, each with two NRTIs, after first-line ART virologic failure
DAWNING: Results

Baseline Characteristics	DTG + 2 NRTIs (n = 312)	LPV/r + 2 NRTIs (n = 312)
Age, years, mean (range)	37.5 (19-64)	38.7 (18-72)
Male sex, n (%)	196 (63)	209 (67)
CD4 T cell count, mean (SD), $\log_{10}$ cells/mm^3	2.1 (0.5)	2.2 (0.4)
CD4 T cell count <200 cells/mm^3	166 (53%)	151 (48%)
Mean HIV RNA, mean (SD), $\log_{10}$ copies/mL	4.2 (0.9)	4.2 (0.9)
HIV RNA >100,000 copies/mL, n (%)	70 (22)	63 (20)
Duration of previous ART, median (IQR), weeks	86.4 (48.4-230.9)	90.9 (45.0-199.5)
Prior NNRTI: efavirenz	242 (78%)	242 (78%)
Prior NNRTI: nevirapine	70 (22%)	69 (22%)
Prior NNRTI: rilpivirine	0	1 (<1%)

Source: Aboud M, et al. Lancet Infectious Dis. 2019;19:253-64.

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DTG vs LPV/r, each with two NRTIs, after first-line ART virologic failure
DAWNING: Results

Baseline Characteristics	DTG + 2 NRTIs (n = 312)	LPV/r + 2 NRTIs (n = 312)
NRTIs in new regimen		
TDF/FTC or TDF/3TC	132 (42%)	121 (39%)
AZT/3TC	128 (41%)	134 (43%)
TDF + AZT	36 (12%)	41 (13%)
Fully susceptible NRTIs in new regimen		
0 to <1	30 (10%)	36 (12%)
1 to 2	221 (71%)	212 (68%)
2	61 (20%)	64 (21%)

Source: Aboud M, et al. Lancet Infectious Dis. 2019;19:253-64.

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DTG vs LPV/r, each with two NRTIs, after first-line ART virologic failure
DAWNING: Results

Baseline Characteristics (NRTI Resistance Mutations)	DTG + 2 NRTIs (n = 312)	LPV/r + 2 NRTIs (n = 312)
K65R	95 (30%)	92 (29%)
K70E	33 (11%)	37 (12%)
M184V/I only	77 (25%)	85 (27%)
M184V/I plus other major NRTI mutation	184 (59%)	167 (54%)
Other major NRTI mutation	90 (29%)	88 (28%)
Thymidine analog mutation (TAMs)	71 (23%)	81 (26%)

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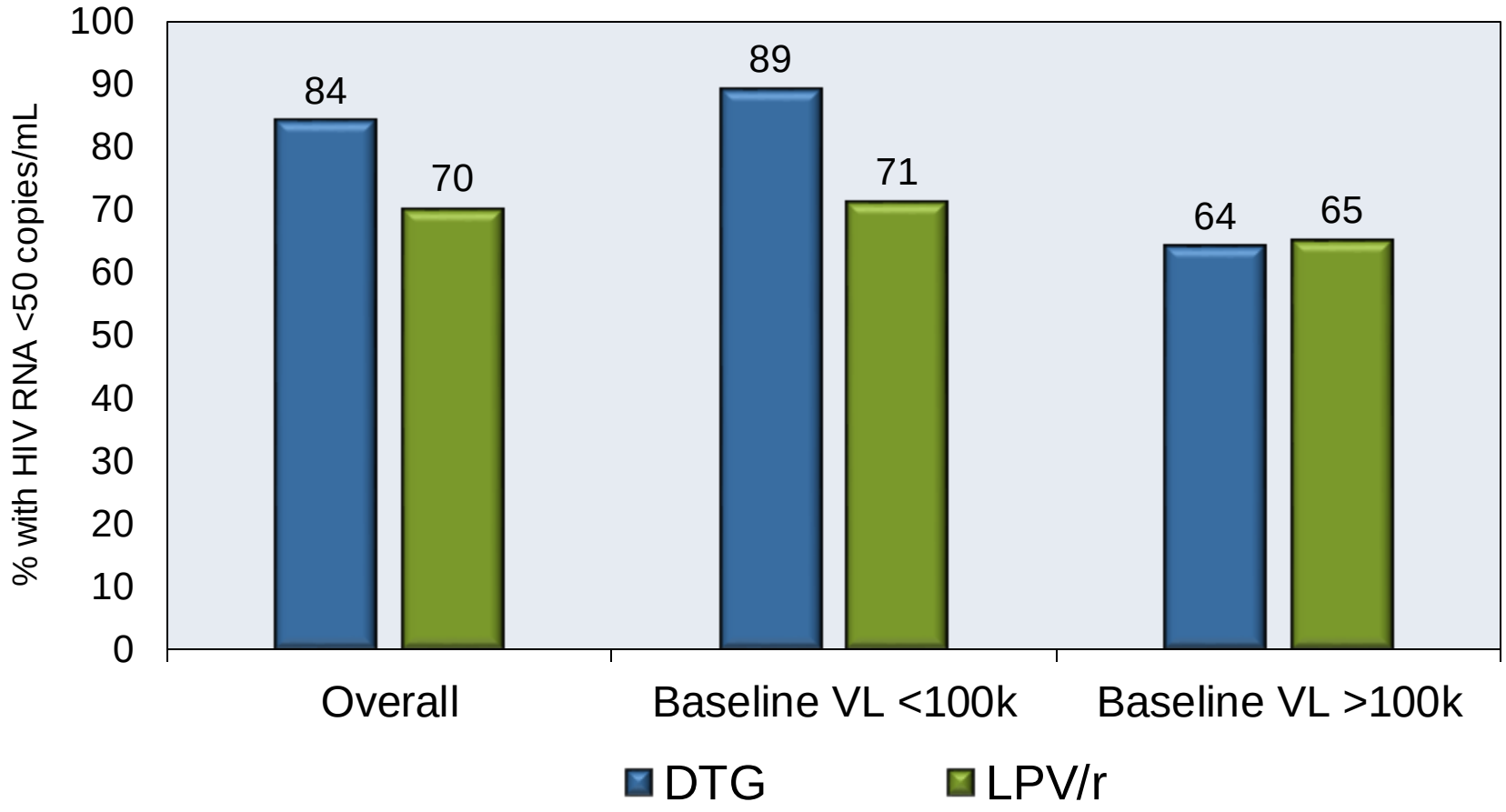
DTG vs LPV/r, each with two NRTIs, after first-line ART virologic failure
DAWNING: Results

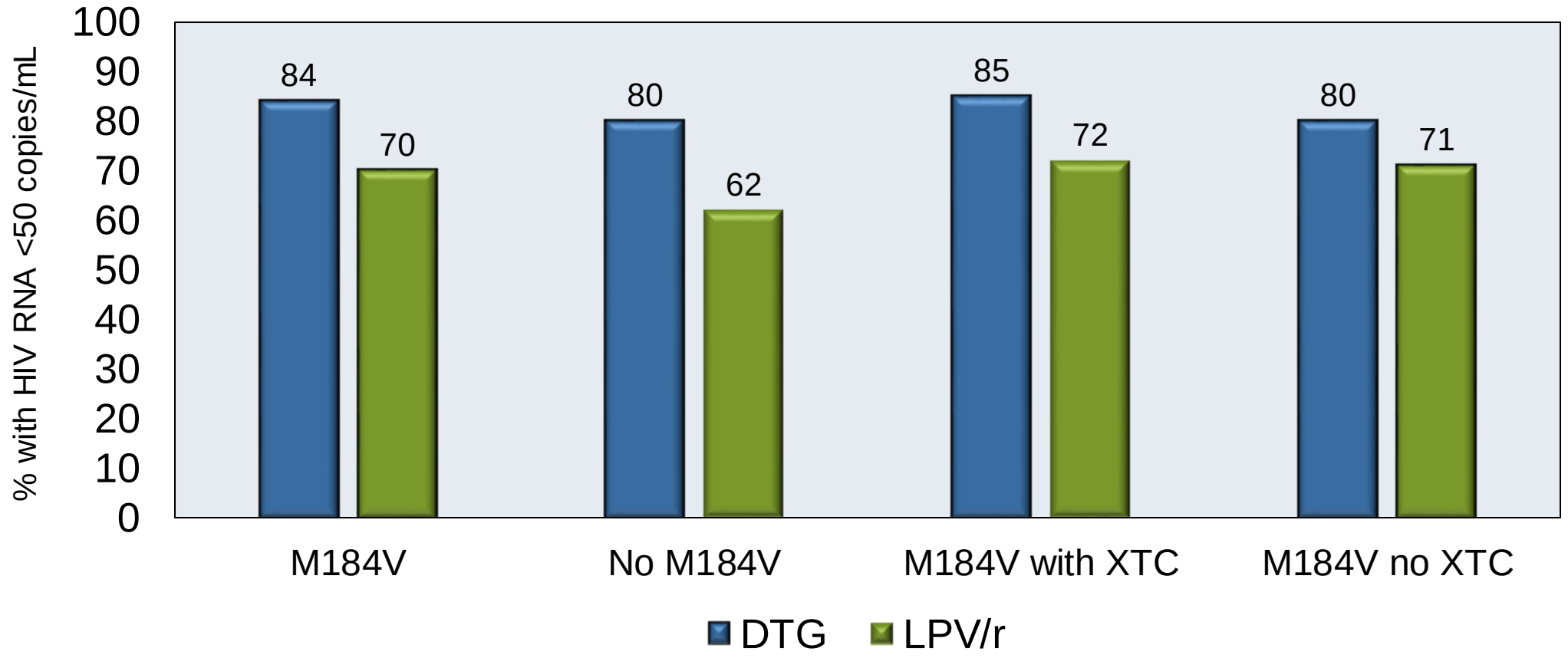
Virologic response at 48 weeks (intention-to-treat analysis), stratified by baseline viral load (VL)



Source: Aboud M, et al. Lancet Infectious Dis. 2019;19:253-64.

DTG vs LPV/r, each with two NRTIs, after first-line ART virologic failure
DAWNING: Results

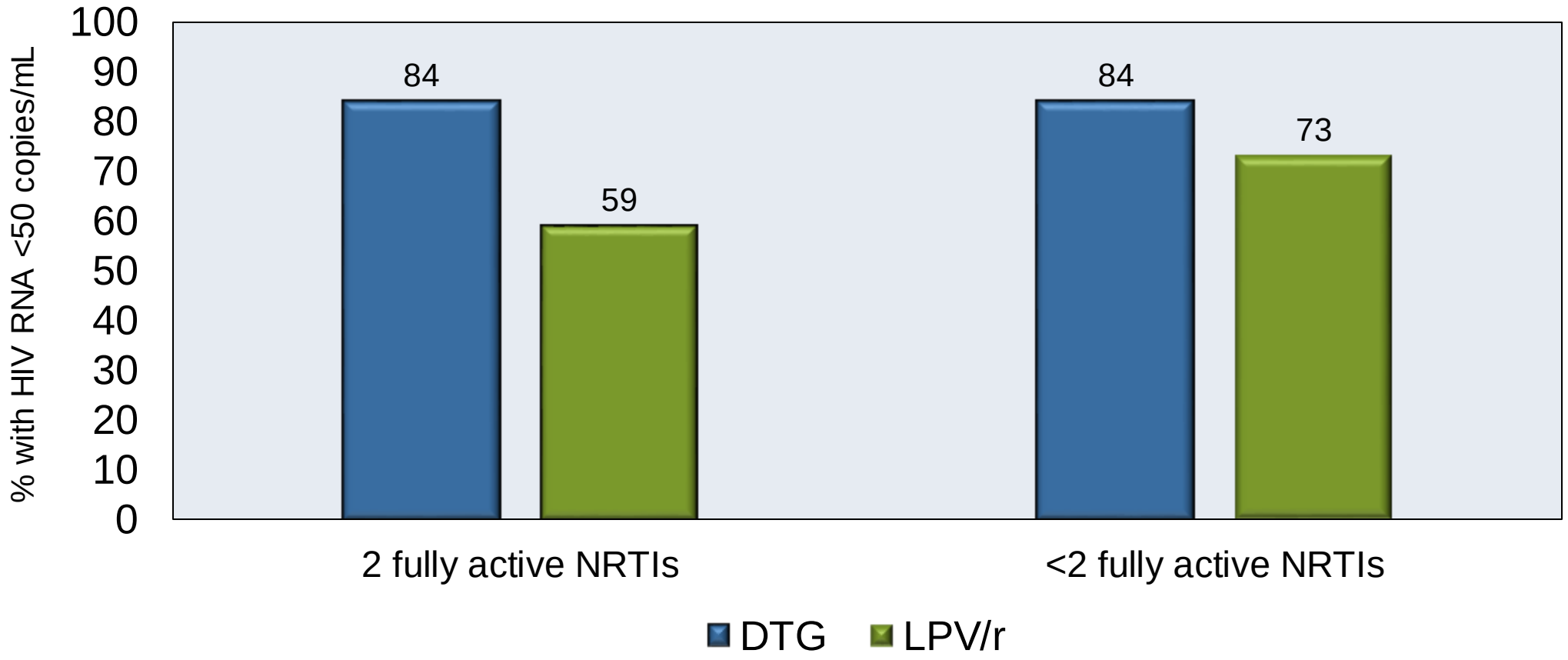
Virologic response at 48 weeks, stratified by M184V and use of XTC (FTC or 3TC)



Source: Aboud M, et al. Lancet Infectious Dis. 2019;19:253-64.

DTG vs LPV/r, each with two NRTIs, after first-line ART virologic failure
DAWNING: Results

Virologic response at 48 weeks, stratified by number of fully active NRTIs



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DTG vs LPV/r, each with two NRTIs, after first-line ART virologic failure DAWNING: Results

Cases of virologic failure with emergent dolutegravir resistance

DTG arm: 11 participants met criteria for virologic failure (VF); 2 had emergent DTG resistance
LPV/r arm: 30 met criteria for VF; 3 emergent NRTI resistance, zero emergent PI resistance

HIV Subtype	Study NRTIs	Baseline HIV RNA (copies/mL)	HIV RNA at Virologic Failure (copies/mL)	Baseline NRTI RAM(s)	Emergent INSTI RAM(s)	Emergent NRTI RAM(s)
B	TDF/FTC	461,000	2,464	M184V + K219K/E	G118R	D67N
C	AZT/3TC	1.2 million	454	M184V + K70E	Multiple	None

Source: Aboud M, et al. Lancet Infectious Dis. 2019;19:253-64.

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DAWNING: Conclusions and Limitations

- After 48 weeks, DTG plus 2 NRTIs showed superior efficacy compared to LPV/r plus 2 NRTIs following virologic failure on NNRTI plus 2 NRTIs
- Supports DTG + 2 NRTIs as second-line ART, even if only one NRTI fully active
- Limitations: open-label, baseline resistance testing performed (not generalizable to low-resource settings), use of LPV/r as comparator, use of TDF (not TAF)
- Outstanding questions: efficacy of TDF/FTC versus AZT/3TC in new regimen, efficacy and safety of switching in the absence of genotype

Source: Aboud M, et al. Lancet Infectious Dis. 2019;19:253-64.

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NADIA
Dolutegravir (DTG) vs. ritonavir-boosted darunavir (DRV/r), each with TDF/3TC or AZT/3TC, following virologic failure on first-line ART

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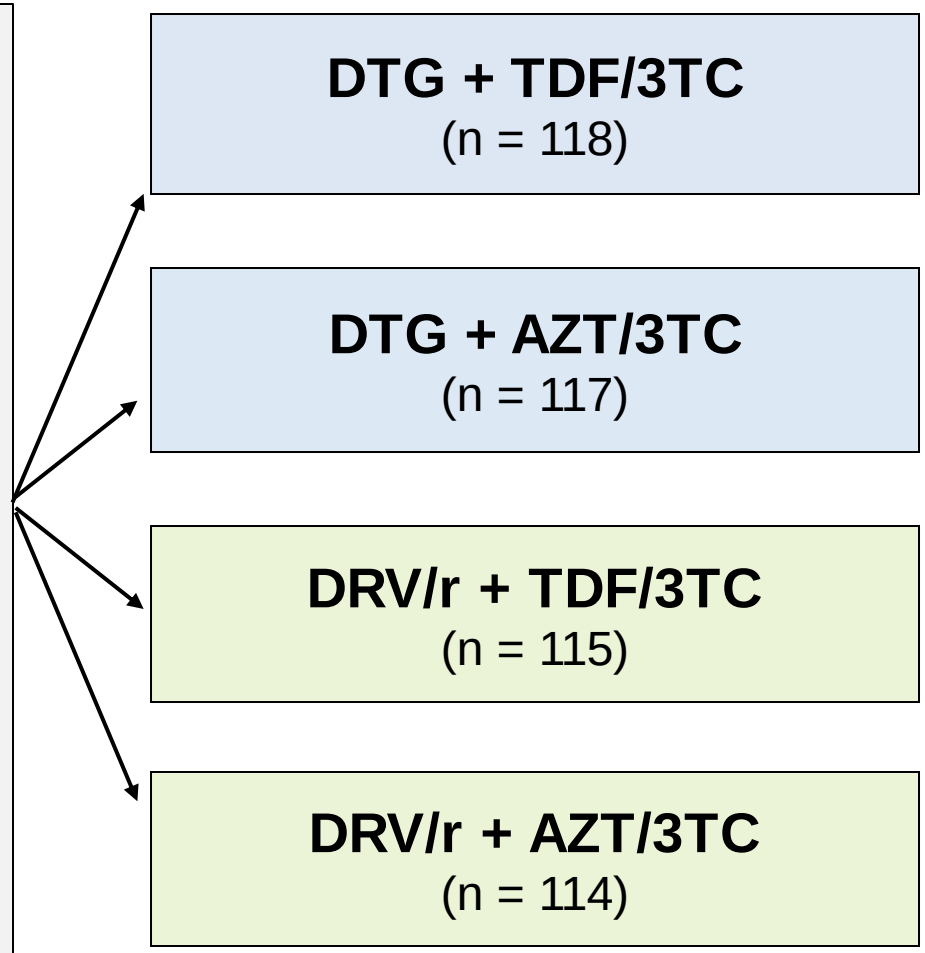
DTG vs DRV/r, each with TDF/3TC or AZT/3TC, after first-line ART virologic failure
NADIA: Design

- **Design**
  - Open-label, prospective, multicenter, two-by-two factorial, randomized, non-inferiority, 96-week trial conducted in Uganda, Kenya, and Zimbabwe
- **Including Criteria**
  - Age ≥12 with HIV-1
  - Virologic failure after at least 6 months taking NNRTI plus 2 NRTIs (HIV RNA ≥1,000 copies/mL twice)
  - No history of taking a boosted PI or INSTI
  - Nurse-led visits, standard of care visit frequency, emphasis on adherence counseling
  - No genotype at enrollment



Source: Paton N, et al. N Engl J Med. 2021;385:330-341.

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DTG vs DRV/r, each with TDF/3TC or AZT/3TC, after first-line ART virologic failure
NADIA: Results

Baseline Characteristics	DTG (n = 235)	DRV/r (n = 229)
Age, years, median (IQR)	33 (28-40)	35 (28-42)
Female sex, n (%)	140 (59.6)	142 (62.0)
CD4 T cell count, median (IQR), cells/mm^3	189 (58-388)	202 (84-357)
CD4 T cell count <200 cells/mm^3	125 (53.2)	113 (49.3)
Median HIV RNA (IQR), $\log_{10}$ copies/mL	4.5 (3.9-5.1)	4.4 (3.8-5.1)
HIV RNA ≥100,000 copies/mL, n (%)	66 (28.1)	62 (27.1)
Duration of previous ART, median (IQR), years	3.6 (1.4-6.3)	3.7 (1.7-5.9)
K65R present at baseline	120 (52.6)	106 (47.1)
M184V/I present at baseline	196 (86.0)	195 (86.7)

Source: Paton N, et al. N Engl J Med. 2021;385:330-341.

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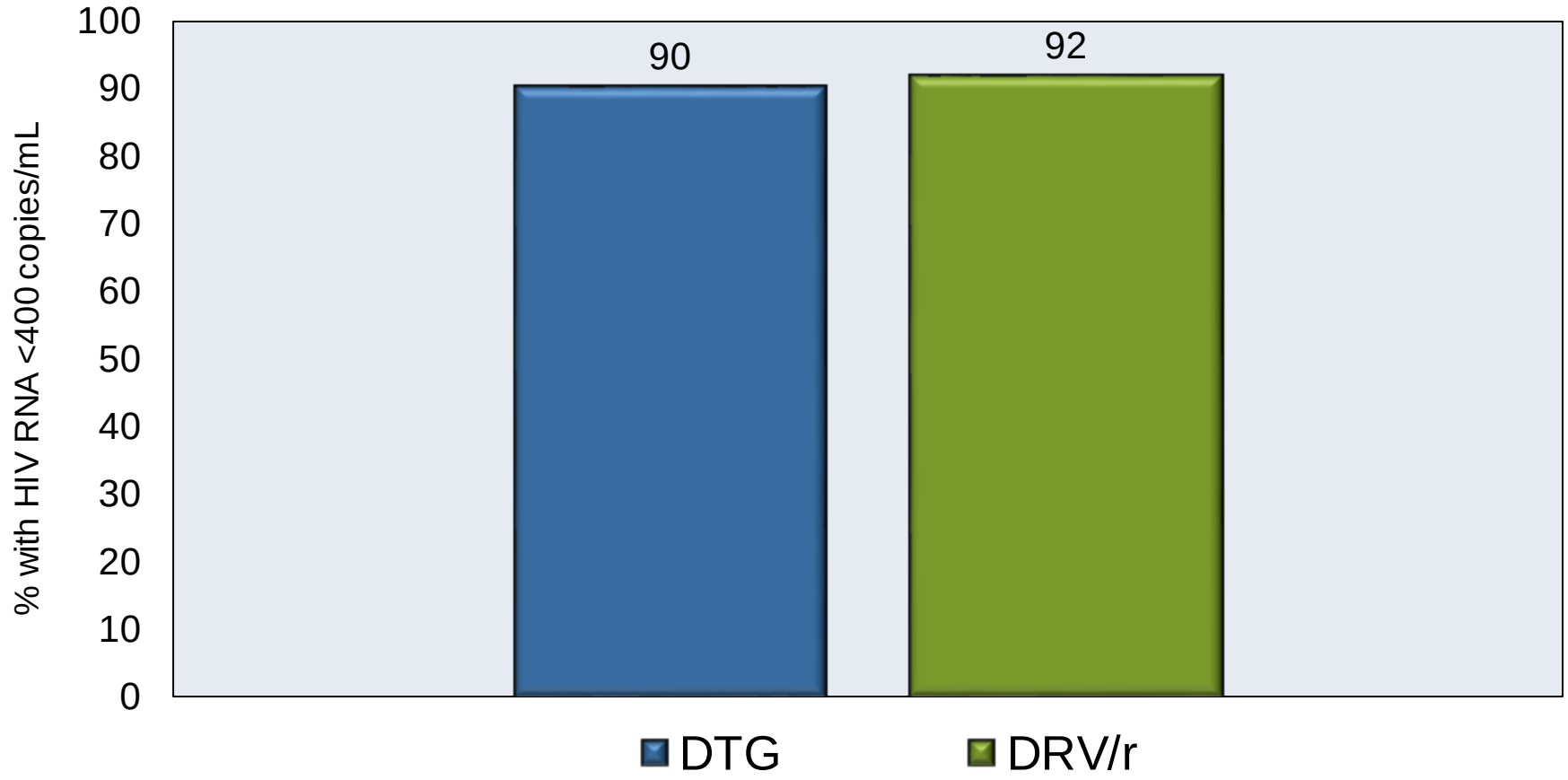
DTG vs DRV/r, each with TDF/3TC or AZT/3TC, after first-line ART virologic failure
NADIA: Results

Virologic response at 48 weeks (by intention-to-treat analysis)



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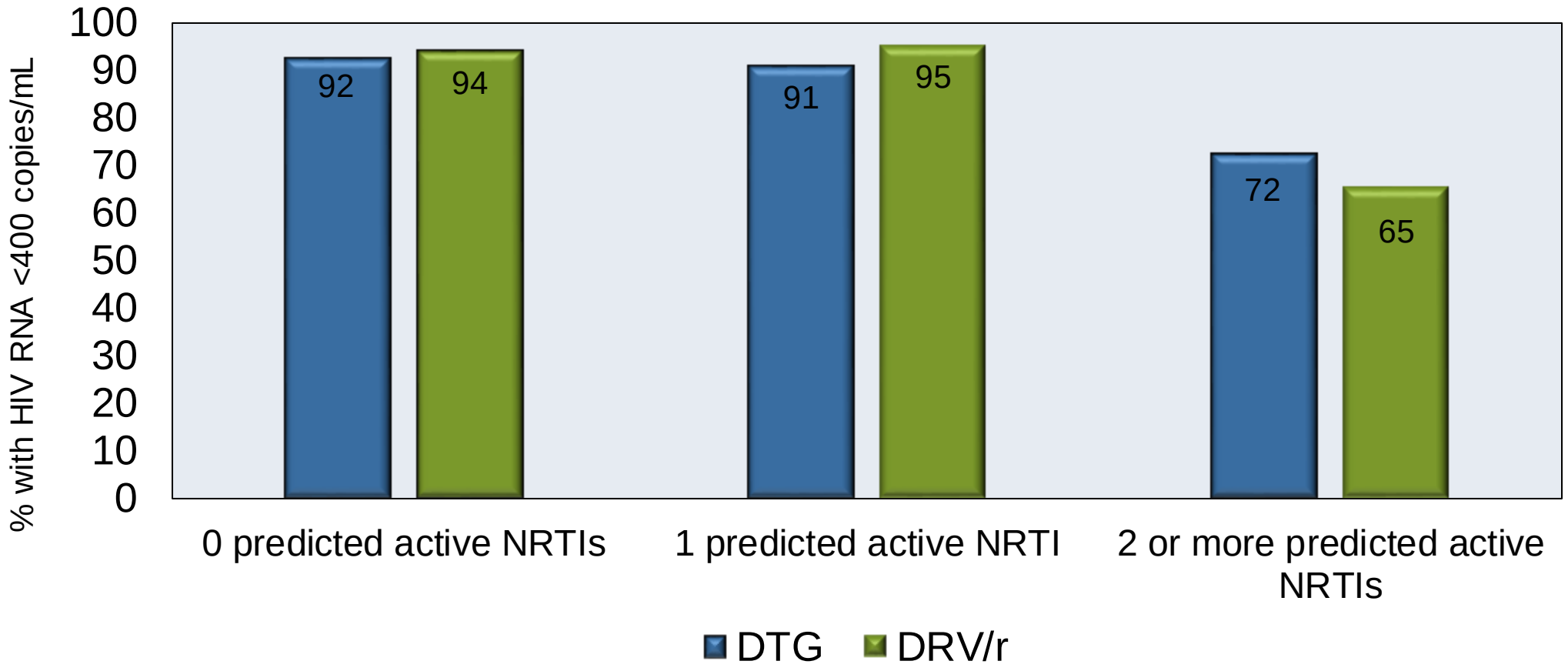
DTG vs DRV/r, each with TDF/3TC or AZT/3TC, after first-line ART virologic failure
NADIA: Results

Virologic response at 48 weeks, stratified by number of predicted active NRTIs



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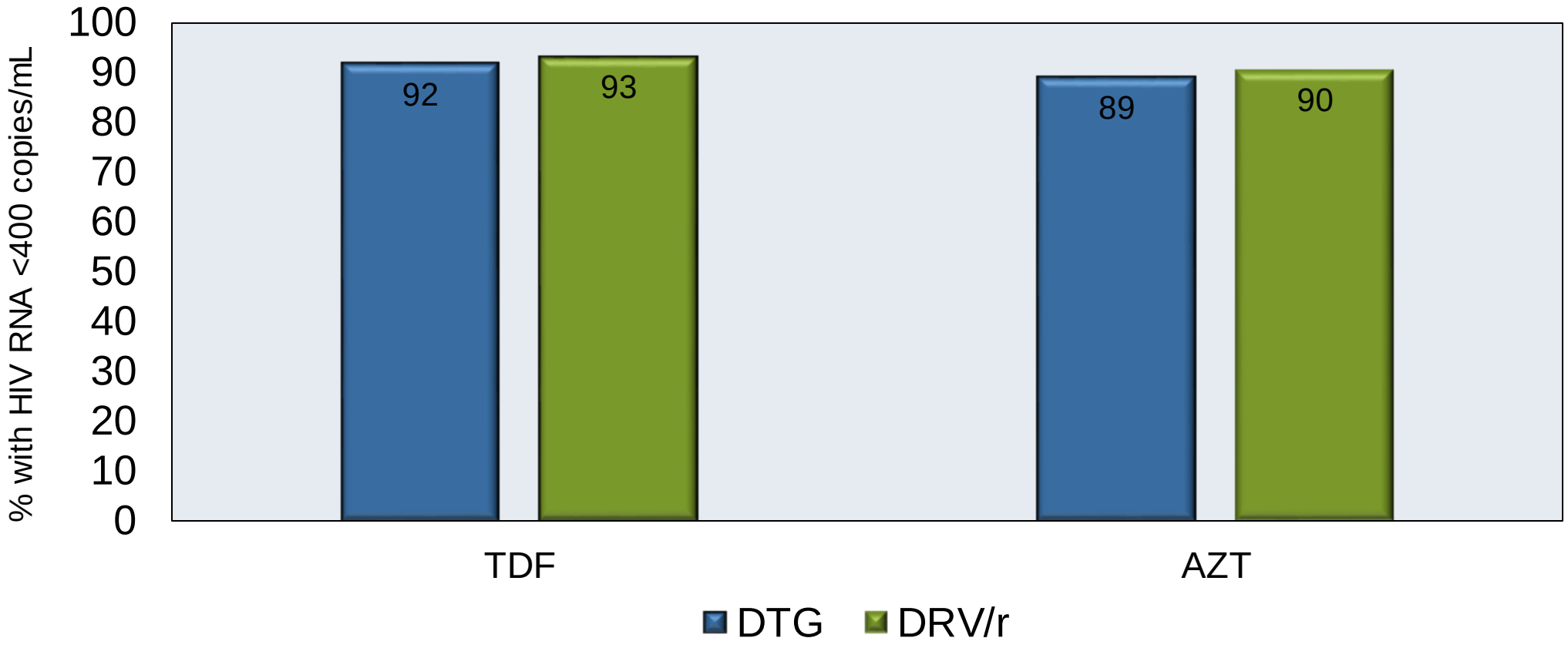
DTG vs DRV/r, each with TDF/3TC or AZT/3TC, after first-line ART virologic failure
NADIA: Results

Virologic response at week 48, stratified by NRTI backbone (TDF/3TC or AZT/3TC)



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NADIA
Week 96 results presented at CROI 2022

- DTG + 2 NRTIs remained non-inferior to DRV/RTV + 2 NRTIs
- TDF/3TC now superior efficacy compared to AZT/3TC
- 9 cases of emergent DTG resistance (6 in AZT/3TC group, 3 TDF/FTC)
- Conclusions:
  - DTG + 2 NRTIs can be used as second-line ART, even if NRTIs predicted to have limited or no activity, but emergent DTG resistance may be a concern
  - DRV/r + 2 NRTIs has efficacy equivalent to DTG + 2 NRTIs in second-line treatment, without concern for resistance

Source: Paton N, et al. CROI 2022. Abstract 137.

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Applications to Clinical Practice

See also:
VISEND study, CROI 2022

- How should we apply these results to clinical practice?
  - DTG (or BIC) or DRV/r effective with <2 fully active NRTIs (e.g. with M184V); is this the end of AZT once and for all as part of HIV treatment?
  - Would you offer DTG (or BIC) plus TDF/FTC or TAF/FTC in the setting of M184V and K65R? Or M184V + TAMs? Are you comfortable if there is <1 active NRTI?
  - Cases of intermediate-to-high-level resistance to DTG occurred in NADIA; should this give us pause? Should we opt for DRV/r instead of DTG in certain scenarios?
- Returning to case, with M184V and viral load 1,250 copies/mL, which regimen would you recommend? What if the viral load were 12k copies? Or 100k copies?

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