HIV replication: principles and prevention

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Johannesburg

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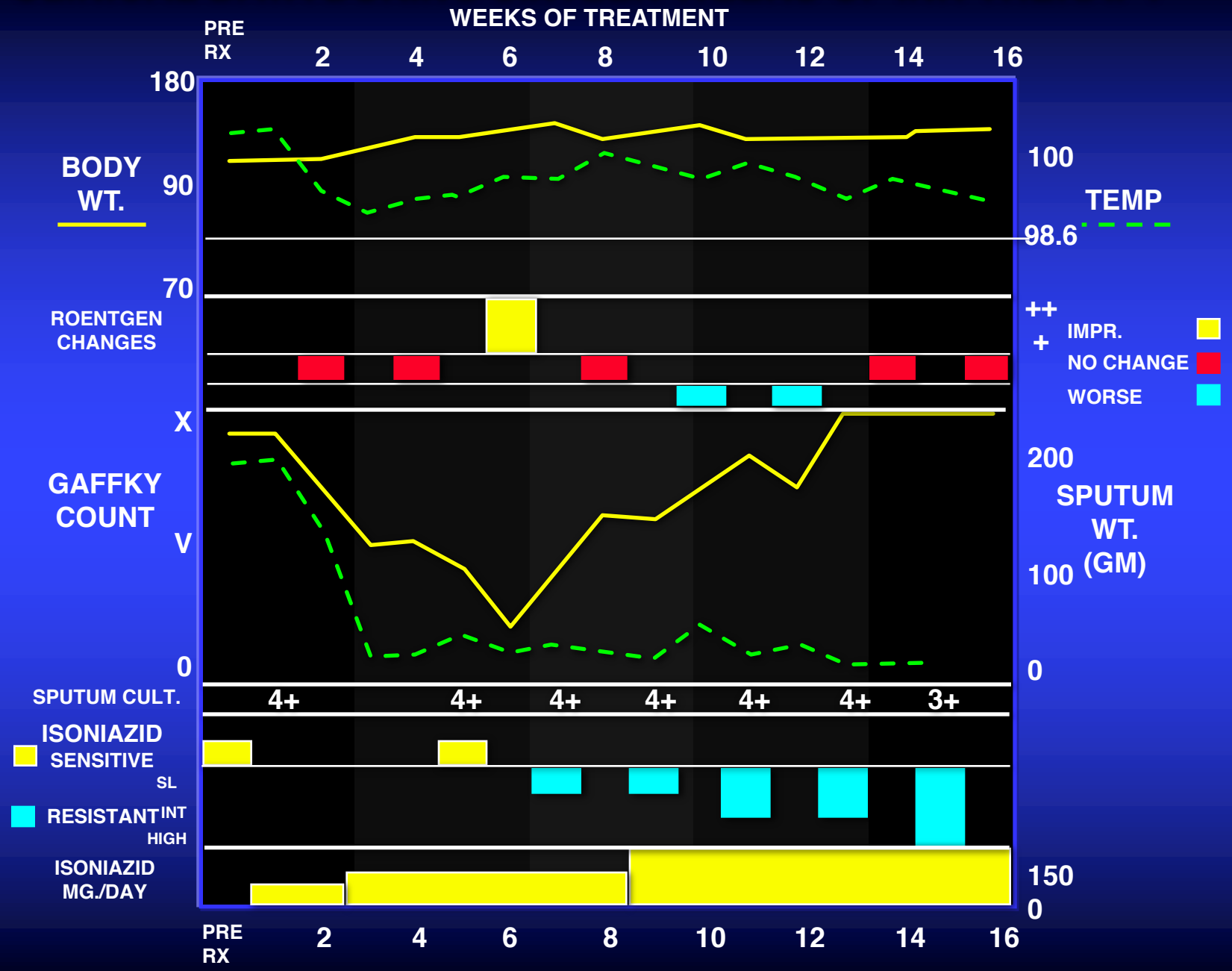
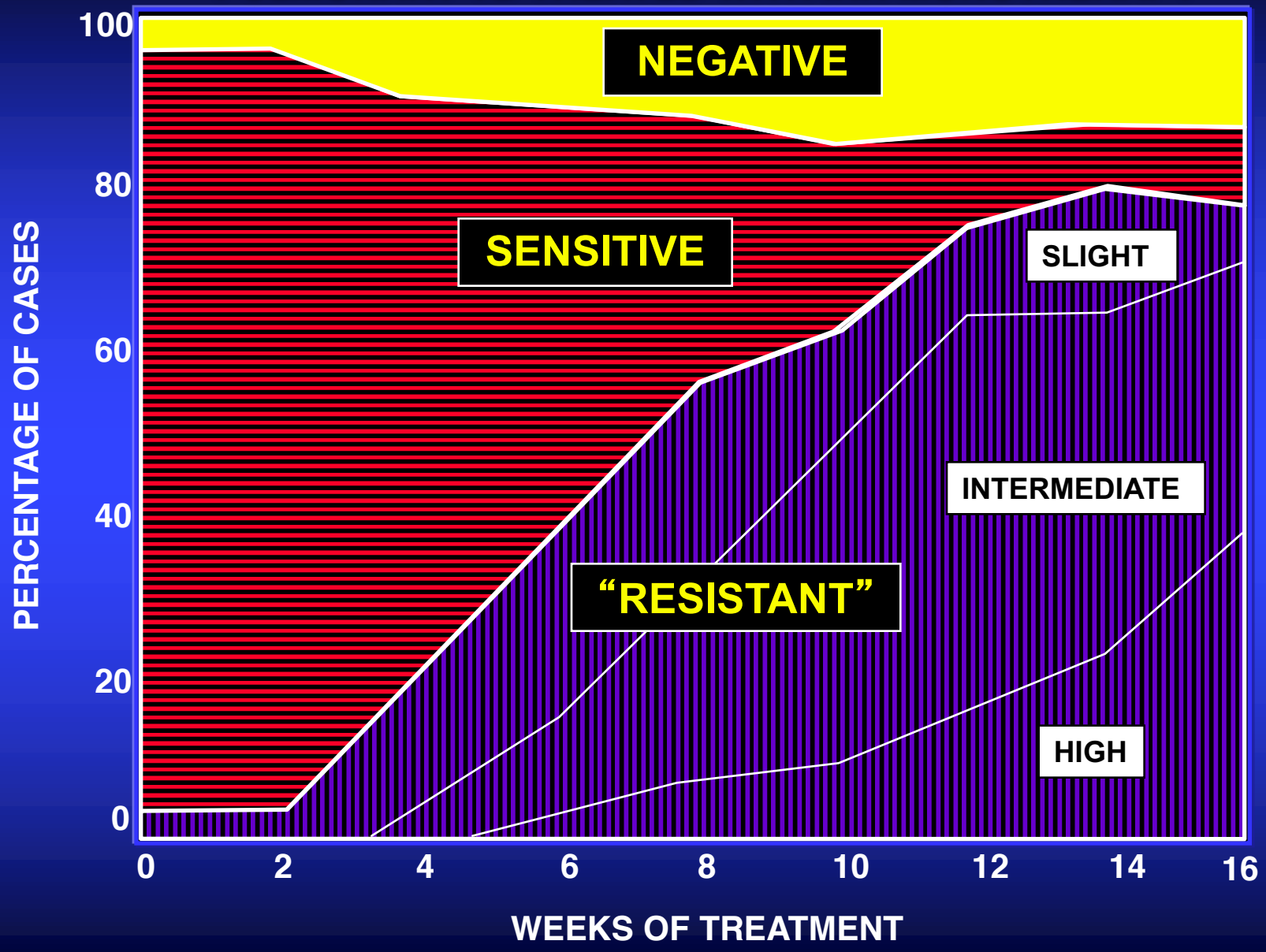
CLINICAL DATA DURING SIXTEEN WEEKS OF INH THERAPY



Coates et al, The Clinical Significance... N Engl J Med 248:1085, 1953

INH SUSCEPTIBILITY OF ISOLATES FROM PATIENTS WITH PULMONARY TB TREATED WITH INH MONOTHERAPY



Coates et al, The Clinical Significance... N Engl J Med 248:1083, 1953

PREEXISTENCE OF DRUG RESISTANT MUTANTS OF TB

Number of plates	Inoculum* per plate	Drug conc.	Colonies per plate (actual)	Prevalence of resistance mutants
		µg./ml.		
4	5×10^6	INH† 1.0	99.101, 106,107	1 in 5×10^4
4	5×10^7	SM‡ 2.0	55, 59 64,70	1 in 1×10^6
100	1×10^8	INH 1.0 SM 2.0	No growth	<1 in 1×10^{10}

* Number of viable, bacterial units from a seven to 10 day old vigorously growing, well dispersed *H37Rv* culture in liquid medium (ST).

† Isoniazid

‡ Streptomycin

Cohn et al, J Clin Invest 38:1349, 1959

HIV-1 Drug Resistance is the RESULT and the CAUSE of drug failure

- **RESULT: Emergence of drug-resistant virus is an inevitable consequence of the failure to fully suppress HIV-1 (HCV, HBV, influenza virus, TB, etc) replication with antimicrobial therapy.**

- **CAUSE: Drug resistance is a major factor contributing to the failure of antiretroviral therapy.**

Diversity of RNA Virus Populations

- RNA viruses constitute a *quasispecies.*
- Genetically distinct viral variants evolve from an initial monoclonal or oligoclonal virus inoculum.
- Variants are generated due to error-prone nature of RT.

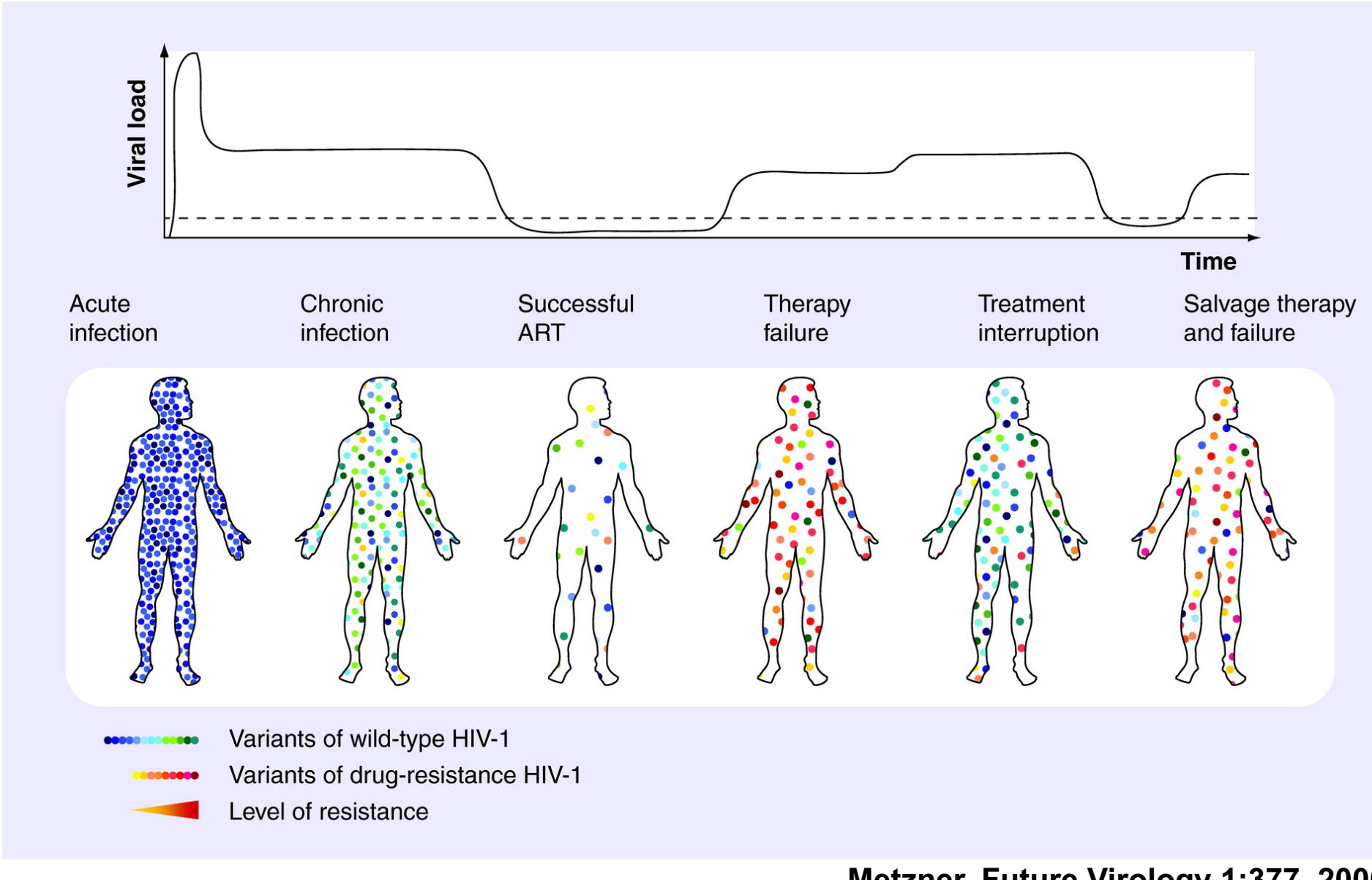
Drug-Resistant Mutants Preexist in Untreated Patients

- The HIV genome contains 10^4 nucleotides.
- The mutation rate of HIV is ~3 x 10^{-5} nucleotides/ replication cycle.
- ~10^{11} virions are generated by 10^7 - 10^8 rounds of replication each day. Thus every possible mutant is generated daily with high level ongoing replication.

Rapid Turnover of Viral Quasispecies

- Most of the virus population in plasma is cleared and replaced each day.
- Rapid turnover allows rapid emergence of drug-resistant variants under selective pressure.
- Resistant variants may be replaced by residual wild-type virus if selective pressure is removed.
- Resting latently infected cells may continue to harbor drug-resistant provirus.

HIV-1 infection and a model of the distribution of viral quasispecies in the era of antiretroviral therapy



Metzner, Future Virology 1:377, 2006

HIV drug resistance is generated by one of two major mechanisms

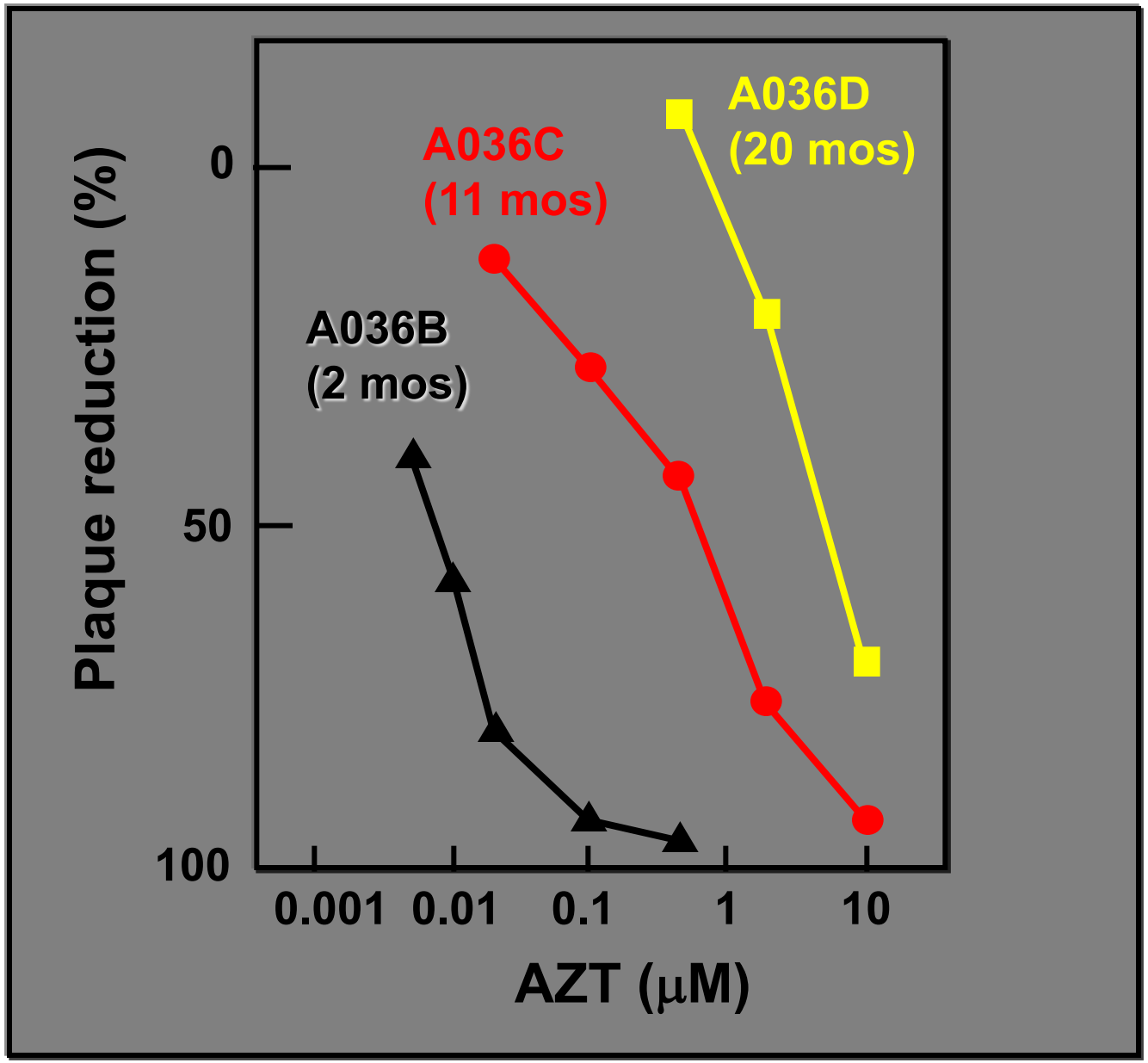
- Acquired drug resistance following non-suppressive treatment (secondary resistance)

- Transmitted drug resistance (TDR) (primary resistance)

(PDR combines both TDR and resistance acquired from previous treatment, disclosed or not, after infection)

- Both mechanisms are too prevalent.
- Prevention strategies for these two mechanisms are completely different.

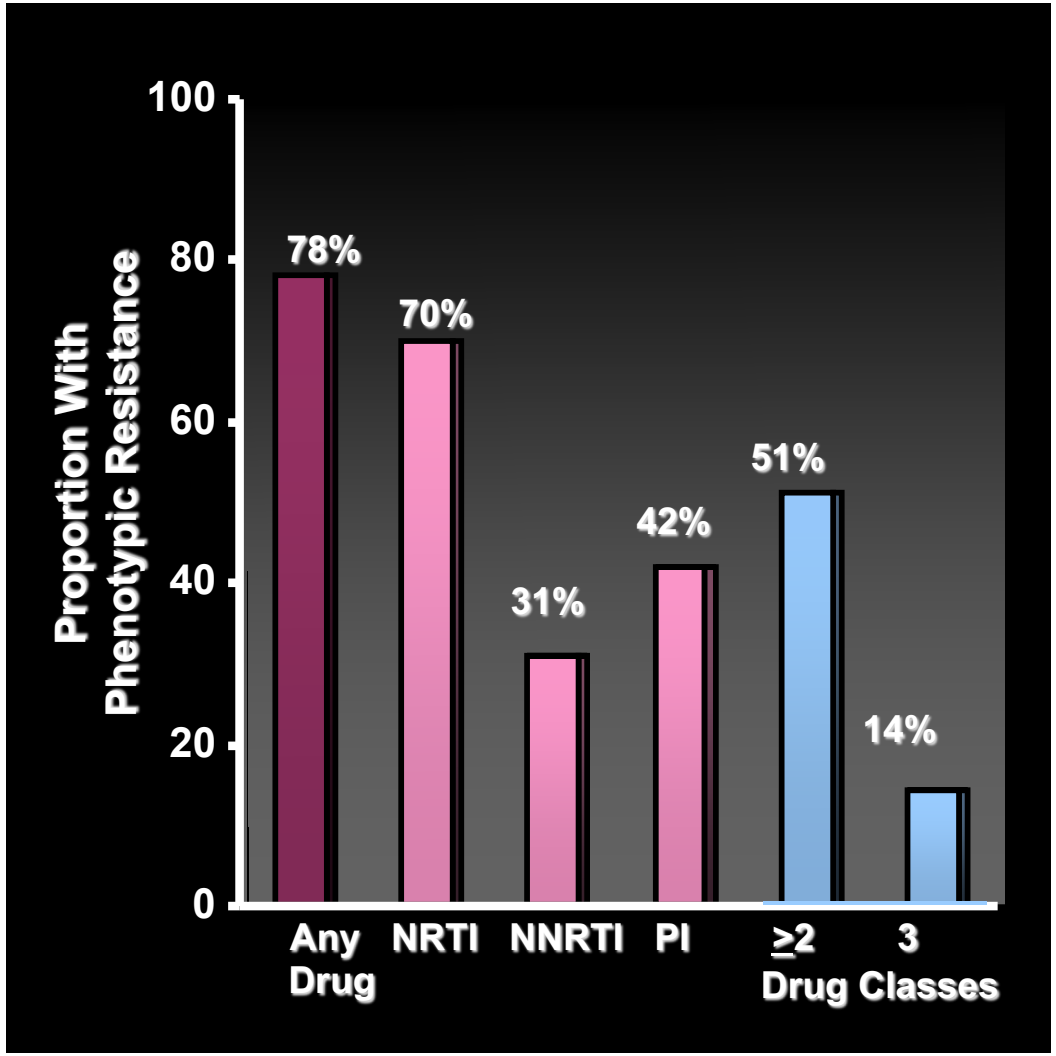
AZT Susceptibility of Sequential Isolates of HIV-1 From a Patient Administered AZT



Larder, Darby and Richman, Science 1989; 243:1731.

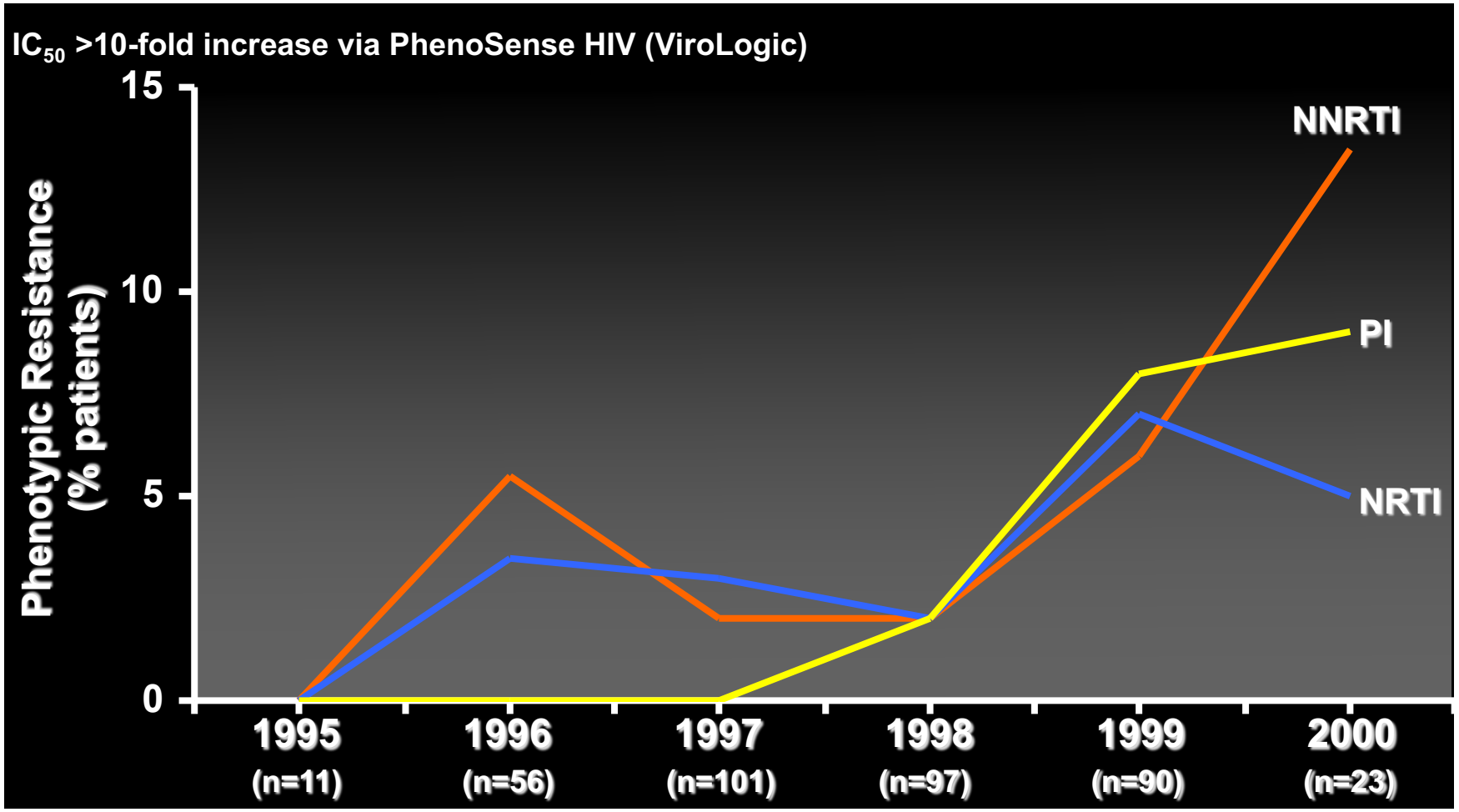
HCSUS: Prevalence of HIV Drug Resistance

- HCSUS population
  - Representative as possible to all HIV-positive persons receiving medical care in early 1996
  - 1080 samples with HIV RNA >500 copies/mL
- Resistance more common
  - Lowest CD4 count nadir
  - Higher HIV RNA
  - More access to care
- Resistance less common
  - Patients cared for by the most experienced providers

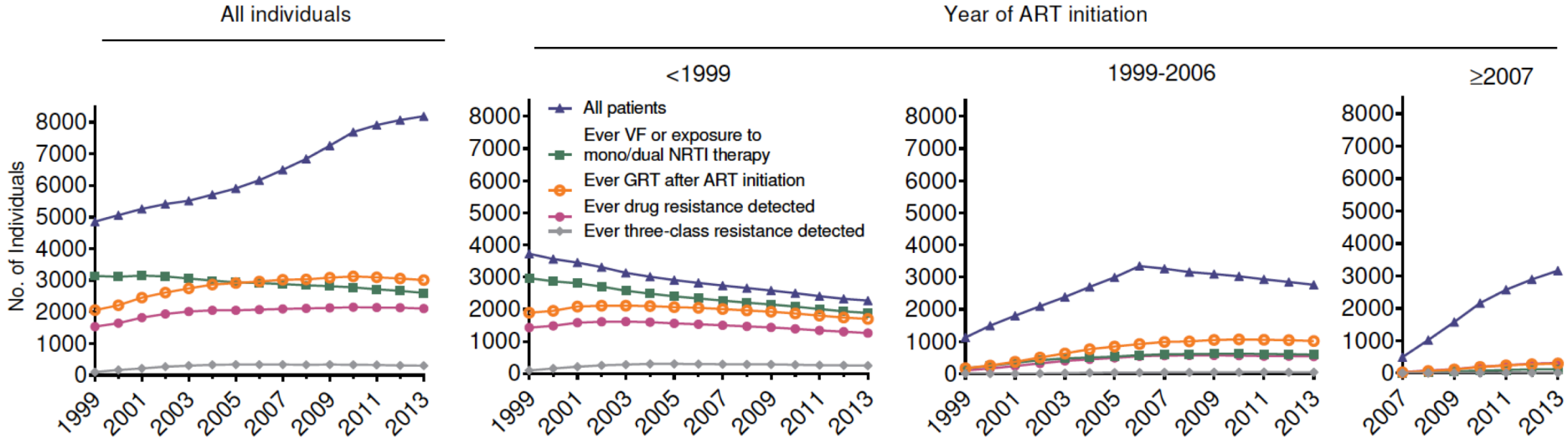


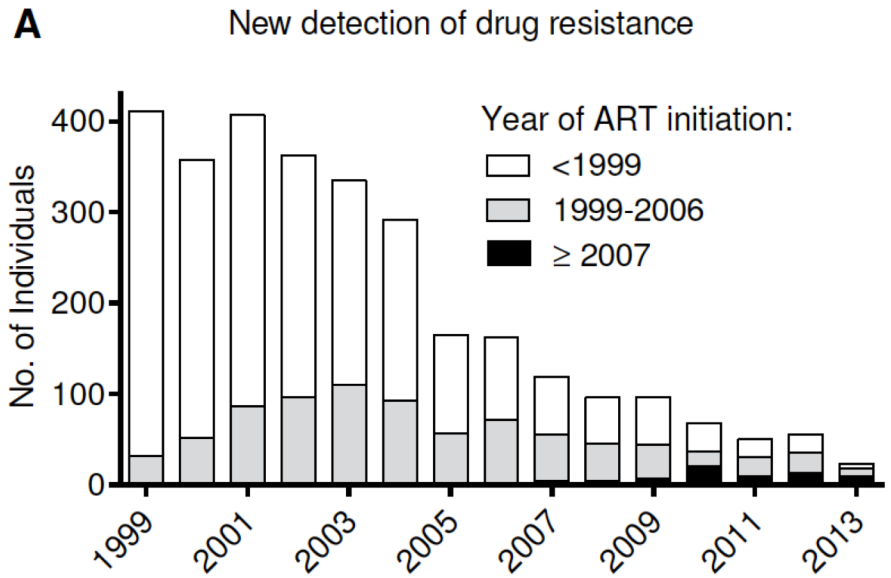
Richman et al, AIDS 18:1393, 2004

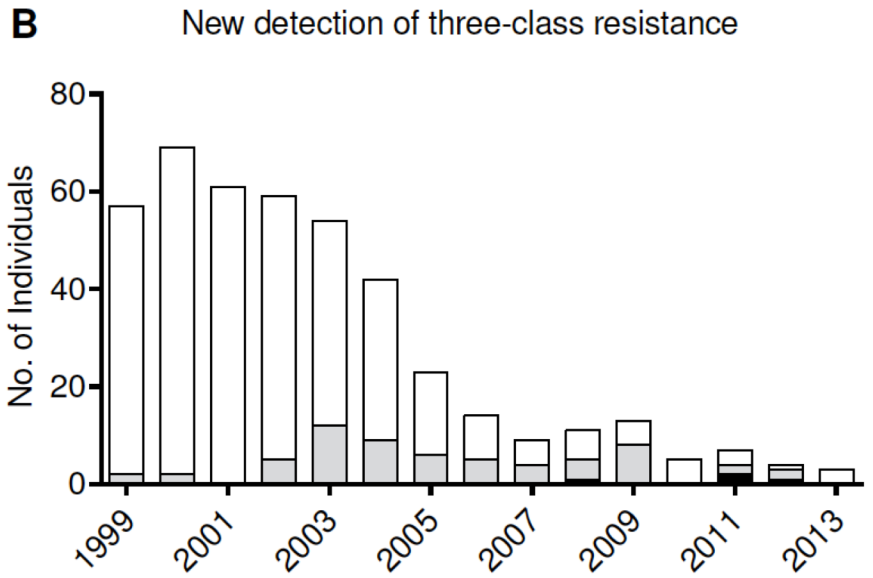
Transmission of Drug-Resistant HIV in Treatment-Naïve Patients



Little SJ, et al. *N Engl J Med.* 2002;347:385-394

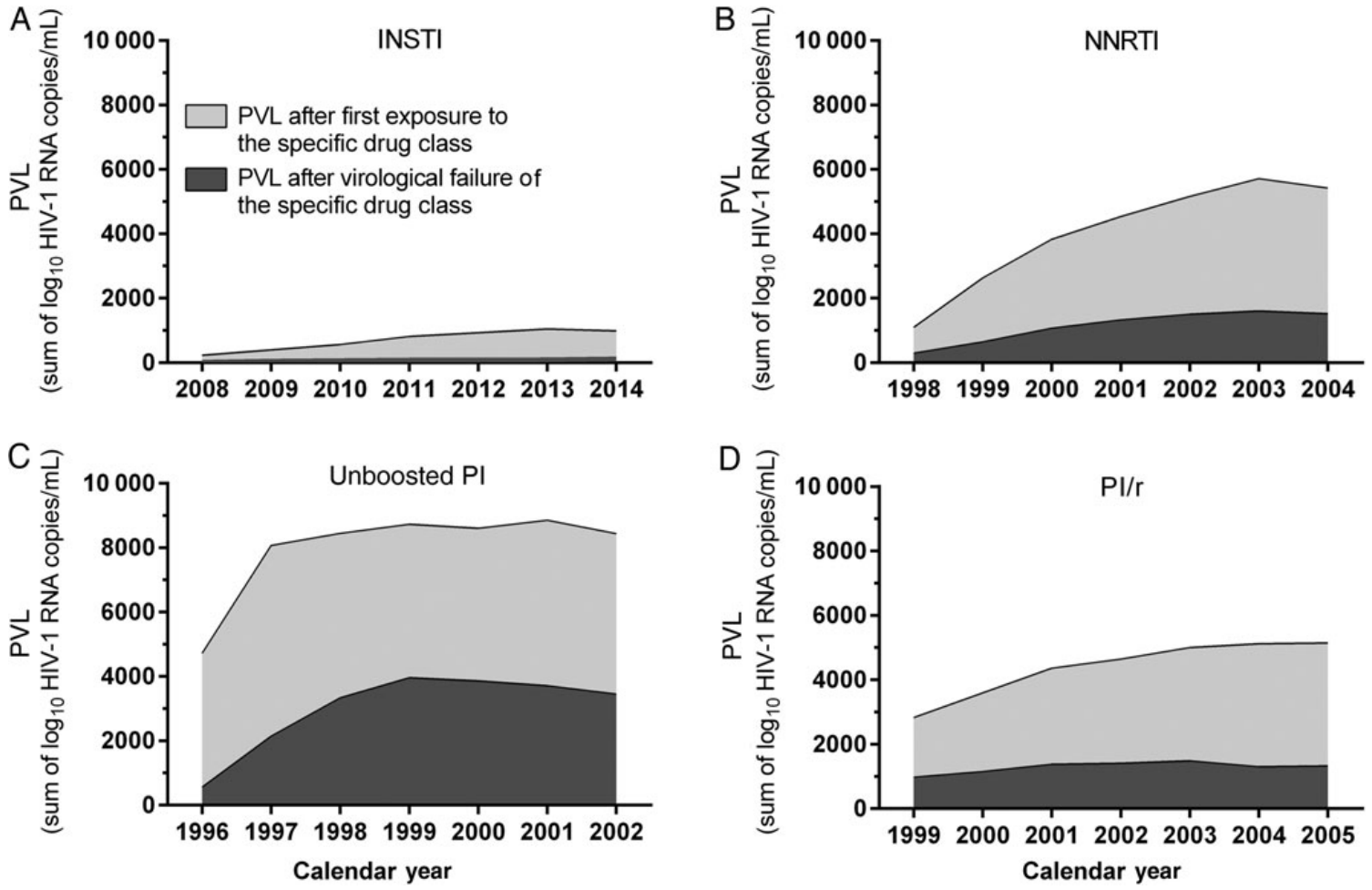






Scherrer et al, CID, 2016

Slow resistance development and transmission in resource-rich settings

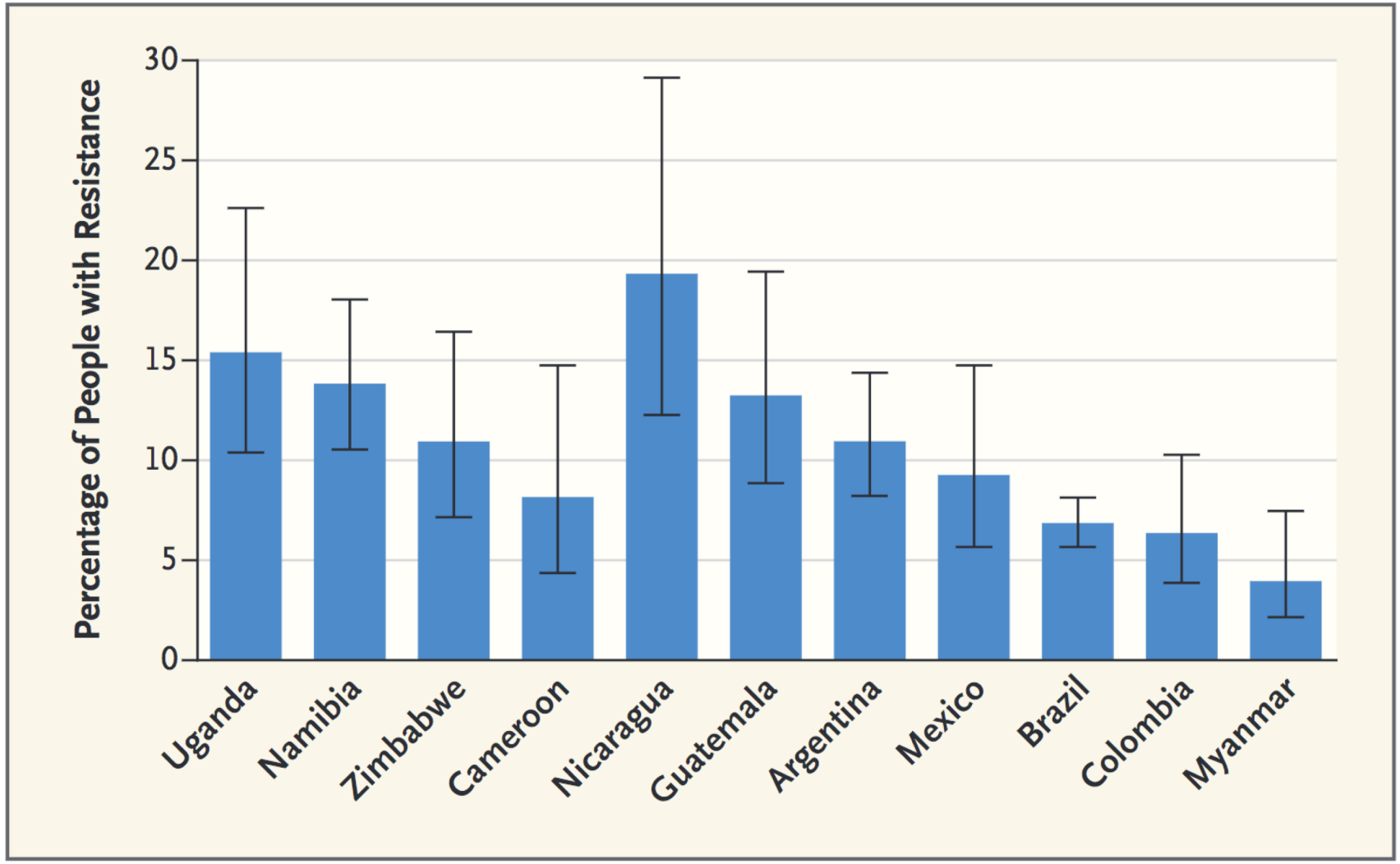


Scherrer A, et al. J Infect Dis 2017

How did this reduction of resistance in resource-rich countries with more expanded treatment happen?

- **Better drugs**
  - More potent and better half-lives (TDF/FTC, better PIs, integrase inhibitors)
  - More tolerable and less toxic (thymidine analogues are history)
  - Fixed dose combinations

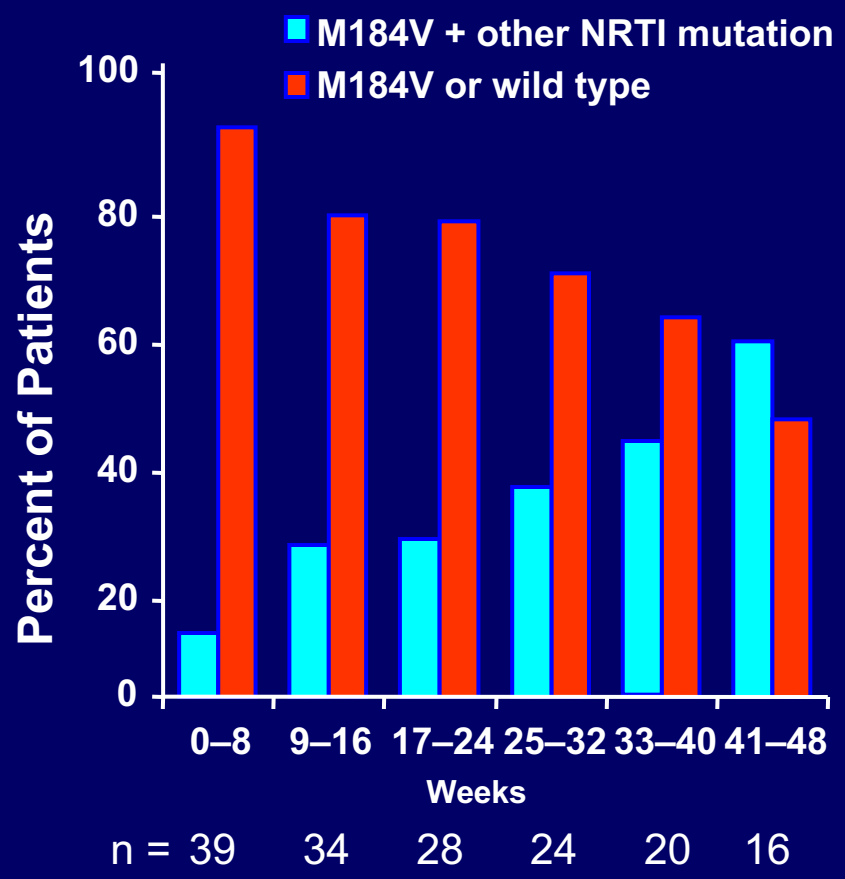
- **Better monitoring of failure and then use of drug resistance testing and better drugs for treatment failure**



Pretreatment HIV Drug Resistance to Nonnucleoside Reverse Transcriptase Inhibitors in 11 Countries.

Shown are the percentages of people tested who had resistance to efavirenz or nevirapine. I bars denote 95% confidence intervals. Data are from the World Health Organization.[1]

Cost of continuing a regimen failing as defined by virologic criteria

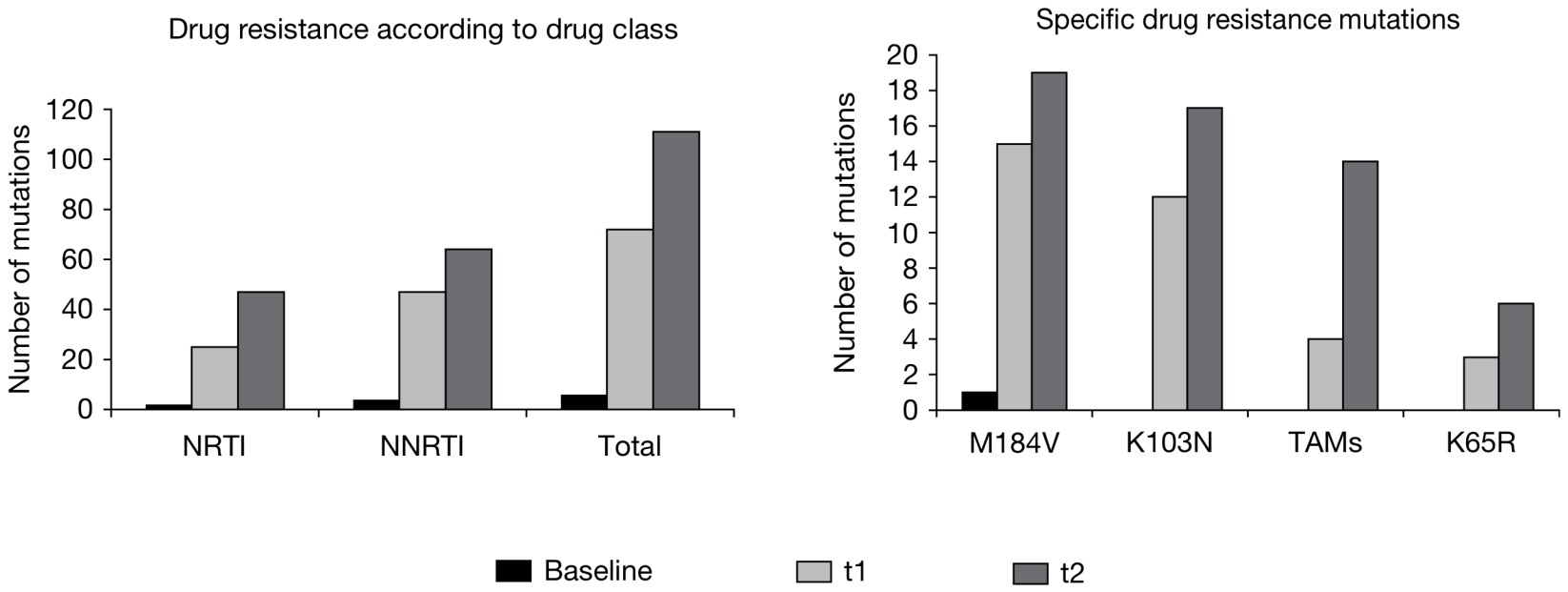


- CNA3005: ZDV/3TC/ABC vs. ZDV/3TC/IDV
- "First genotype" performed at time of rebound
- "Last genotype" performed prior to changing ART
- Early breakthrough with wild type or M184V
- Increasing NRTI mutations associated with cross-resistance to all RTIs

Melby T, et al. 8th CROI; 2001; Chicago, Ill. Abstract 448

Rapid accumulation of DRMs when first-line ART is continued despite virological failure

Longitudinal genotyping analysis at first detection of VF (t1) and 6-12 months after (t2)



Steep increase in TAMs (+250%) and K65R (+100%)
NNRTI susceptibility is already lost at first detection of VF
Precedes WHO-defined failure criteria

Barth et al. Antiviral Therapy 2012

Prevention of acquired drug resistance requires addressing the causes

- **The patient**
  - adherence
- **The prescribing care provider**
  - selecting an optimal regimen
  - counseling the patient
- **The drugs**
  - Potency
  - tolerability
  - Pharmacokinetics
- **The heathcare delivery system**
  - Provide viral load monitoring with prompt turnaround and threshold <100 copies/mL
  - Provide assays for drug resistance (or drug levels).
  - Avoid stockouts

Measures are still needed to preserve the integrase class over time - 1

- **Low level viremia ≠ treatment success**
  - High threshold may be even more dangerous with DTG, since viruses resistant to DTG are often not very fit and viral load may remain low
- **Delayed response to viral rebound puts individuals and society at risk**
- **Use tools** (like viral load monitoring and objective adherence assessment) **to generate insight in virological failure**

Measures are still needed to preserve the integrase class over time - 2

- Avoid adding 1 new drug to a failing regimen
  - What is the risk of a switch from a failing regimen with TLE to TLD?
  - Surveillance in those who start DTG with unsuppressed viral load should be promptly initiated if resistance testing is not applied at switch

Summary

- The principles of HIV drug resistance are well established (Darwinian evolution).
- The mistakes and lessons learned in the developed world have been recapitulated in low and middle income countries.
- Prevention of further increases in drug resistance
  - Better regimens (TLD/TFD)
  - Avoid stockouts
  - Monitor viral load with prompt access to results
  - If and when available, access drug resistance tests and drug levels
  - Interventions to improve adherence and reduced risk behaviors