Global drug resistance following ART scale up

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Public health approach to ART

First Line:

2 NRTI + NNRTI (EFV or NVP)

- Viral failure of 15-35% in high prevalence areas[1]

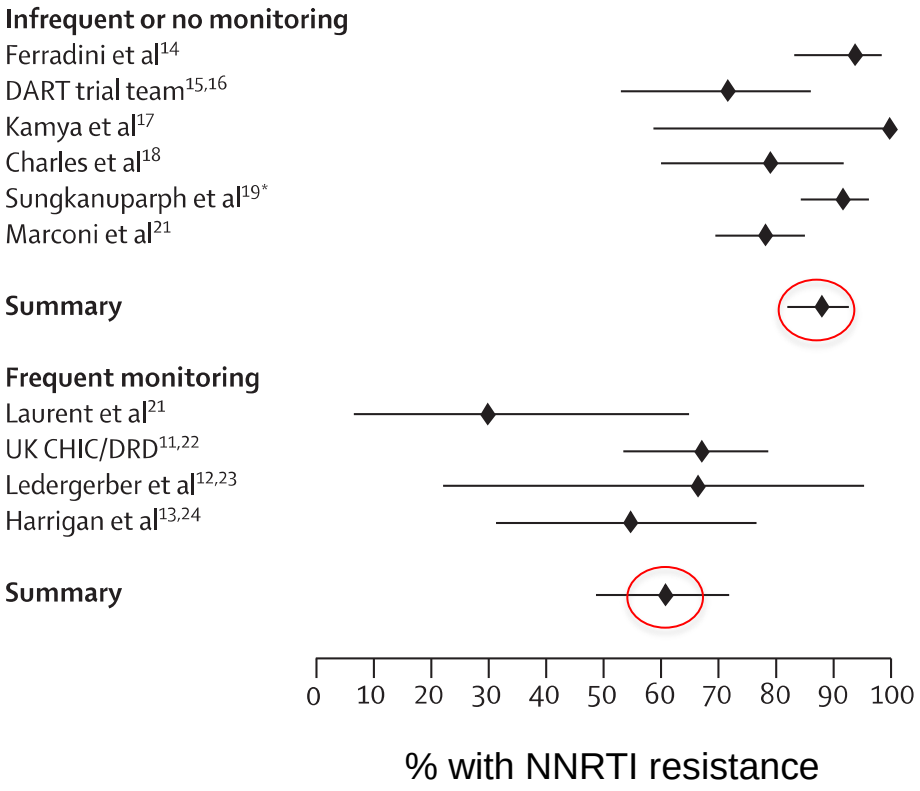
Second Line:

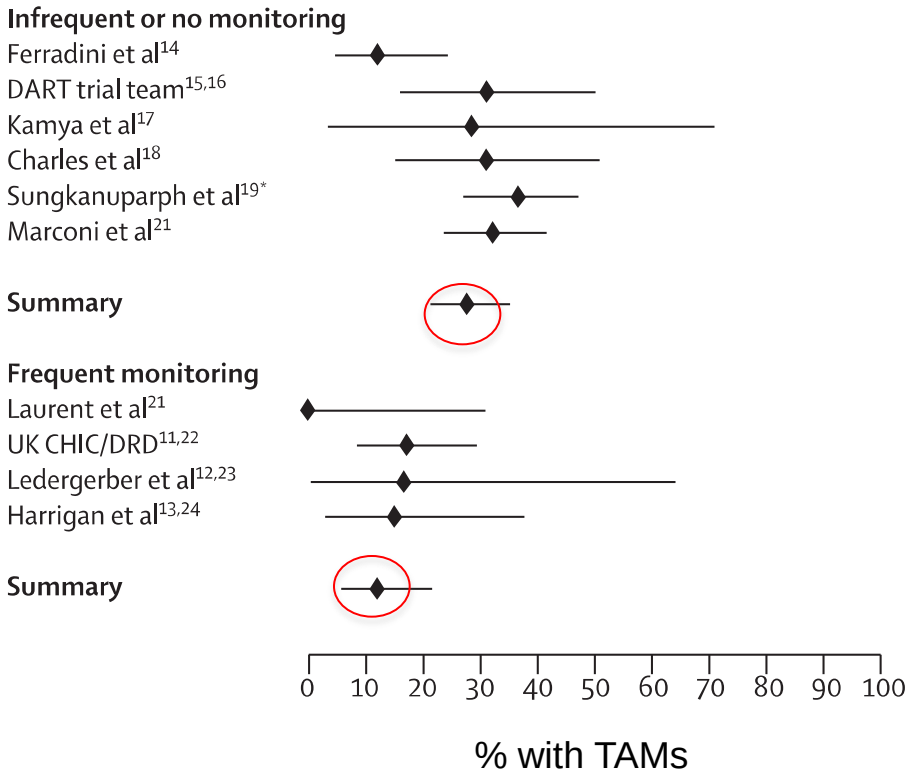
2 NRTI + bPI (ATV/r, LPV/r, DRV/r)

Cytosine analogue maintained

[1]Boender et al, Clin Infect Dis 2015

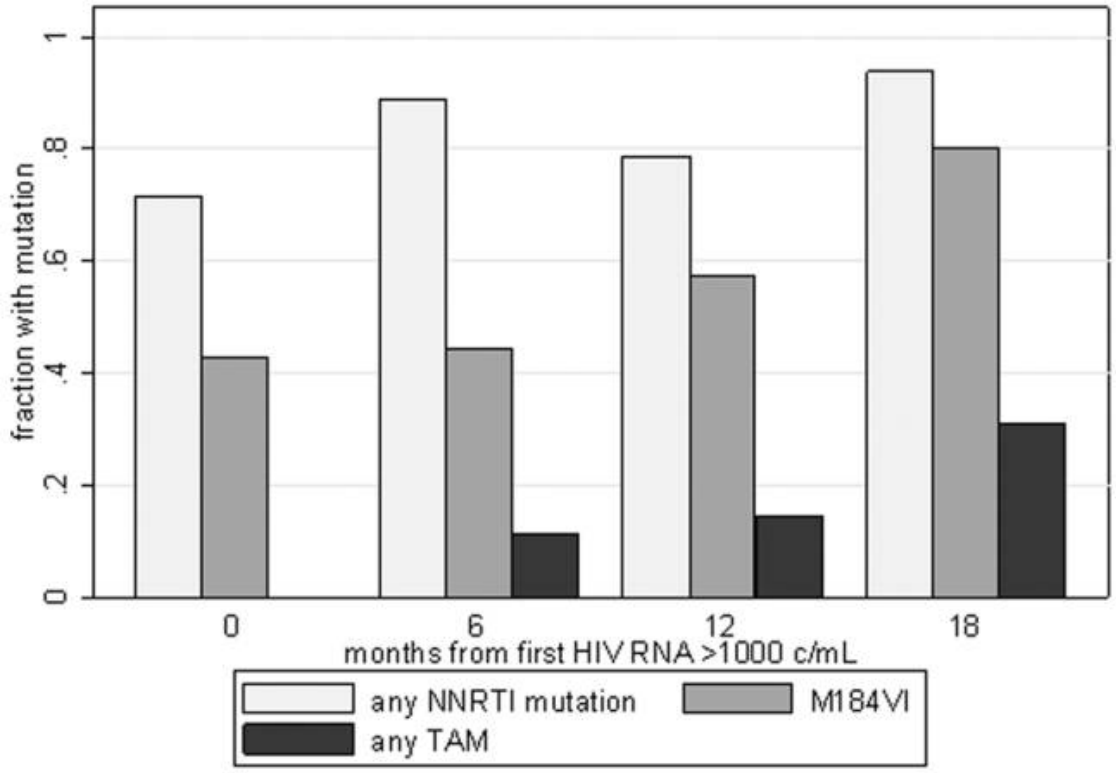
Lack of viral load monitoring linked to increased resistance following AZT or d4T failure at 12mo





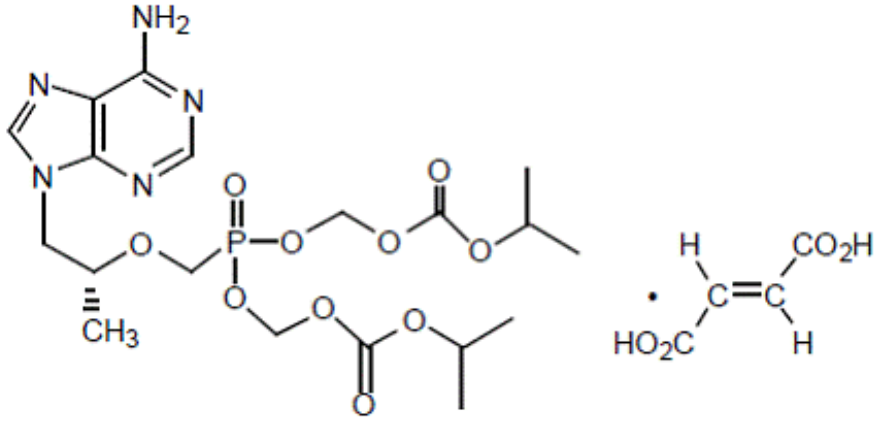
Gupta RK et al, *Lancet Infect Dis 2009*

Duration of viral failure of AZT/d4T based cART linked to emergence of resistance



Hoffmann CJ et al, *Clin Infect Dis 2009*

Tenofovir as treatment



- Tenofovir is now the preferred NRTI as 1st line cART (also the preferred anti-HBV drug)
- TDF+FTC outperforms ABC+3TC at high viral loads[1]
- Effective treatment for HBV
- Scale up of TDF globally is occurring…

[1]Sax PE et al, NEJM 2009

Tenofovir resistance

- Single amino acid change leads to TDF resistance (K65N/R, K70E/G/Q)

- Scattered reports of high (>50%) prevalence of TDF resistance in TDF virologic failures from Nigeria[1] and South Africa[2].

- ***Prevalence of TDF resistance in clinical trials was low (0% of virologic failures in GS 934 at 144 weeks[3]).***

[1]Etiebet MA et al*, AIDS 2013*; [2]Sunpath H et al, *AIDS 2012*; [3]Margot et al, *JAIDS 2009*

SAME AGENT WITH LOW GENETIC BARRIER FOR BOTH TREATMENT AND PreP…

Aims

- To quantify regional prevalence of tenofovir resistance
- To identify risk factors for tenofovir resistance
- To assess transmission potential of TDF resistance

Methodology

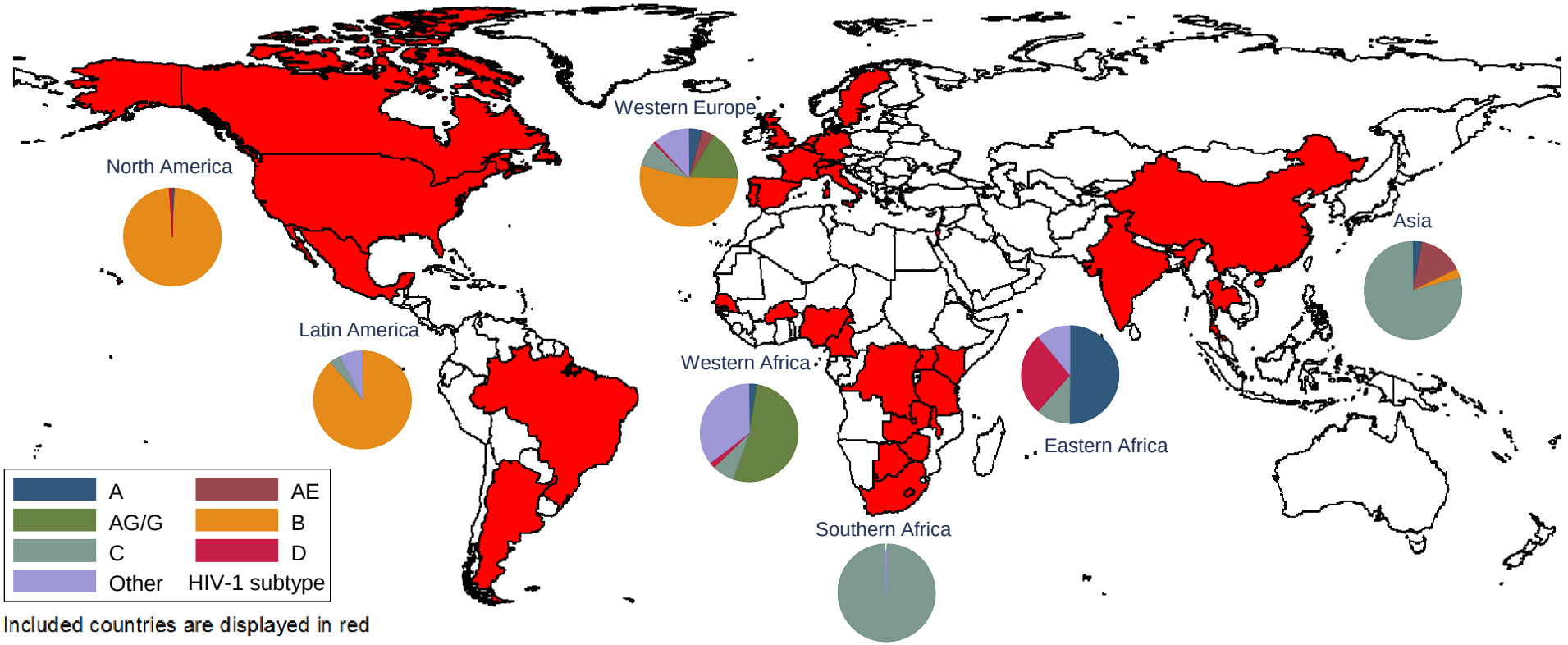
- Retrospective multi-centre study
- Covariates of interest: region, baseline CD4, baseline viral load, co-administered drugs (NVP vs EFV; and 3TC vs FTC), age, sex.

Methodology

- >15 years old at cART initiation
- First line virologic failure (local thresholds)
- TDF as first line drug + FTC/3TC + EFV or NVP
- Genotypic resistance test successful
- Absence of Thymidine analogue mutations

Results

Countries contributing data and HIV-1 subtype distribution by region

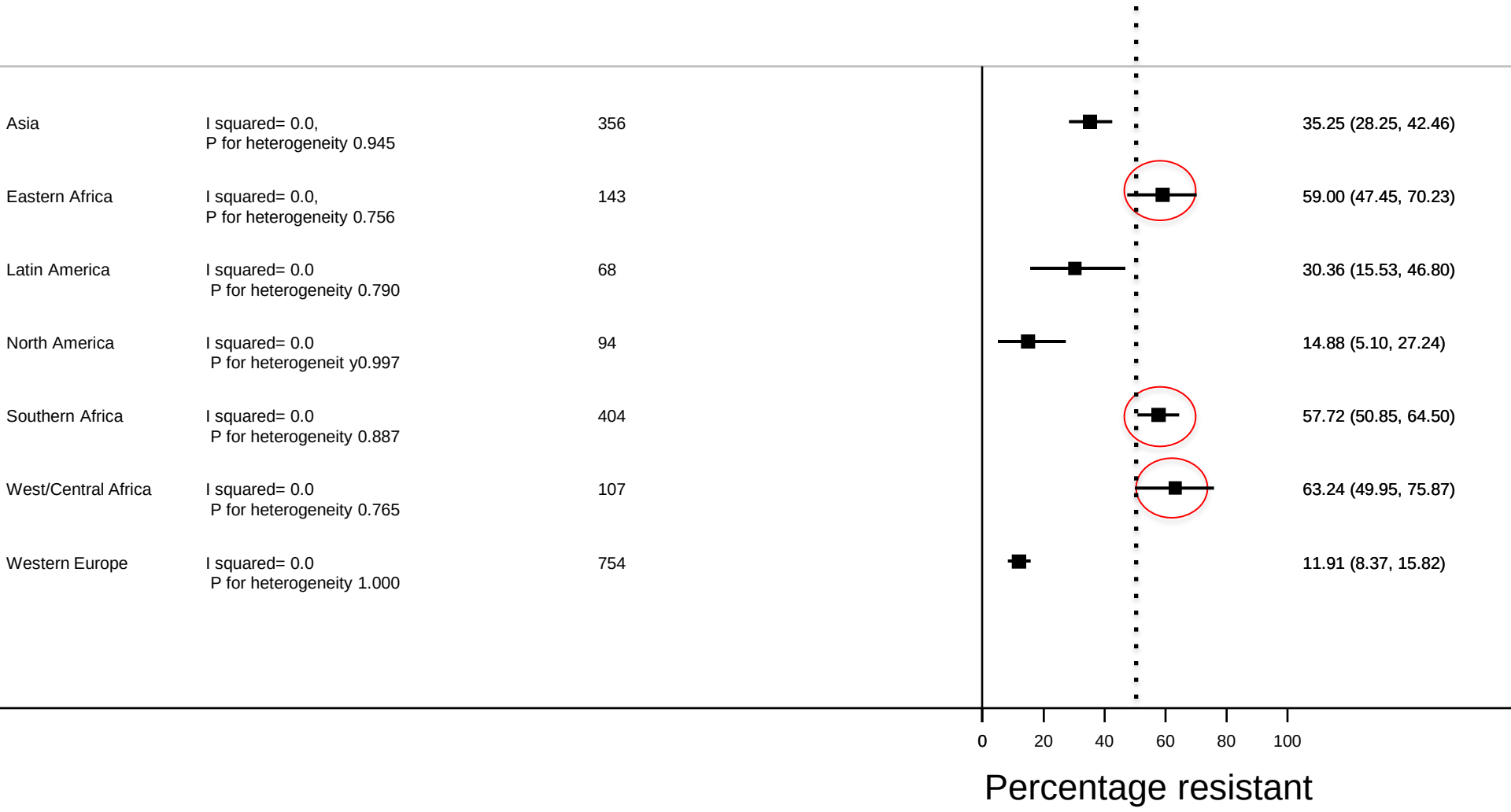


N=1926
36 countries represented
Included cohorts and some clinical trials
Around a third of data previously unpublished

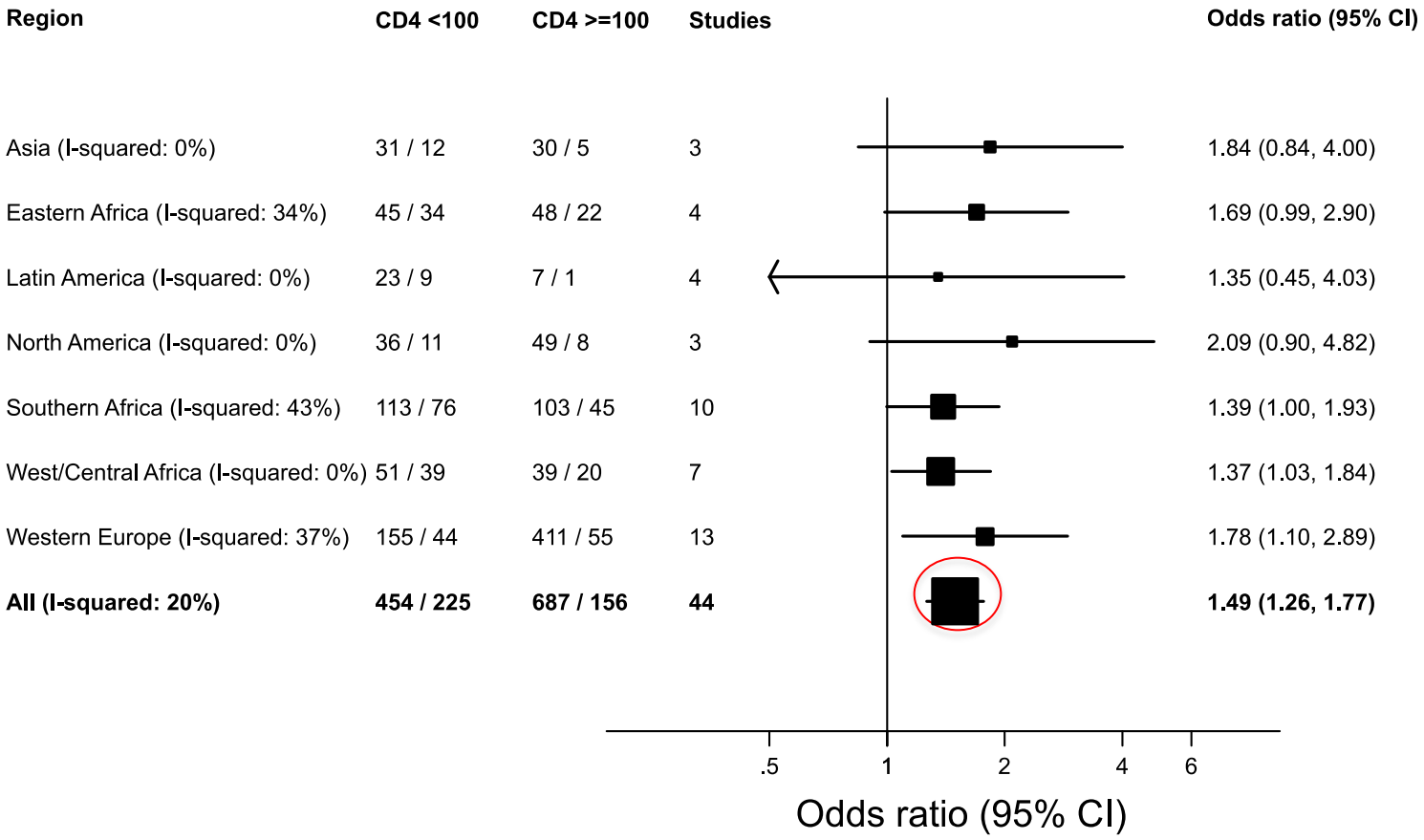
TenoRes Study Group, *Lancet Infect Dis 2016*

Prevalence of tenofovir resistance

Region	Evidence of heterogeneity	Participants	Percentage resistant (95% CI)
Asia	I squared= 0.0, P for heterogeneity 0.945	356	35.25 (28.25, 42.46)
Eastern Africa	I squared= 0.0, P for heterogeneity 0.756	143	59.00 (47.45, 70.23)
Latin America	I squared= 0.0 P for heterogeneity 0.790	68	30.36 (15.53, 46.80)
North America	I squared= 0.0 P for heterogeneit y0.997	94	14.88 (5.10, 27.24)
Southern Africa	I squared= 0.0 P for heterogeneity 0.887	404	57.72 (50.85, 64.50)
West/Central Africa	I squared= 0.0 P for heterogeneity 0.765	107	63.24 (49.95, 75.87)
Western Europe	I squared= 0.0 P for heterogeneity 1.000	754	11.91 (8.37, 15.82)



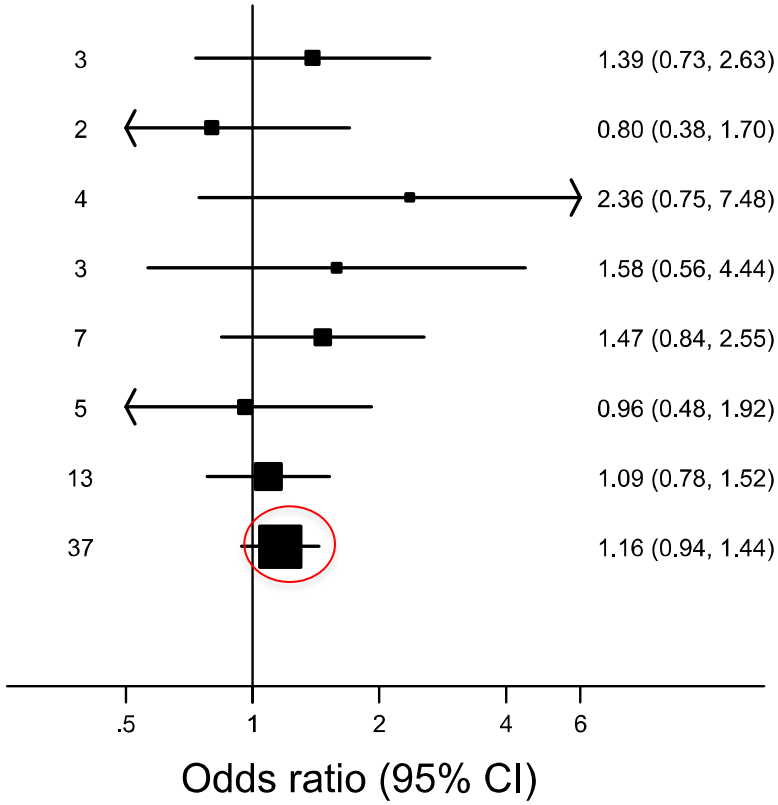
Baseline CD4 impact on TDF resistance



TenoRes Study Group, *Lancet Infect Dis 2016*

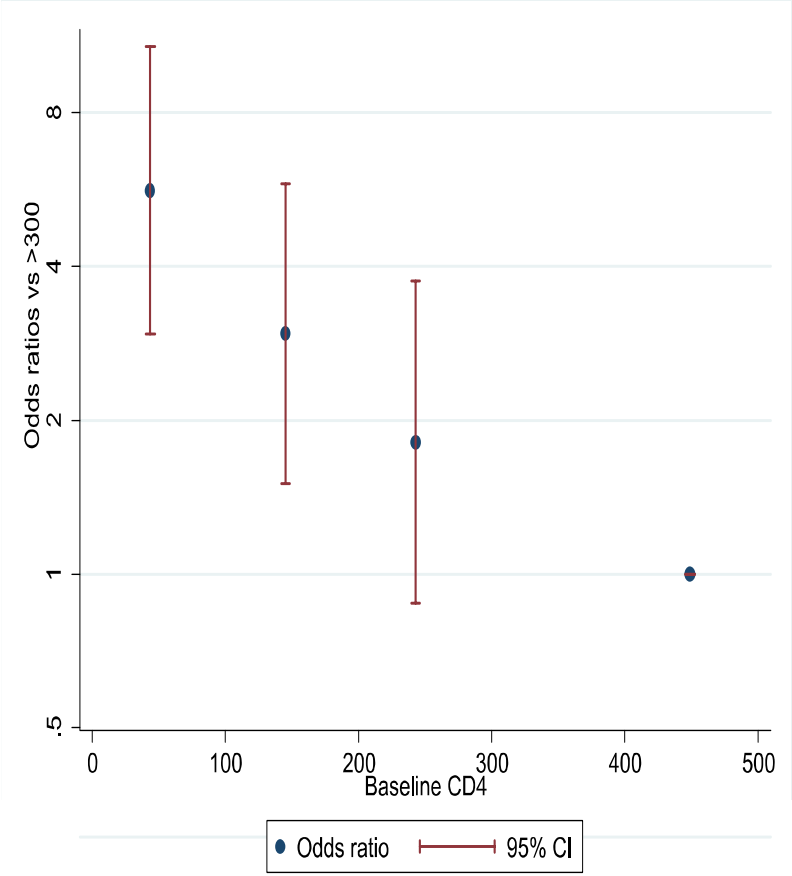
Baseline Viral load impact on TDF resistance

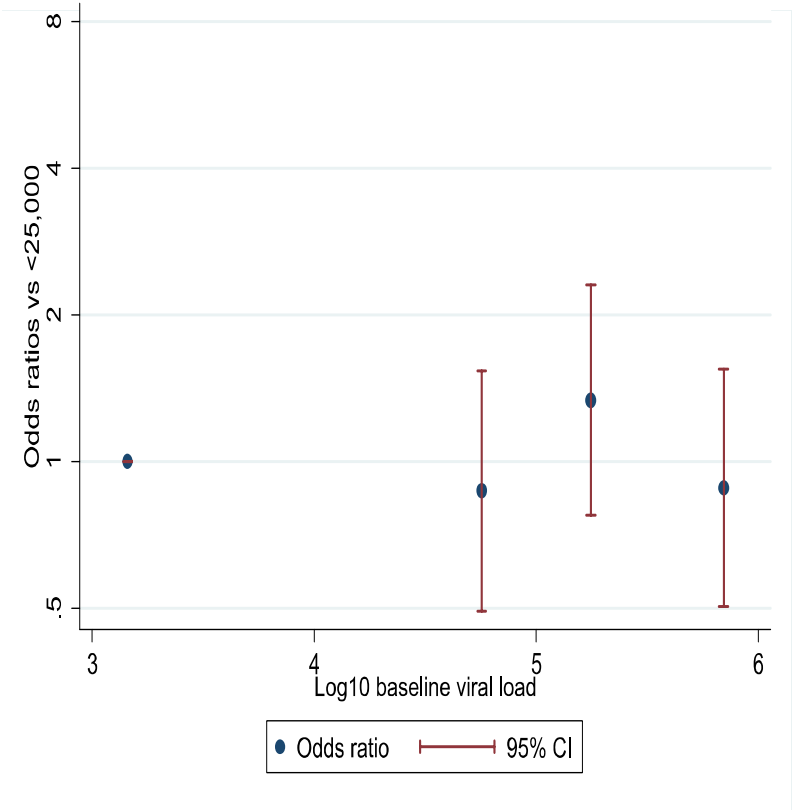
Region	Viral load >=100,000	Viral load <100,000	Studies	Odds ratio (95% CI)
Asia (I-squared: 0%)	16 / 7	17 / 4	3	1.39 (0.73, 2.63)
Eastern Africa (I-squared: 22%)	42 / 21	7 / 4	2	0.80 (0.38, 1.70)
Latin America (I-squared: 0%)	28 / 12	10 / 1	4	2.36 (0.75, 7.48)
North America (I-squared: 14%)	44 / 13	38 / 6	3	1.58 (0.56, 4.44)
Southern Africa (I-squared: 3%)	44 / 17	39 / 11	7	1.47 (0.84, 2.55)
West/Central Africa (I-squared: 19%)	40 / 26	15 / 8	5	0.96 (0.48, 1.92)
Western Europe (I-squared: 0%)	276 / 58	299 / 46	13	1.09 (0.78, 1.52)
All (I-squared: 0%)	490 / 154	425 / 80	37	1.16 (0.94, 1.44)



TenoRes Study Group, *Lancet Infect Dis 2016*

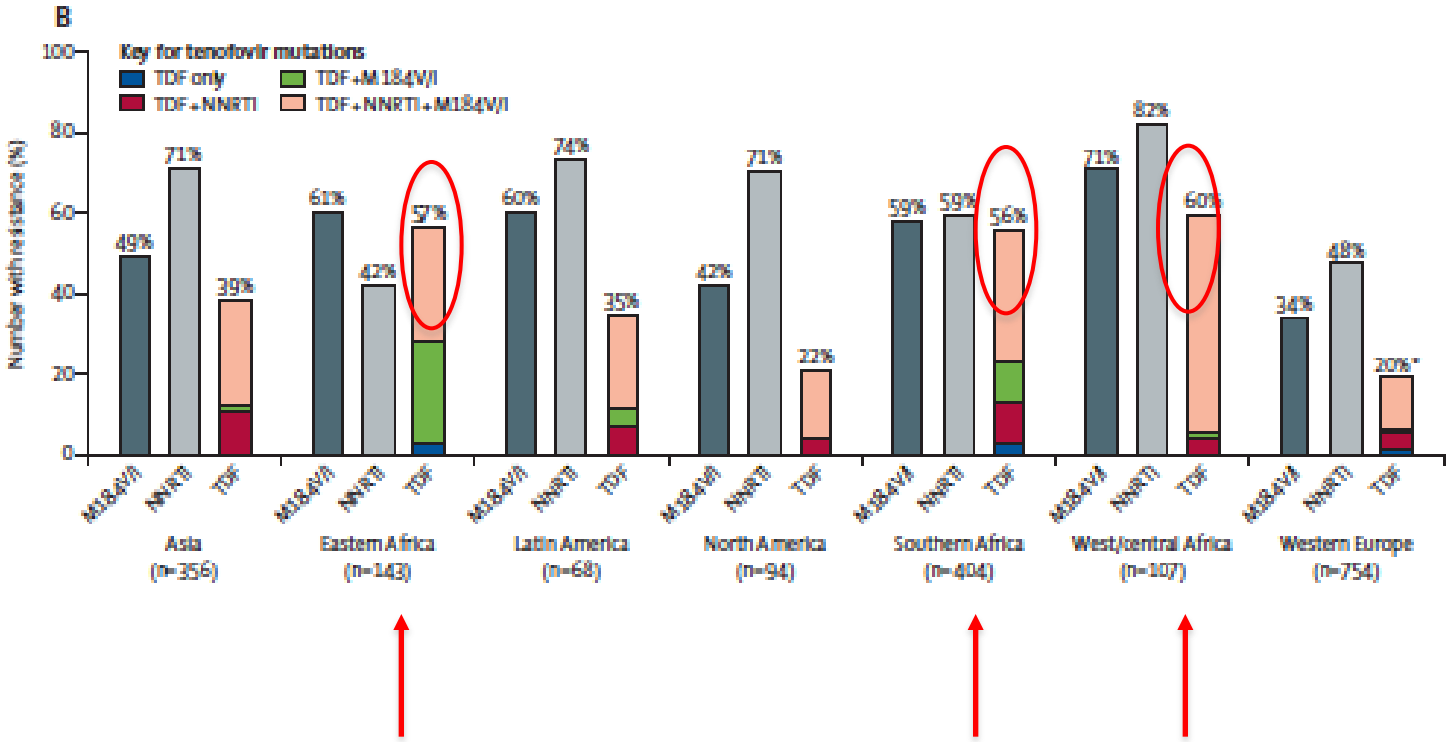
BaselineCD4/Viral load impact on TDF resistance





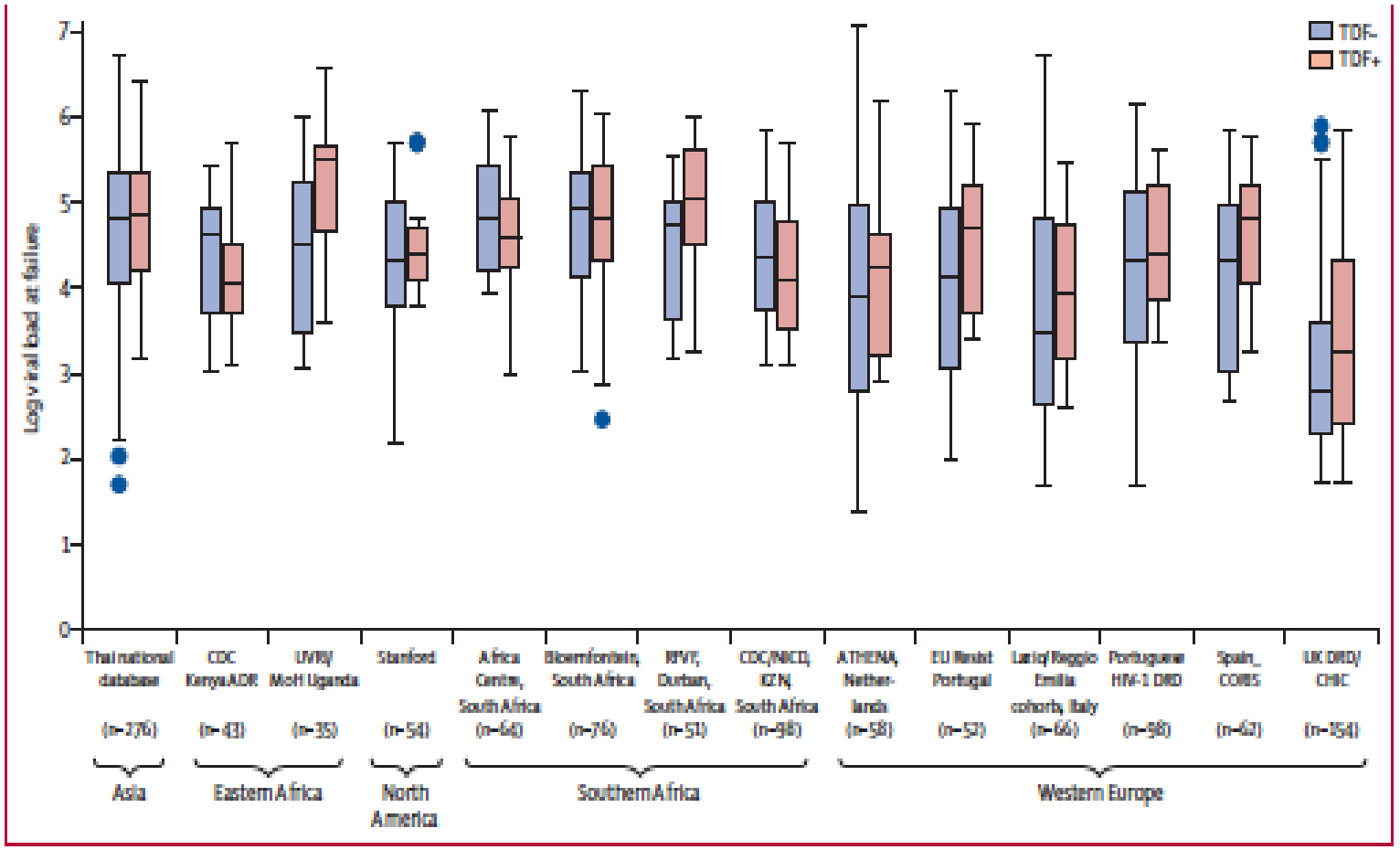
TenoRes Study Group, *Lancet Infect Dis 2016*

TDF Resistance is usually accompanied by high level NNRTI resistance and M184V/I



TenoRes Study Group, *Lancet Infect Dis 2016*

Viral load is not impacted by tenofovir resistance



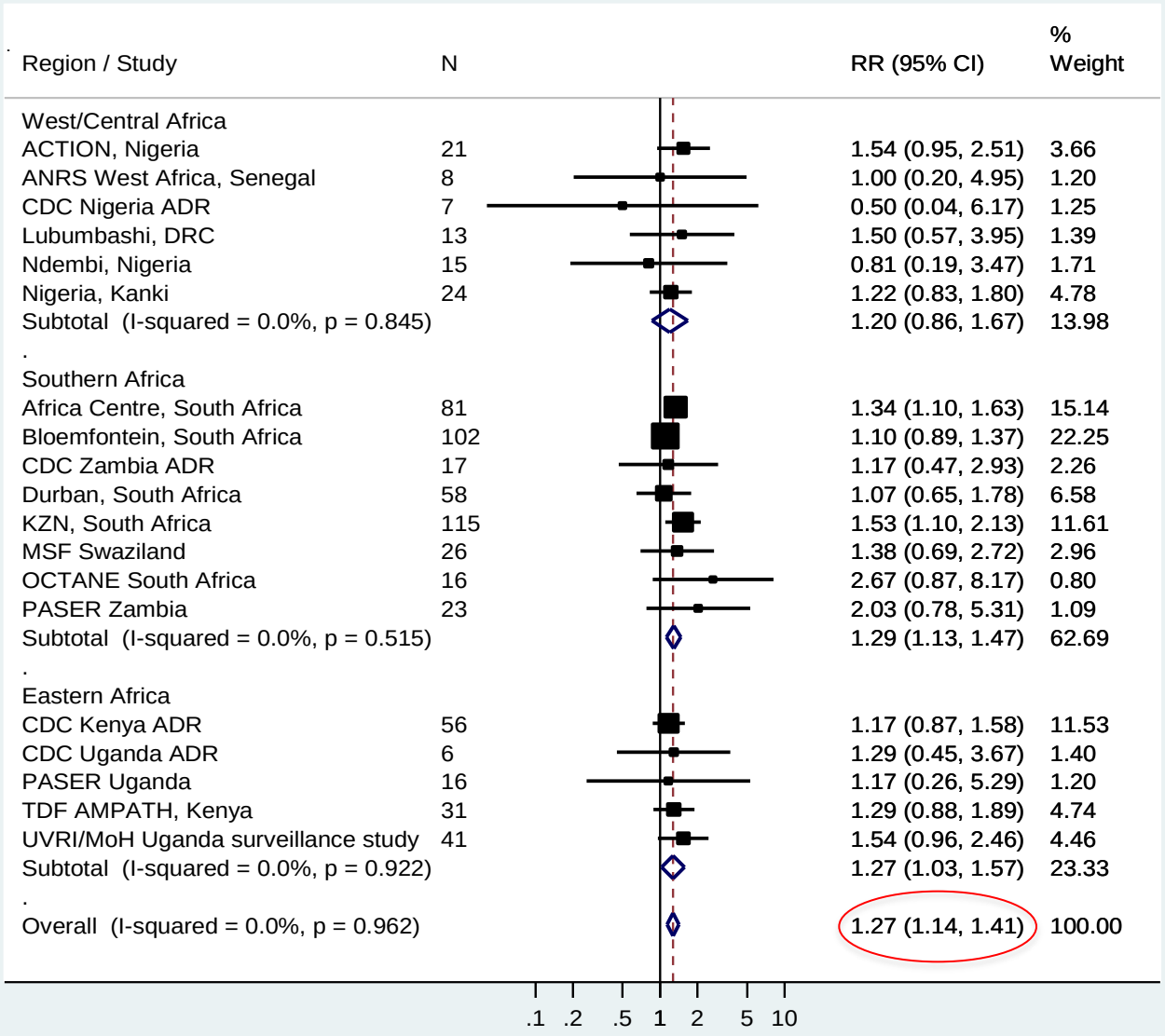
TenoRes Study Group, *Lancet Infect Dis 2016*

Prior thymidine analogue exposure revealed in those with virologic failure of Tenofovir + xTC + NNRTI

	No. with ≥ 1 TAM	Lamivudine resistance (M184V/I)	Tenofovir resistance (K65R/N, K70E/G/Q)	Major NNRTI resistance (Multiple)
Eastern Africa	27	26 (96%)	22 (81%)	16 (59%)
Southern Africa	75	62 (83%)	61 (81%)	57 (76%)
West/Central Africa	14	14 (100%)	11 (79%)	14 (100%)

unpublished

K65R/N or K70E/Q/G are more common in patients with TAMs



unpublished

Prior ART with thymidine analogue based regimens is associated with more extensive drug resistance following virologic failure of Tenofovir + xTC + NNRTI

	No. with ≥ 1 TAM	Lamivudine resistance (M184V/I)	Tenofovir resistance (K65R/N, K70E/G/Q)	Major NNRTI resistance (Multiple)
Eastern Africa	27	26 (96%)	22 (81%)	16 (59%)
Southern Africa	75	62 (83%)	61 (81%)	57 (76%)
West/Central Africa	14	14 (100%)	11 (79%)	14 (100%)

	No. without TAMs	Lamivudine resistance (M184V/I)	Tenofovir resistance (K65R/N, K70E/G/Q)	Major NNRTI resistance (Multiple)
Eastern Africa	143	61%	57%	42%
Southern Africa	404	59%	56%	59%
West/Central Africa	107	71%	60%	82%

unpublished

Conclusions I

- Wide variation in prevalence of TDF resistance
- Presence of K65R/N or K70E/Q/G associated with extensive resistance
- Immune status predicts risk of TDF resistance
- NVP (and 3TC) use associated with higher risk of TDF resistance

Conclusions II

- In vivo fitness is independent of tenofovir resistance

- TAMs indicate suboptimal prior ART exposure and are associated with higher likelihood of tenofovir resistance.

- Viral load monitoring should be used before substitution of TDF for thymidine analogues and during ‘first line’ cART.

The TenoRes study team

Gregson J, PhD; Tang M, MD; Ndembi N, PhD; Hamers RL, MD PhD; Rhee SY, MD; Marconi VC, MD; Diero L, MD; Brooks K, MD[9]; Theys K, PhD; Rinke de Wit TF, MD PhD[4]; Arruda M, Garcia F, MD, Monge S, PhD, Günthard HF, MD, PhD; Hoffmann CJ, MD; Kanki P, MD; Kumarasamy N, MD; Kerschberger B, Mor O, Charpentier C, PhD, Todesco E, PhD ; Rokx C, MD, PhD; Gras L, PhD; Halvas EK, PhD; Sunpath H, MD; Di Carlo D, Antinori A, Andreoni M, Latini A, Mussini C, Aghokeng A, PhD; Sonnerborg A, MD, PhD; Neogi U, PhD; Fessels WJ, Agolory S, Yang C, PhD; Blanco JL, MD, PhD; Juma JMc, Smit E, Schmidt D, Lameck D, Watera C, Asio J, Kirungi W, Tostevin A, PhD; PhD El-Hay T, Clumeck N MD, PhD; PhD Goedhals D, MD; van Vuuren C, MD; Bester A, MD; Sabin C, PhD; Mukui I, MD; Santoro MM, PhD; Perno CF, MD, PhD; Hunt G, PhD; Morris L, MD PhD; Camacho R, PhD; de Oliveira T, PhD; Pillay D, MD PhD; Dunn D PhD, Kaleebu P, PhD; Raizes E, MD; Kantor R MD PhD; Shafer RW, PhD; Gupta RK, MD PhD

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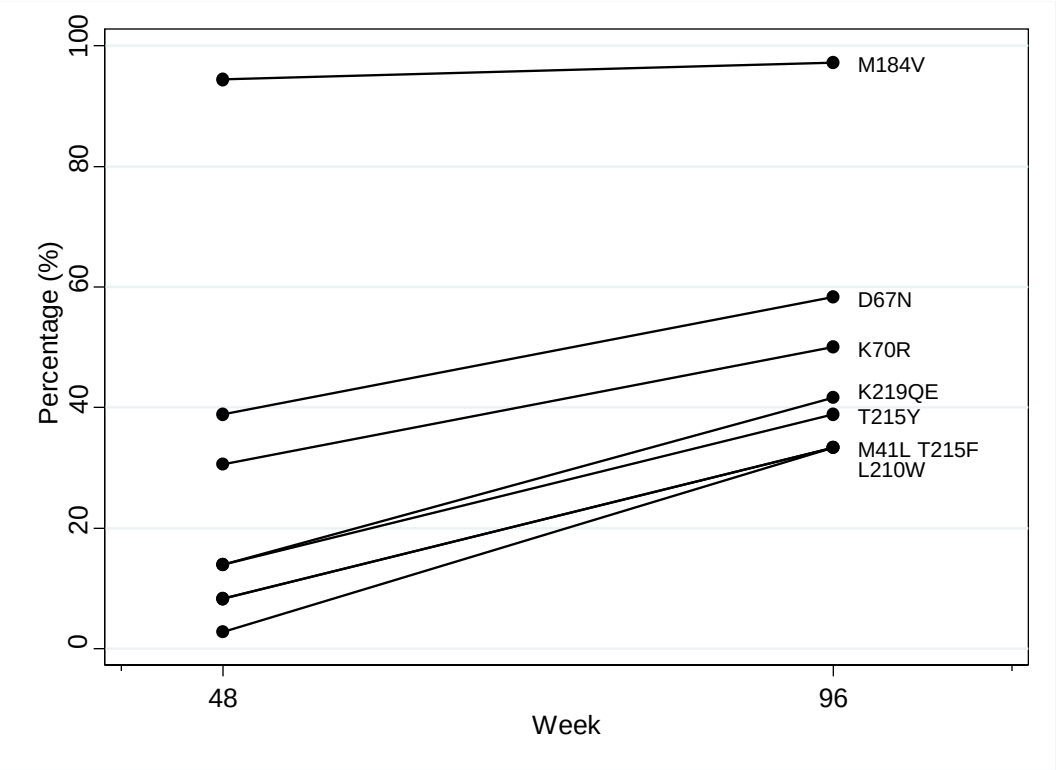
Thank you!

Statistical notes

DerSimonian-Laird weighting and estimates of heterogeneity taken from Mantel-Haenszel model

TAMs accumulate at 1.5 per year following initiation of AZT+3TC+NVP



DART-NORA: Prevalence of Thymidine analogue mutations and M184V in patients with paired genotypes (n=36) at week 48 and 96

DART Virology Group, in preparation