# HIV Drug resistance- implications for therapy

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UCL

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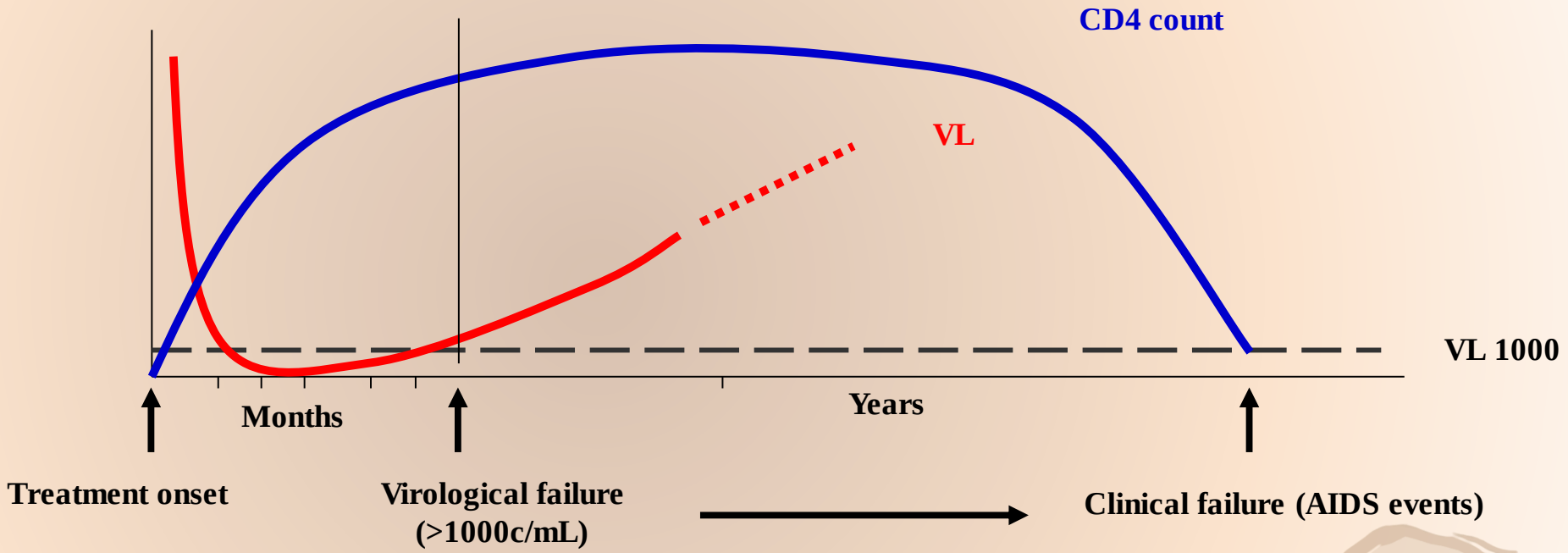
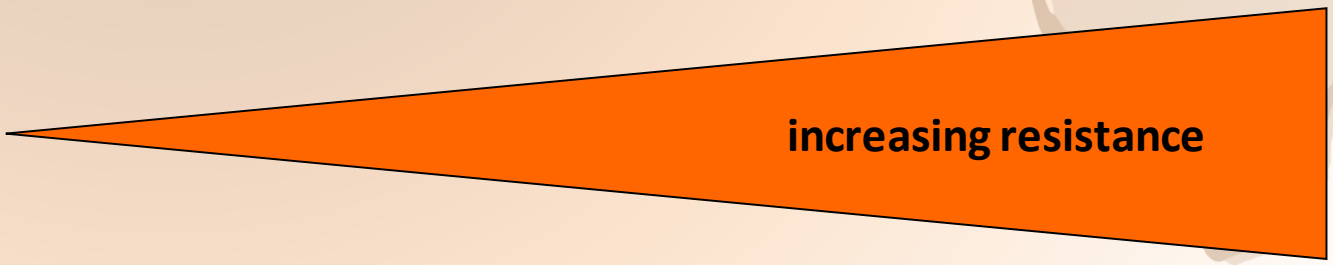
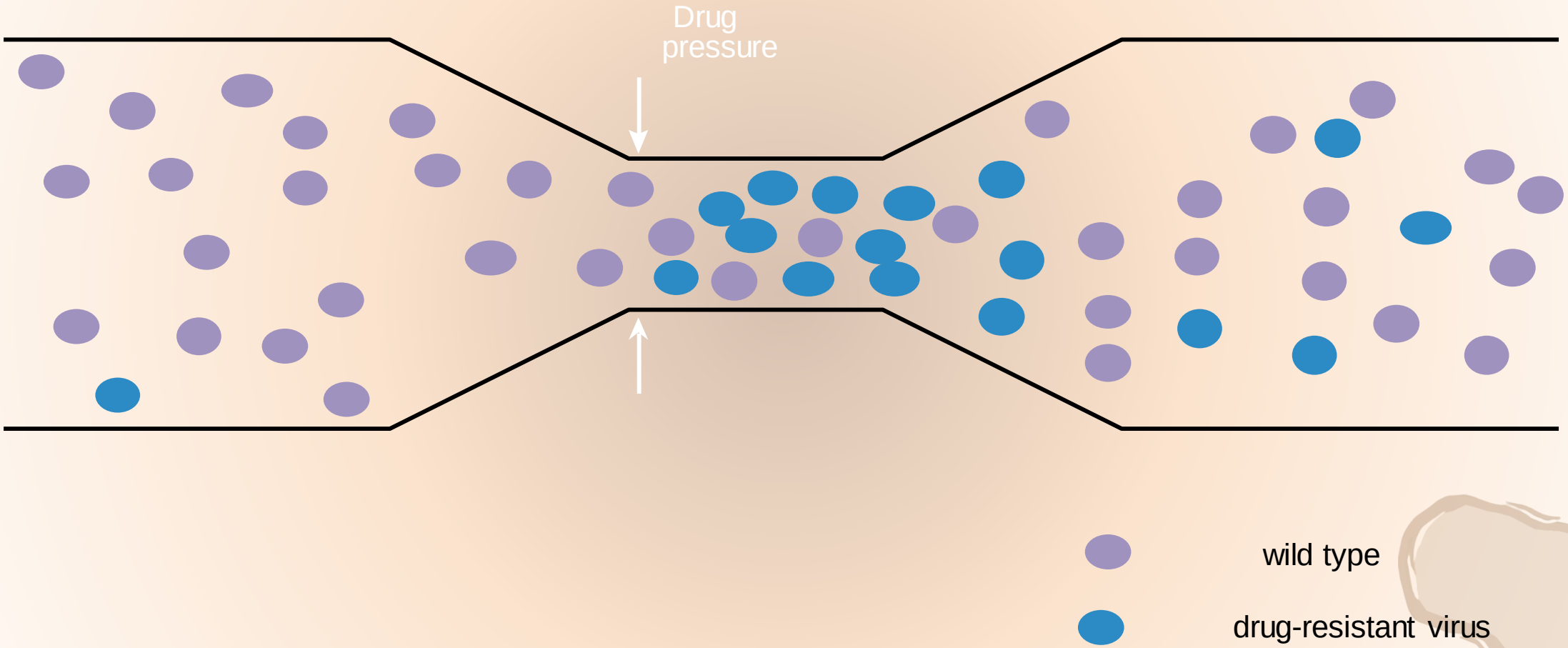
# Potential implications of HAART without virological monitoring: Therapy failure?



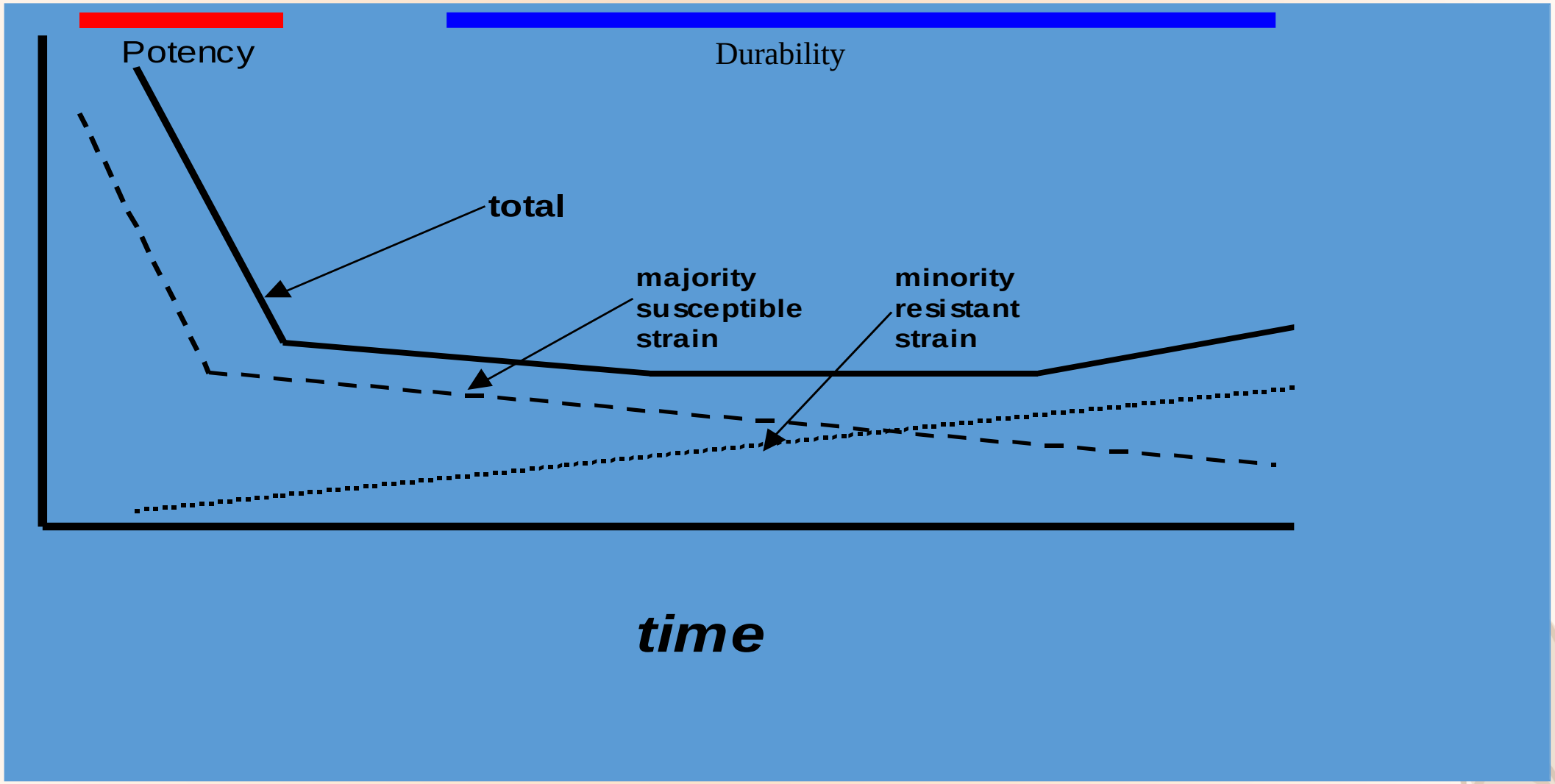



# All viruses are archived and can re-emerge




***Resistance testing only detects the majority virus population in plasma***

# IMPACT OF VIRAL VARIATION/QUASISPECIES

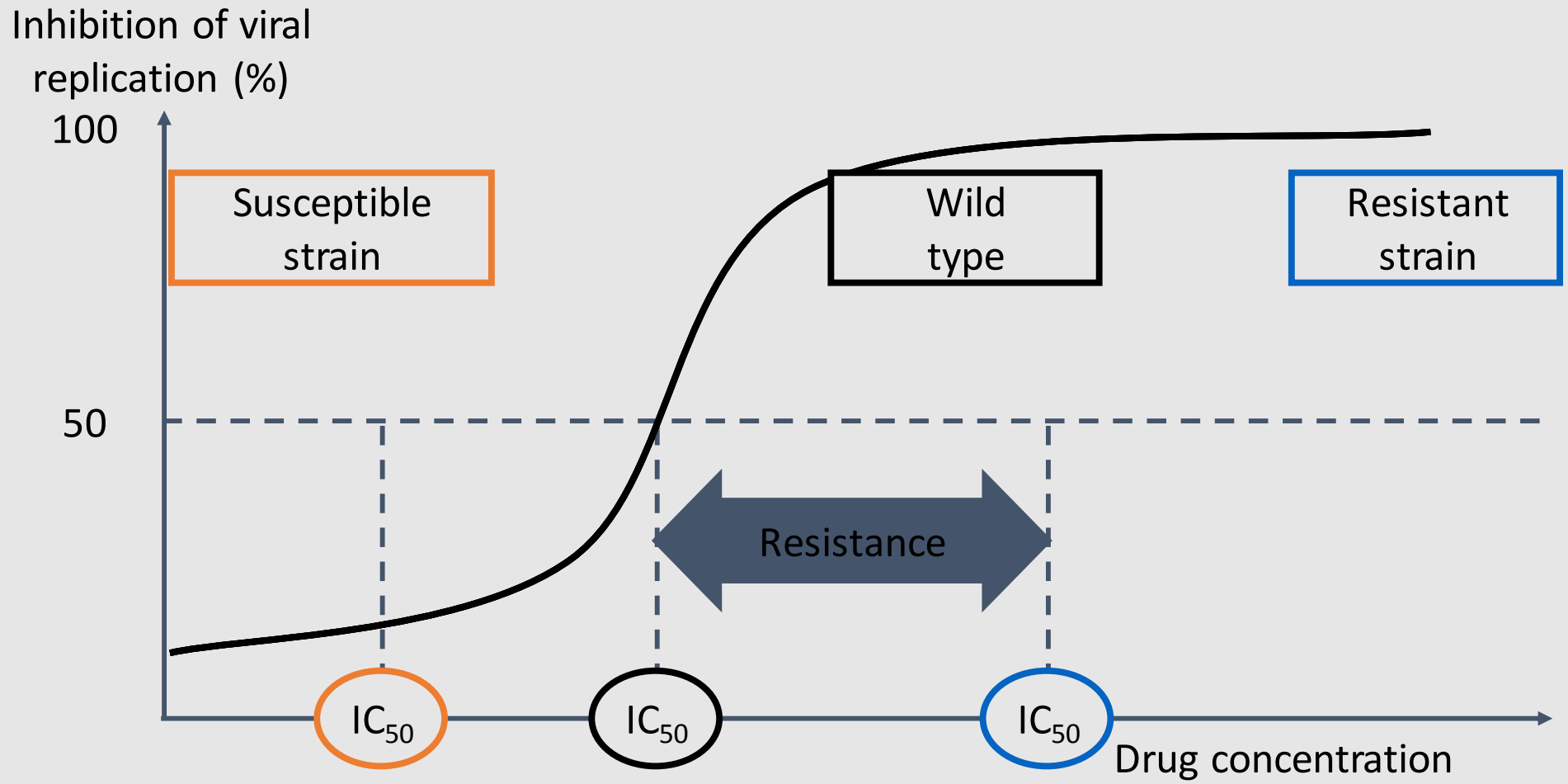



***-FIRST PHASE VIRAL DECLINE AS AN "IN VIVO" PHENOTYPE***

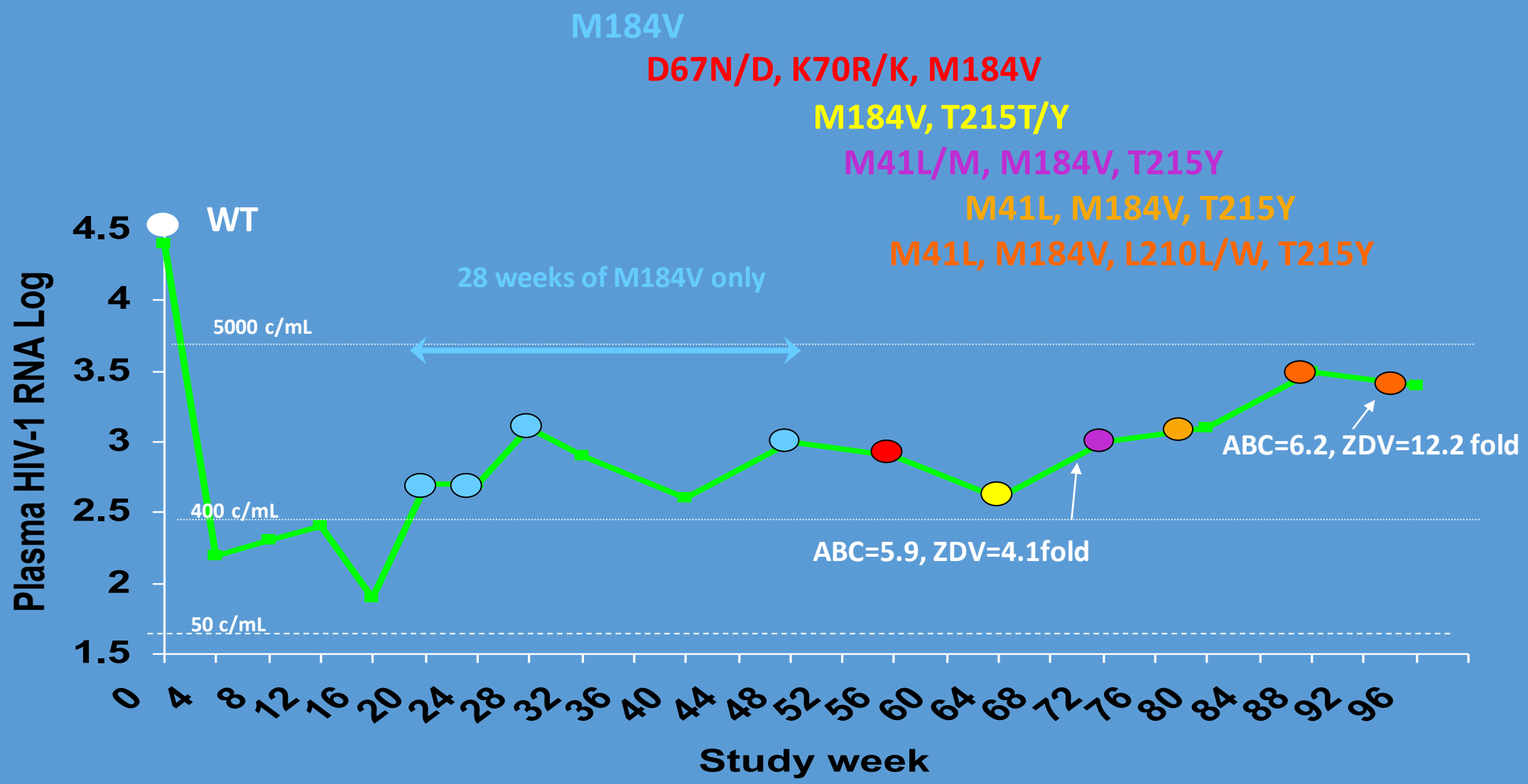
# HOW TO DEFINE RESISTANCE?

- Genotype- mutations, collections of mutations
- In vitro phenotype – fold resistance, gene of choice
- Clinical response- complexity of multiple drugs

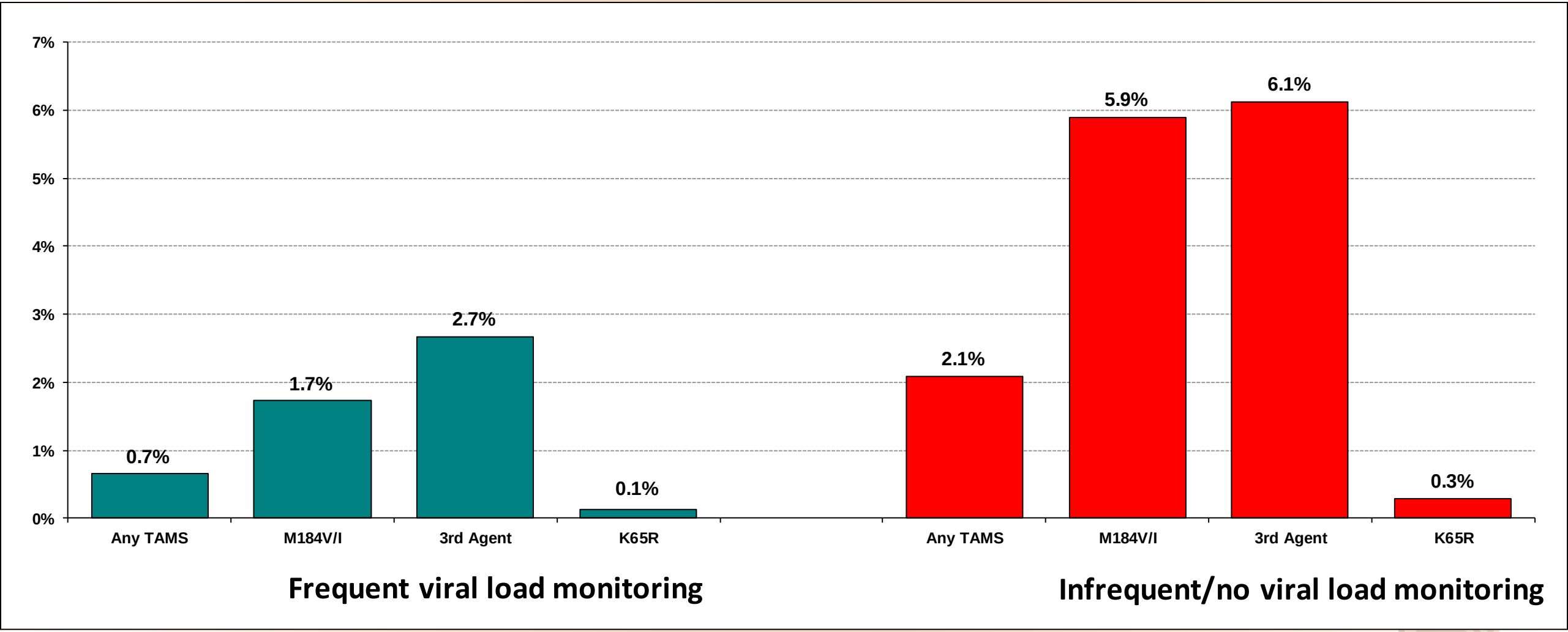
# Phenotyping



# ZDV/3TC/ABC: Example of Slow Stepwise Appearance of Mutations in Subjects With Virologic Failure

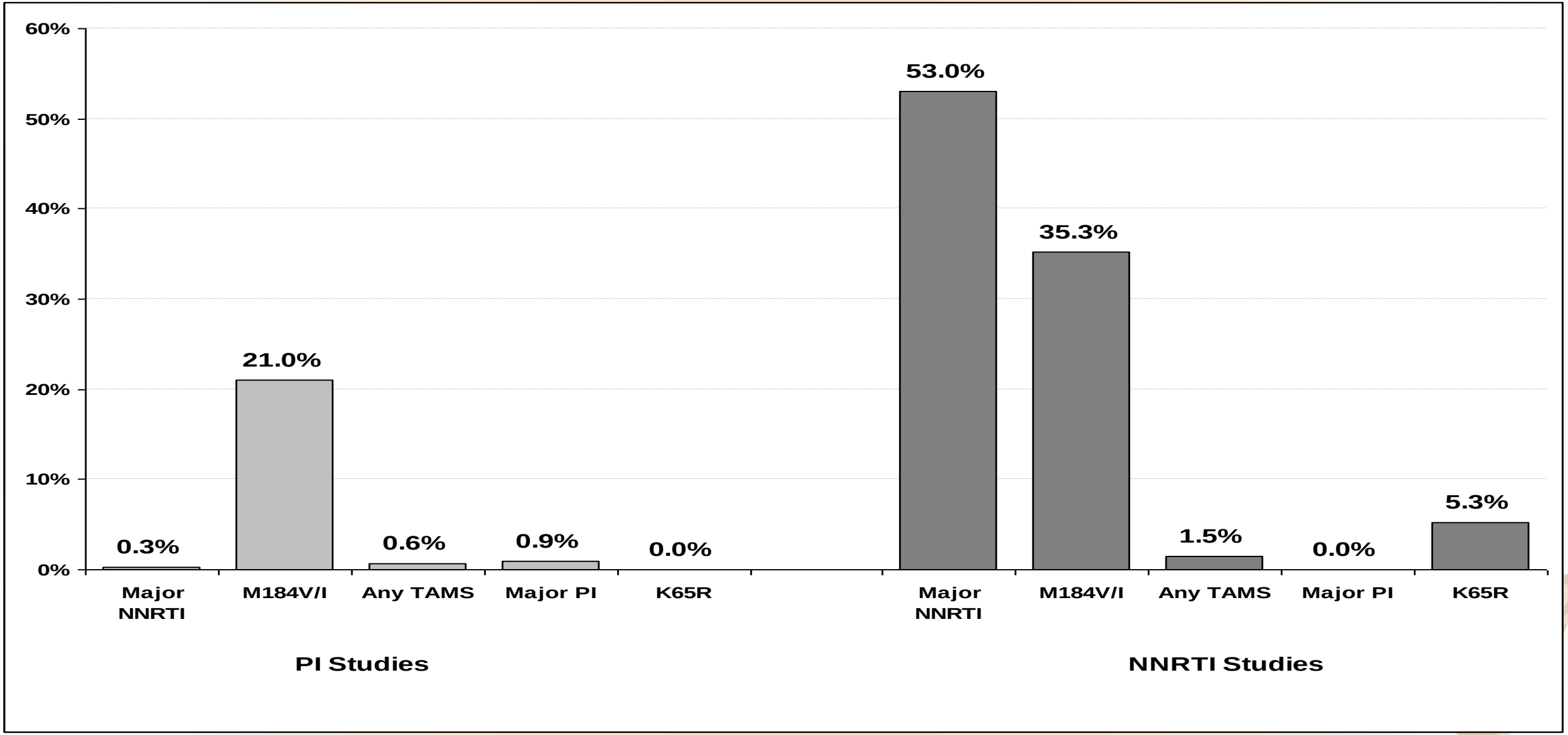


# The intensity of virological monitoring is associated with resistance to 1st line HAART



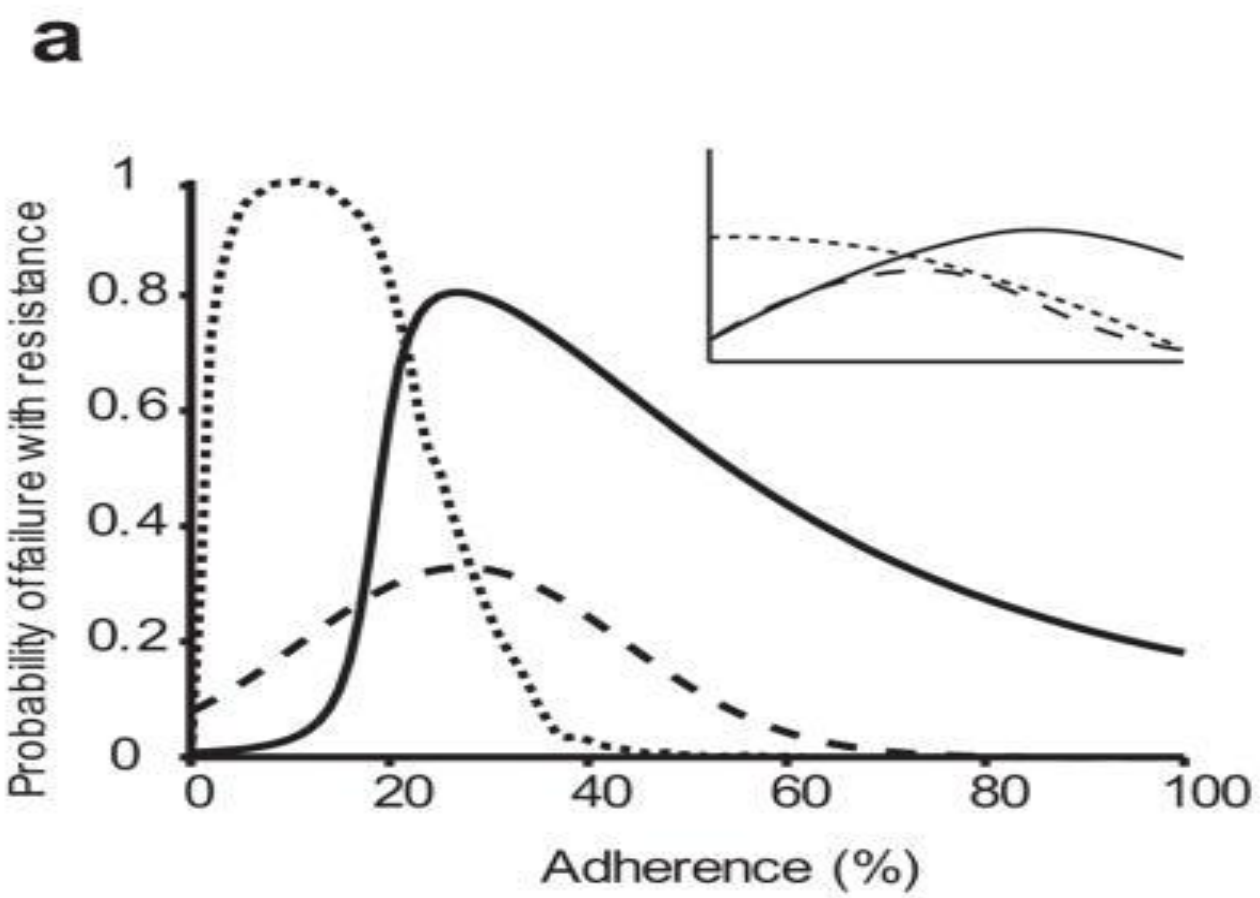

Gupta et al CID 2009

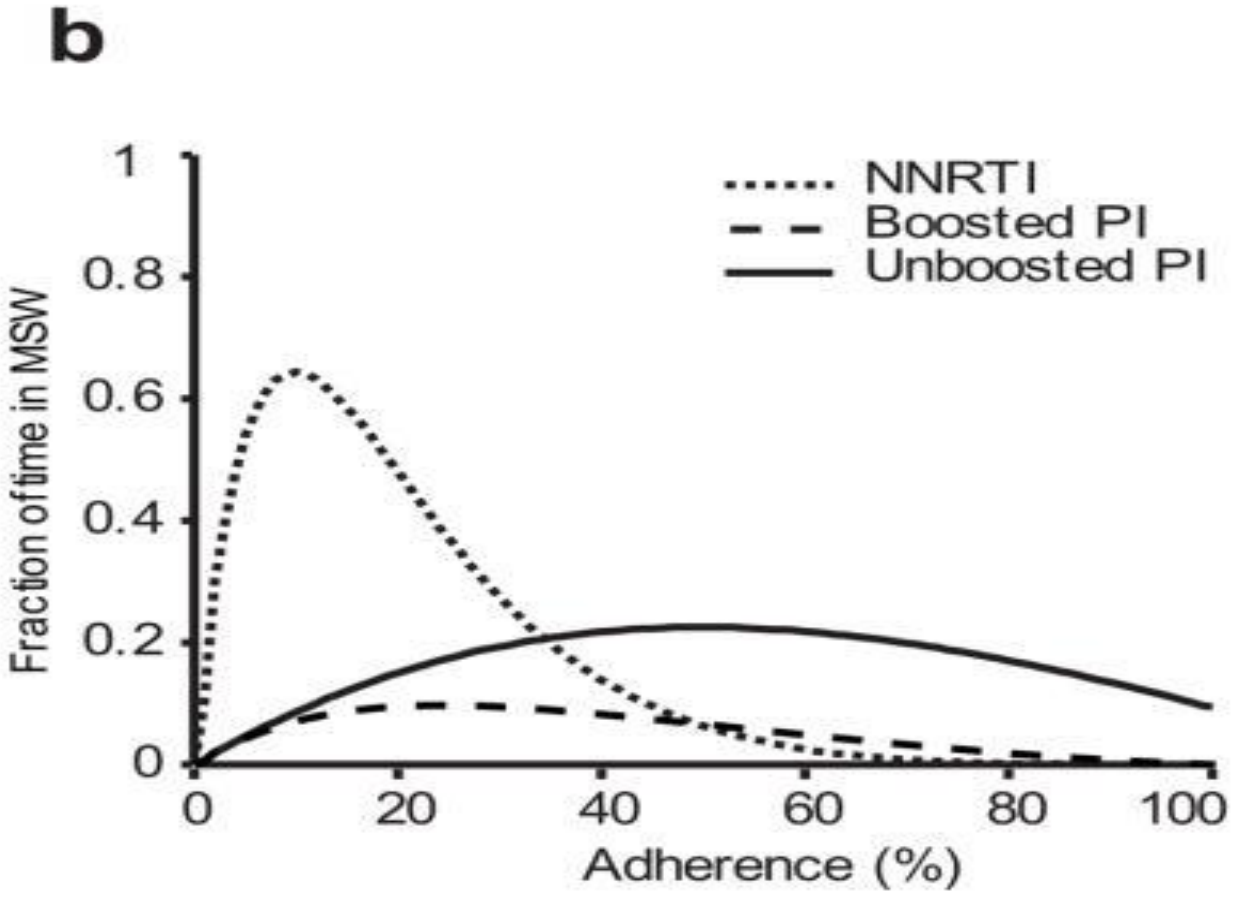
# INCIDENCE OF RESISTANCE IN VIROLOGICAL FAILURES ON 1ST LINE NNRTI- OR bPI-CONTAINING REGIMENS: A META ANALYSIS




Gupta et al, LID 2009

# Antiviral dynamics determines HIV evolution and predicts therapy outcome



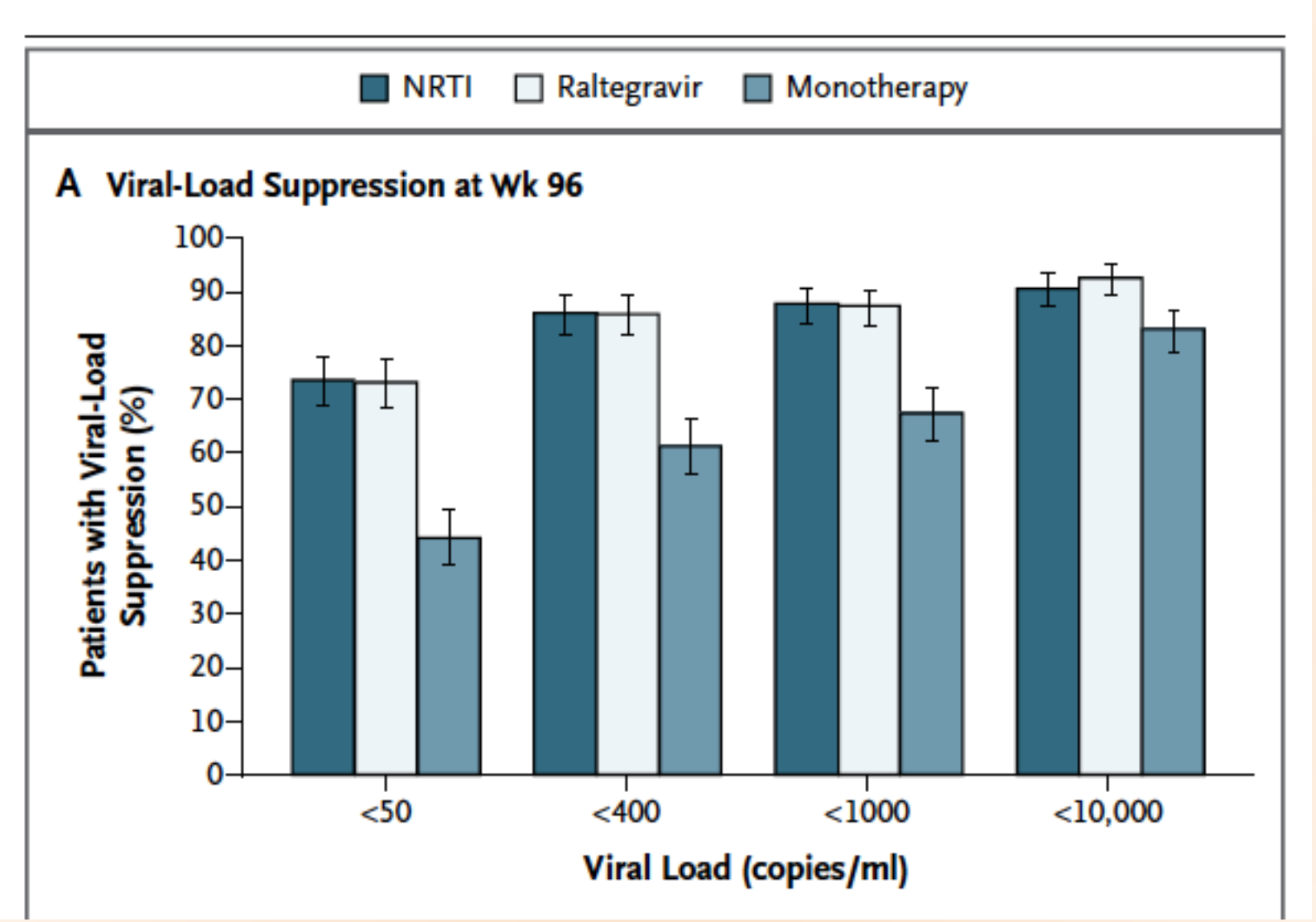




Rosenbloom et al, Nat Med 2012

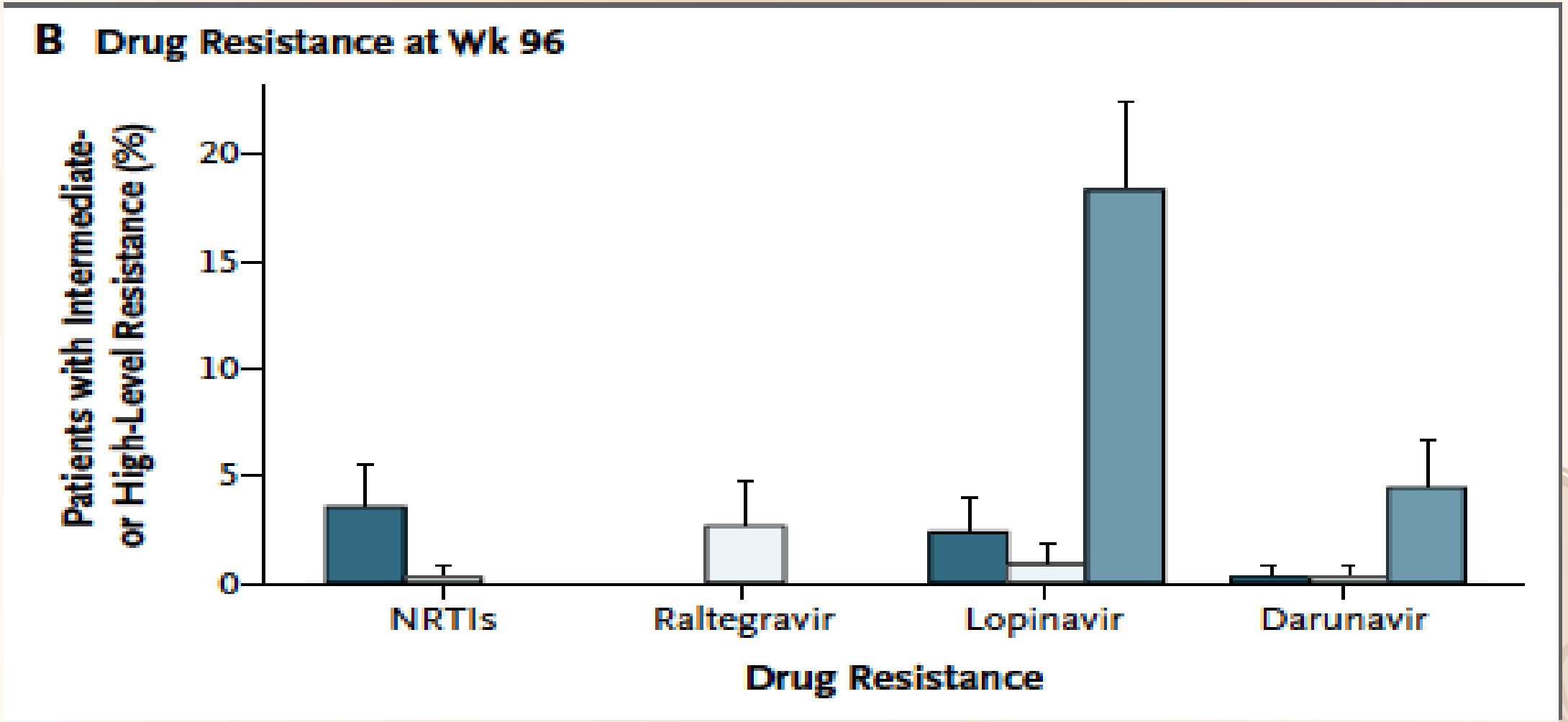
# Assessment of Second-Line Antiretroviral Regimens for HIV Therapy in Africa

Nicholas I. Paton, M.D., Cissy Kityo, M.Sc., Anne Hoppe, Ph.D., Andrew Reid, M.R.C.P., Andrew Kambugu, M.Med., Abbas Lugemwa, M.D., Joep J. van Oosterhout, Ph.D., Mary Kiconco, M.P.H., Abraham Siika, M.Med., Raymond Mwebaze, M.Med., Mary Abwola, M.Med., George Abongomera, M.Sc., Aggrey Mweemba, M.Med., Hillary Alima, M.P.H., Dickens Atwongyeire, M.B., Ch.B., Rose Nyirenda, M.Sc., Justine Boles, M.Sc., Jennifer Thompson, M.Sc., Dinah Tumukunde, M.P.H., Ennie Chidziva, Dipl.G.N., Ivan Mambule, M.B., Ch.B., Jose R. Arribas, M.D., Philippa J. Easterbrook, M.D., James Hakim, F.R.C.P., A. Sarah Walker, Ph.D., and Peter Mugyenyi, F.R.C.P., for the EARNEST Trial Team*

# Virological response



# Emerging resistance

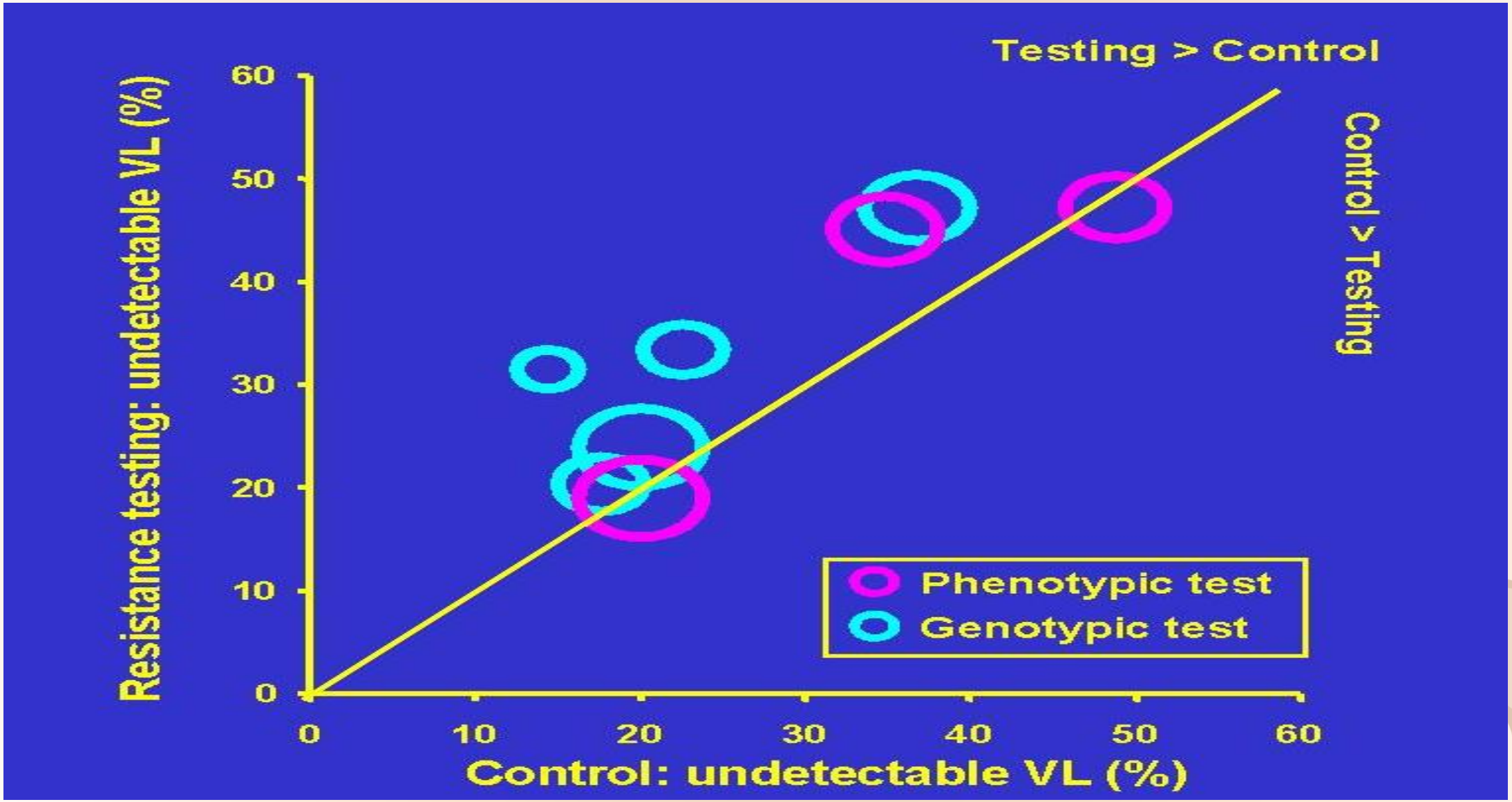


# High rates of re-suppression after virological failure on first line therapy in the absence of routine monitoring: 96 week data from the DART NORA substudy

| | ABC | | | | | NVP | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Week 96 VL (copies/ml) | | | | | Week 96 VL (copies/ml) | | | | |
| Week 48 VL (copies/ml) | <1000 | 1000 - 9,999 | 10,000 - 99,999 | ≥100,000 | Total | <1000 | 1000 - 9,999 | 10,000 - 99,999 | ≥100,000 | Total |
| <1000 | 148 | 16 | 12 | 4 | 180 | 149 | 2 | 5 | 0 | 156 |
| 1000-9,999 | 9 | 7 | 5 | 1 | 22 | 0 | 3 | 1 | 0 | 4 |
| 10,000-99,999 | 1 | 1 | 6 | 6 | 14 | 4 | 1 | 6 | 1 | 12 |
| ≥100,000 | 2 | 0 | 4 | 4 | 10 | 3 | 0 | 2 | 3 | 8 |
| Total | 160 | 24 | 27 | 15 | 226 | 156 | 6 | 14 | 4 | 180 |
| Adjusted total % (95% CI) | 71.1 (65.4-76.1) | 11.6 (7.9-16.7) | 11.5 (8.1-16.1) | 5.8 (3.8-8.9) | | 88.7 (84.6-91.9) | 3.6 (1.6-8.0) | 5.9 (3.8-9.0) | 1.7 (0.8-3.9) | |

Gupta et al Clin Inf Dis 2014

# Evidence on HIV drug resistance testing

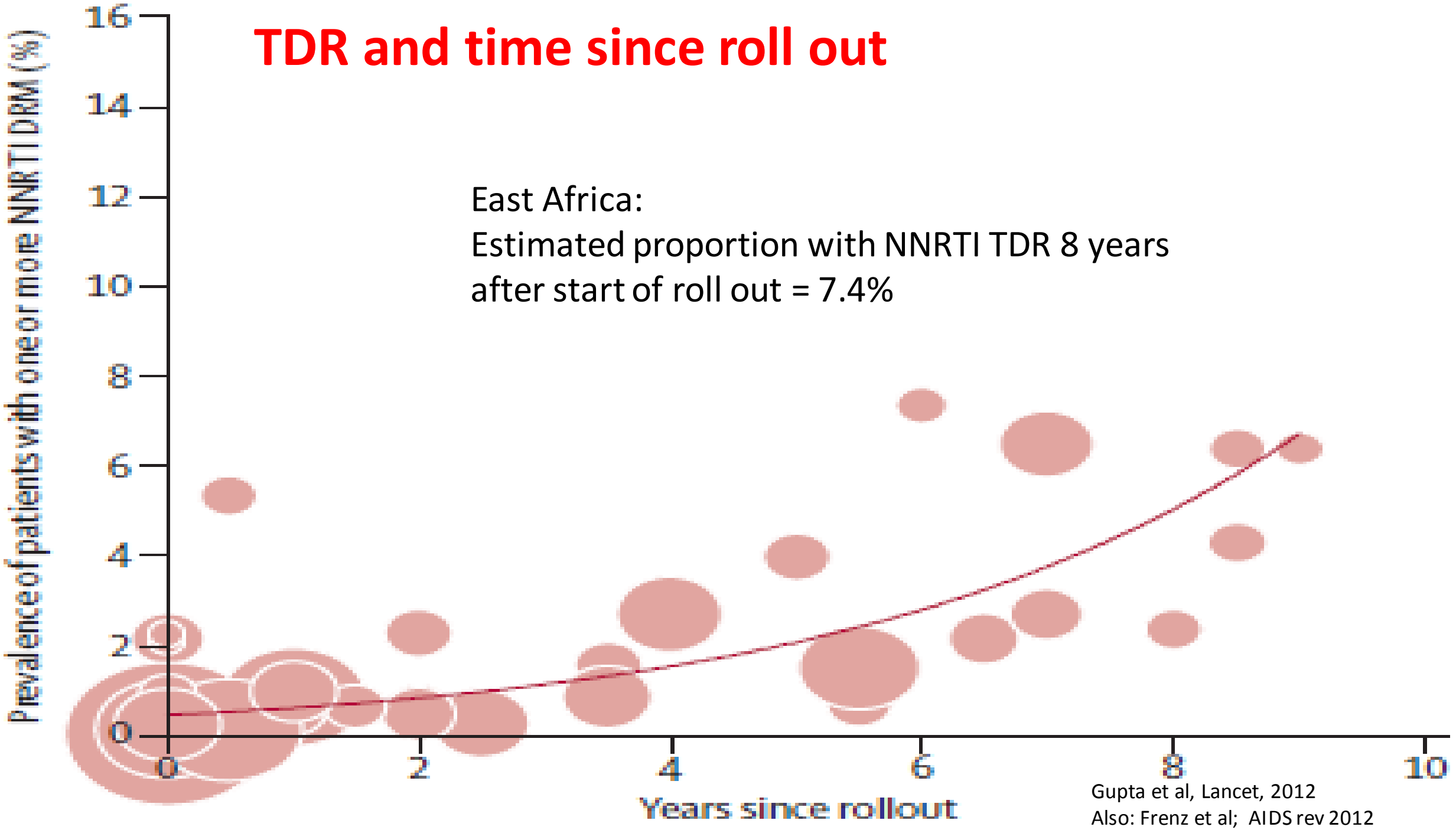



Dunn et a, 2007

# Population impact of drug resistance
# - will spread of HIV drug resistance require change of 1st line therapy?

# TDR and time since roll out

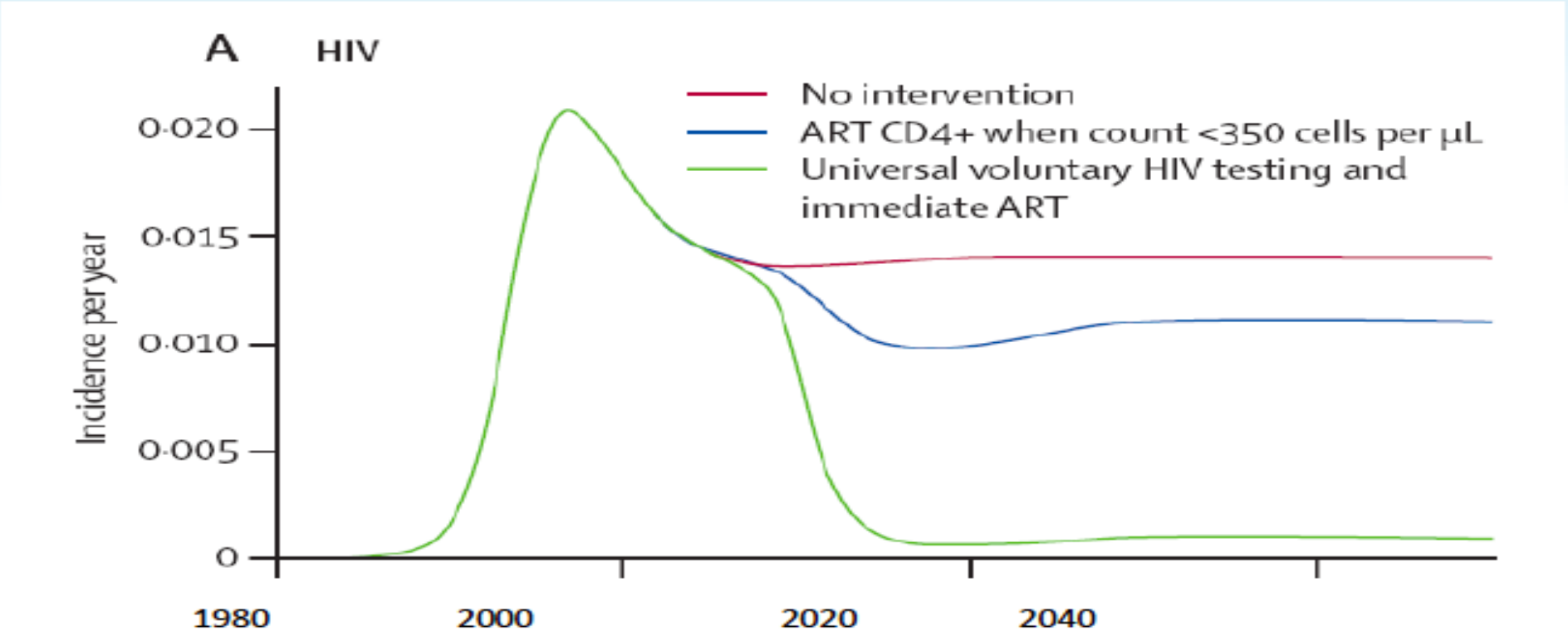
East Africa:
Estimated proportion with NNRTI TDR 8 years after start of roll out = 7.4%




Gupta et al, Lancet, 2012
Also: Frenz et al; AIDS rev 2012

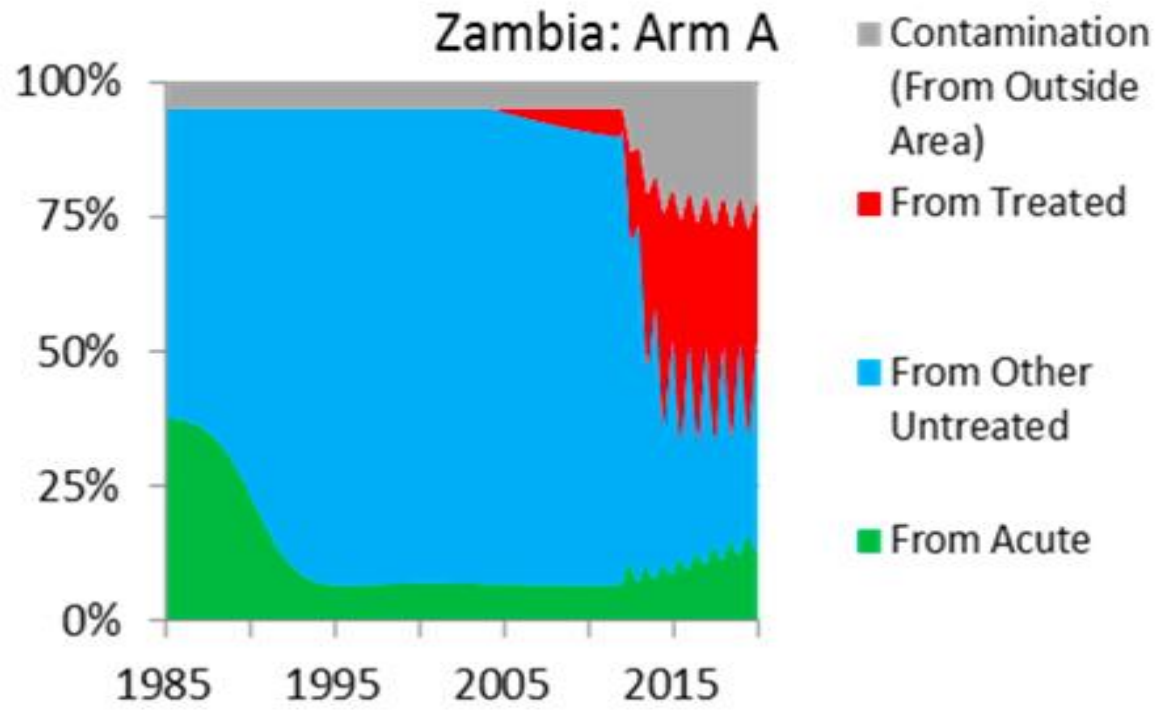
# Models predict a dramatic population effect of HIV Universal test and Treat

Granich et al 2008 Lancet

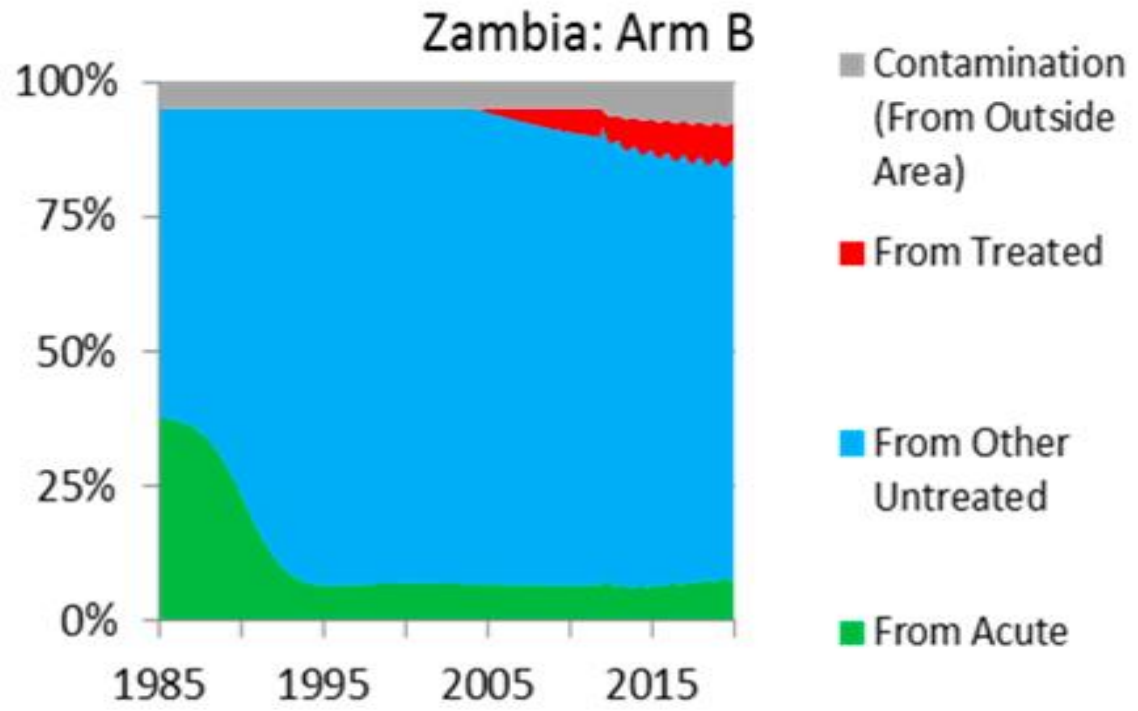


# POPART intervention; modelling outcome

E

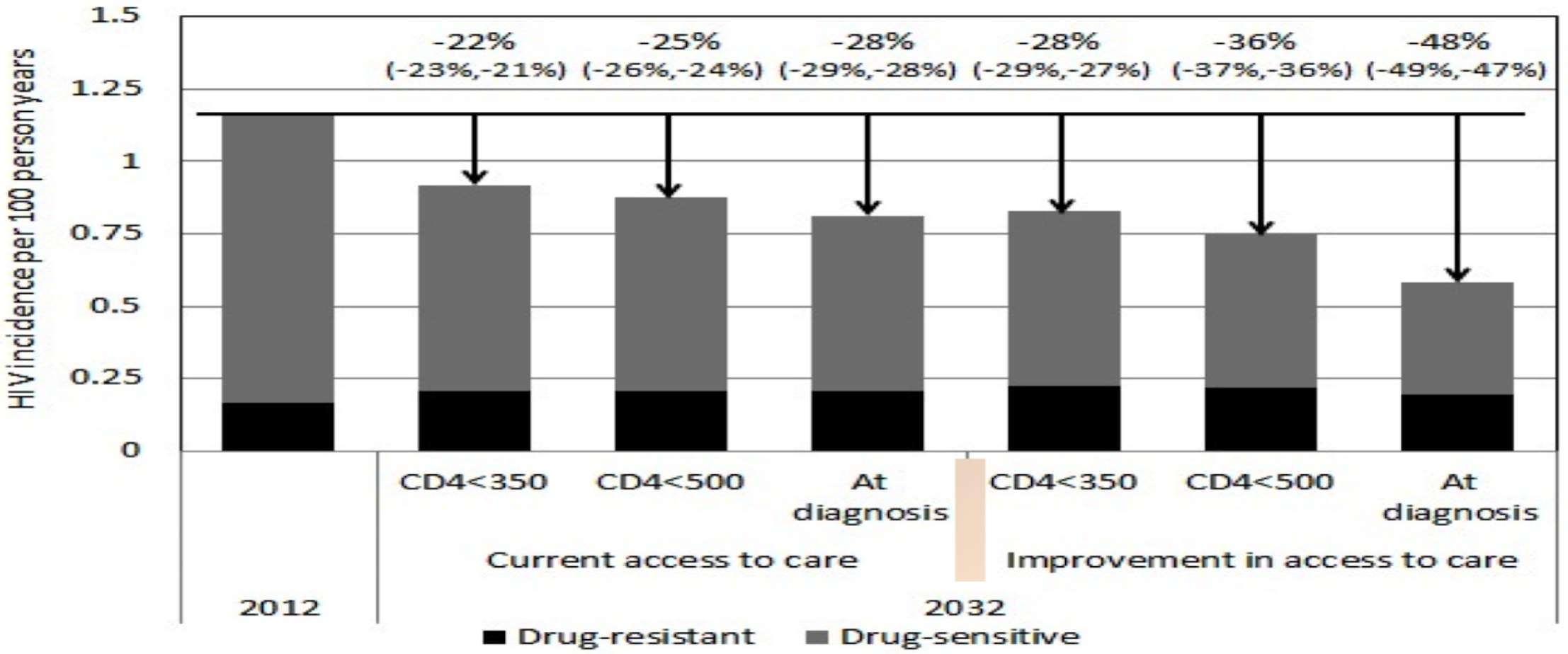



F



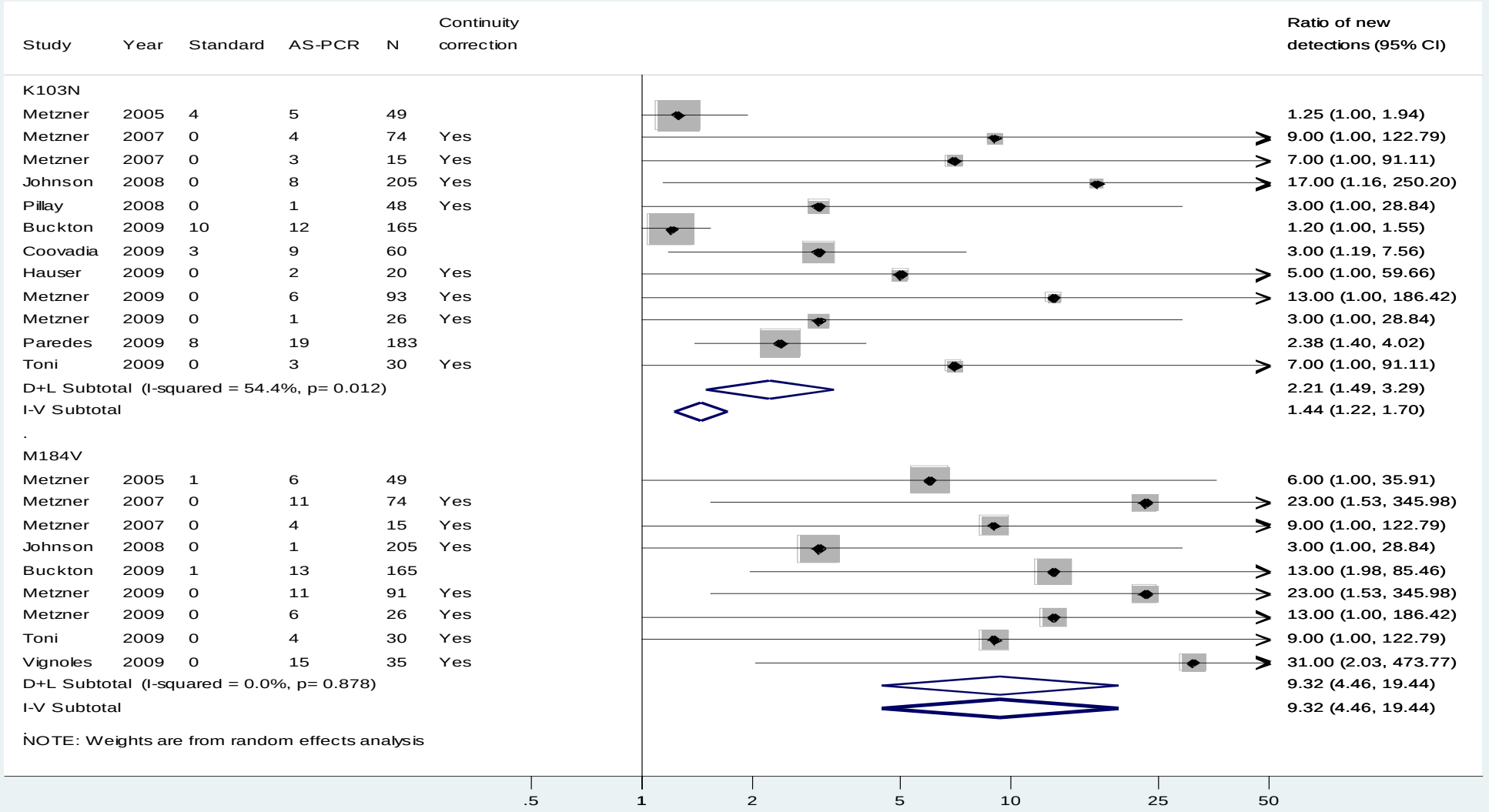

Christophe Fraser

# Will ART expansion in SA lead to a relative increase in HIV drug resistance?




Cambiano, Bertagnolio, Jordon, Pillay, Perriens,Ventner, Lungren, Phillips**. AIDS,** 2014

# Meta-analysis demonstrates importance of M184V minority assays



| Study | Year | Standard | AS-PCR | N | Continuity correction | Ratio of new detections (95% CI) |
|---|---|---|---|---|---|---|
| K103N | | | | | | |
| Metzner | 2005 | 4 | 5 | 49 | | 1.25 (1.00, 1.94) |
| Metzner | 2007 | 0 | 4 | 74 | Yes | 9.00 (1.00, 122.79) |
| Metzner | 2007 | 0 | 3 | 15 | Yes | 7.00 (1.00, 91.11) |
| Johnson | 2008 | 0 | 8 | 205 | Yes | 17.00 (1.16, 250.20) |
| Pillay | 2008 | 0 | 1 | 48 | Yes | 3.00 (1.00, 28.84) |
| Buckton | 2009 | 10 | 12 | 165 | | 1.20 (1.00, 1.55) |
| Coovadia | 2009 | 3 | 9 | 60 | | 3.00 (1.19, 7.56) |
| Hauser | 2009 | 0 | 2 | 20 | Yes | 5.00 (1.00, 59.66) |
| Metzner | 2009 | 0 | 6 | 93 | Yes | 13.00 (1.00, 186.42) |
| Metzner | 2009 | 0 | 1 | 26 | Yes | 3.00 (1.00, 28.84) |
| Paredes | 2009 | 8 | 19 | 183 | | 2.38 (1.40, 4.02) |
| Toni | 2009 | 0 | 3 | 30 | Yes | 7.00 (1.00, 91.11) |
| D+L Subtotal (I-squared = 54.4%, p= 0.012) | | | | | | 2.21 (1.49, 3.29) |
| I-V Subtotal | | | | | | 1.44 (1.22, 1.70) |
| M184V | | | | | | |
| Metzner | 2005 | 1 | 6 | 49 | | 6.00 (1.00, 35.91) |
| Metzner | 2007 | 0 | 11 | 74 | Yes | 23.00 (1.53, 345.98) |
| Metzner | 2007 | 0 | 4 | 15 | Yes | 9.00 (1.00, 122.79) |
| Johnson | 2008 | 0 | 1 | 205 | Yes | 3.00 (1.00, 28.84) |
| Buckton | 2009 | 1 | 13 | 165 | | 13.00 (1.98, 85.46) |
| Metzner | 2009 | 0 | 11 | 91 | Yes | 23.00 (1.53, 345.98) |
| Metzner | 2009 | 0 | 6 | 26 | Yes | 13.00 (1.00, 186.42) |
| Toni | 2009 | 0 | 4 | 30 | Yes | 9.00 (1.00, 122.79) |
| Vignoles | 2009 | 0 | 15 | 35 | Yes | 31.00 (2.03, 473.77) |
| D+L Subtotal (I-squared = 0.0%, p= 0.878) | | | | | | 9.32 (4.46, 19.44) |
| I-V Subtotal | | | | | | 9.32 (4.46, 19.44) |

NOTE: Weights are from random effects analysis

.5 1 2 5 10 25 50

K103N

M184V

# Objective

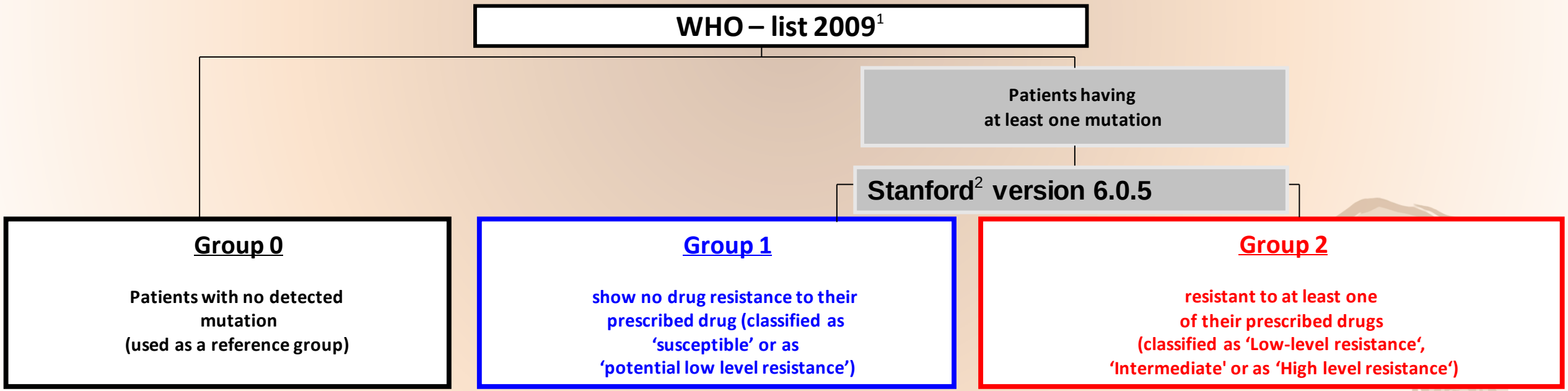
- To assess the impact of transmitted drug resistance mutations on virological and immunological response up to 16 months after starting a combination antiretroviral therapy (cART)
- Specific analyses:
  - Transmitted drug resistance and fully active treatment
  - 2NRTI + 1NNRTI or 2NRTI + 1boosted PI regimen

# Study population

- HIV infected patients regardless of age
- Start of cART after 1.1.1998
- ≥1 sample taken before antiretroviral treatment for genotypic testing

# Methods

- Virologic endpoint:
  - time to first of two consecutive viral load>500 copies/mL after six months of therapy
- Definition TDR (two steps):






[1]Bennett PlosOne 2009, [2]Liu CID 2006

# Characteristics at the time of starting cART

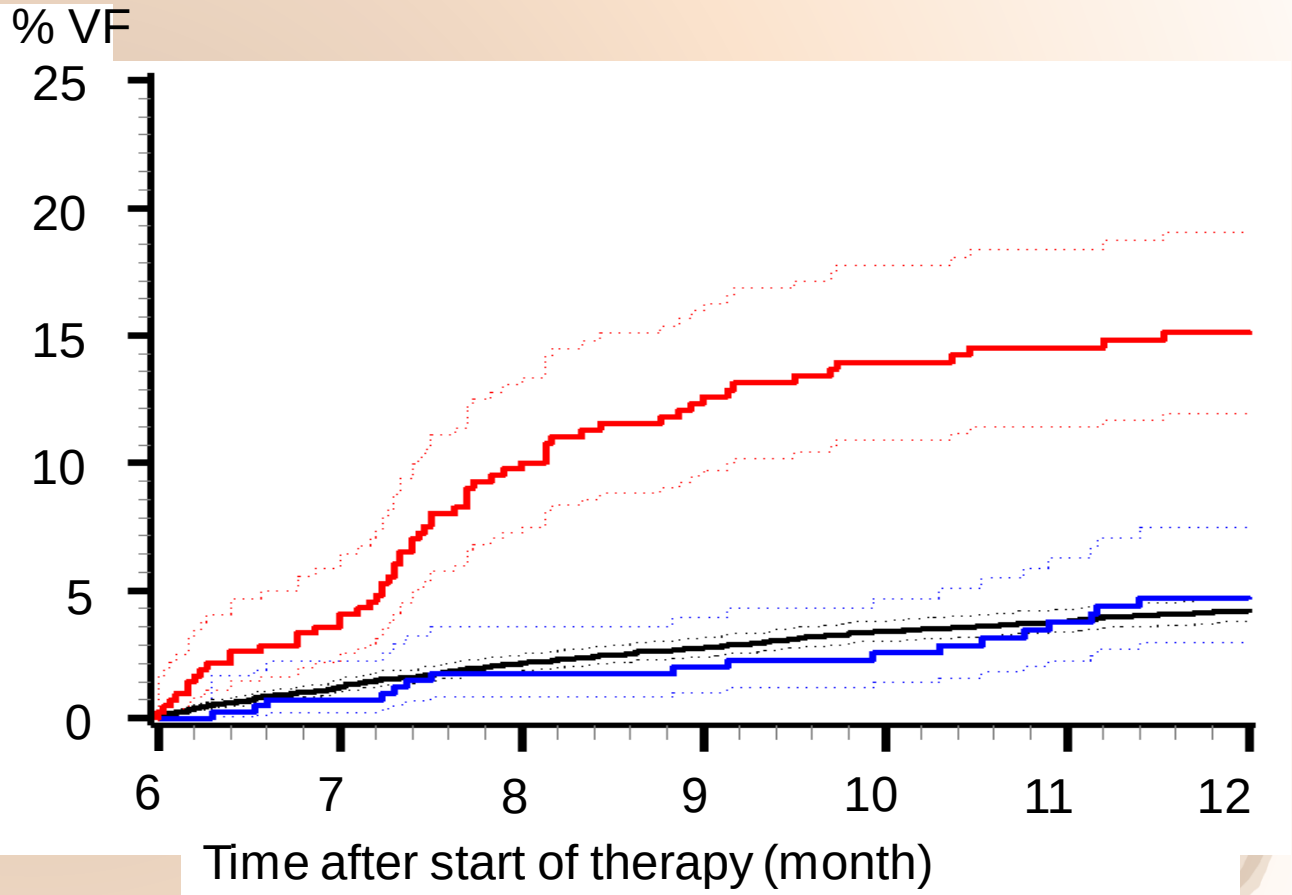
- 10,056 patients from 25 cohorts
  - 76% male
  - Median age 38 years
  - 56% of European origin
  - 69% harboured a subtype B virus
  - Pre-treatment viral load and CD4 counts were 5 log10 cp/mL and 218 cells/μL
  - Transmission risk groups: 50% homosexual, 32% heterosexual, 8% IDUs and 2.1% perinatal
- 9.5% (n=954) patients harboured a virus with ≥1 mutation
  - 49.8% (n=475) received a fully active treatment
  - 50.2% (n=479) harboured a virus predicted to have at least low level resistance for ≥1 prescribed drug

# Virological failure according to TDR

In adjusted analysis*:

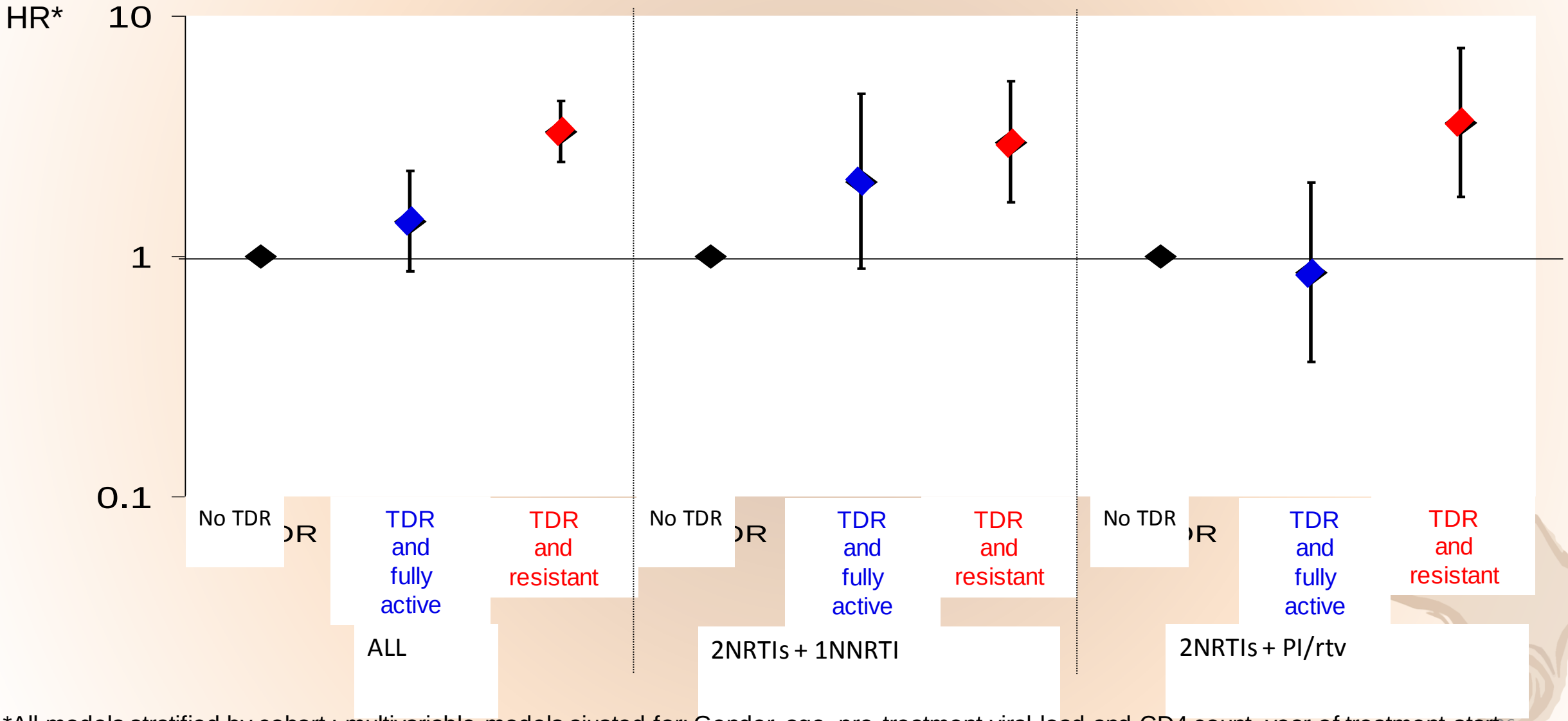
- Patients with resistance to ≥1 drug:
  - significant higher risk of VF compared to patients without mutations
  - HR: 3.3 (2.5; 4.4) $P<10^{-4}$

- patients receiving a fully active cART and patients with mutation:
  - risk of VF was not significantly different
  - HR: 1.4 (0.9; 2.3) $P=0.17$




*All models stratified by cohort ; multivariable models ajusted for: Gender, age, pre-treatment viral load and CD4 count, year of treatment start, previous AIDS diagnosis, subtype, HIV transmission risk group, origin

# Impact of TDR according to treatment strata




*All models stratified by cohort ; multivariable models ajusted for: Gender, age, pre-treatment viral load and CD4 count, year of treatment start, previous AIDS diagnosis, subtype, HIV transmission risk group, origin

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: Efficacy and Tolerability of 3 Nonnucleoside Reverse Transcriptase Inhibitor–Sparing Antiretroviral Regimens for Treatment-Naive Volunteers Infected With HIV-1: A Randomized, Controlled Equivalence TrialNNRTI-Sparing Antiretroviral Regimens for Treatment-Naive Volunteers Infected With HIV-1

Ann Intern Med. 2014;161(7):461-471. doi:10.7326/M14-1084

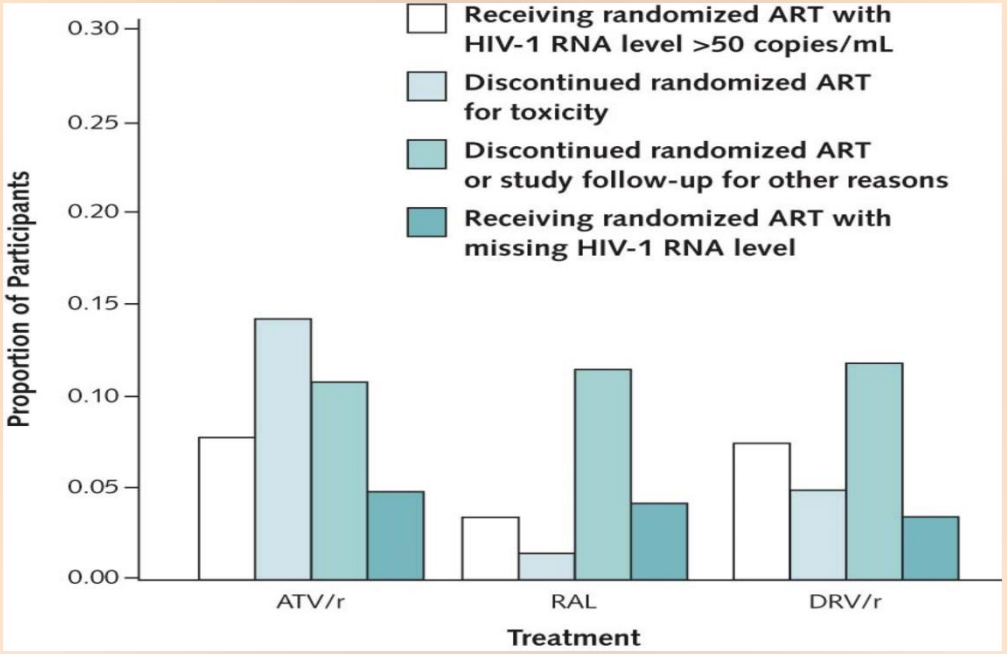



**Figure Legend:**

**Outcomes at week 96, according to the FDA snapshot definition.**

**ART = antiretroviral therapy; ATV/r = atazanavir plus ritonavir; DRV/r = darunavir plus ritonavir; FDA = U.S. Food and Drug Administration; RAL = raltegravir.**

# Conclusion

- Differential resistance on 1st line therapy
- Impact of resistance is a function of therapeutic availability
- increase transmission of resistance likely with extended roll out