Lessons learned from HIV: treatment

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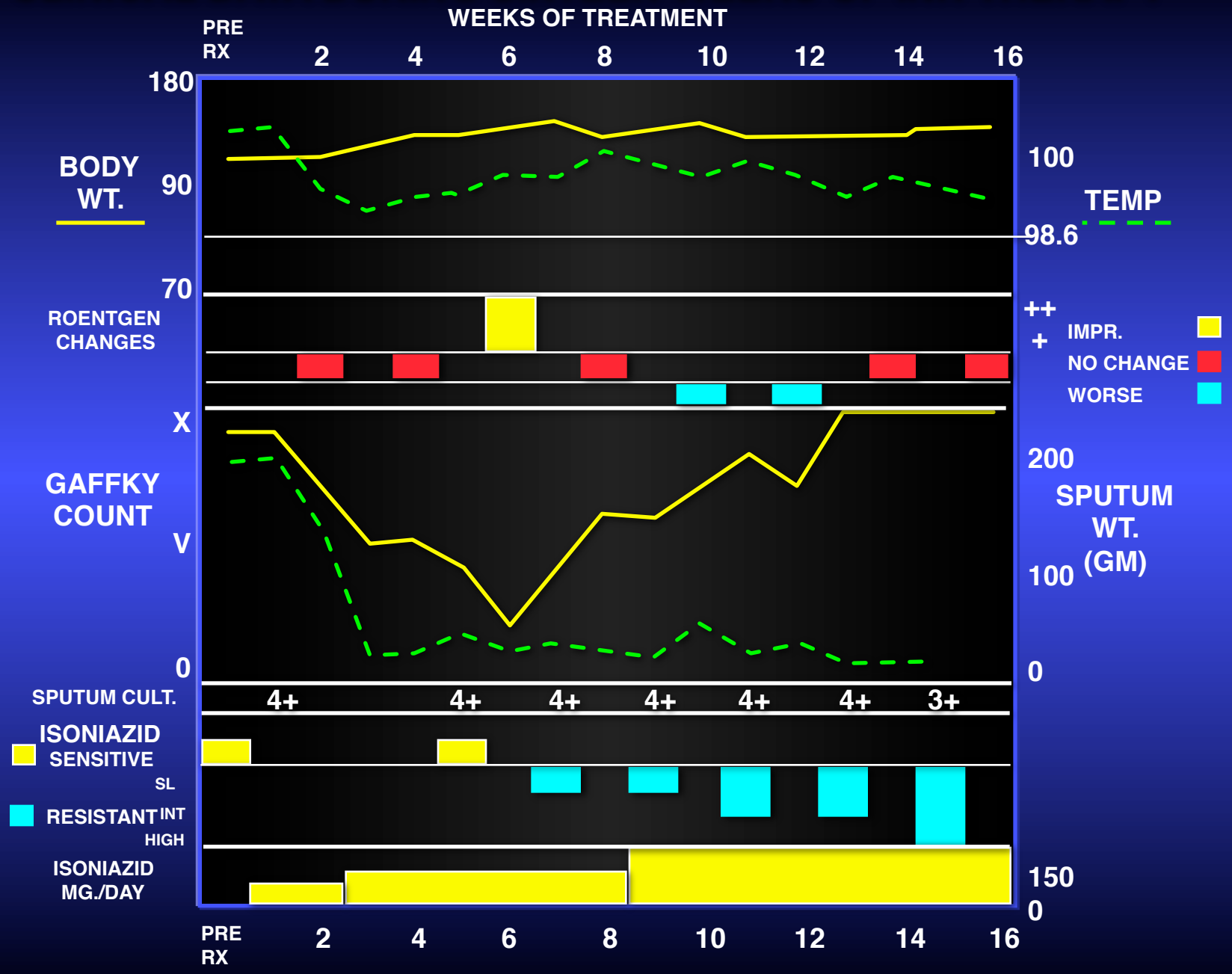
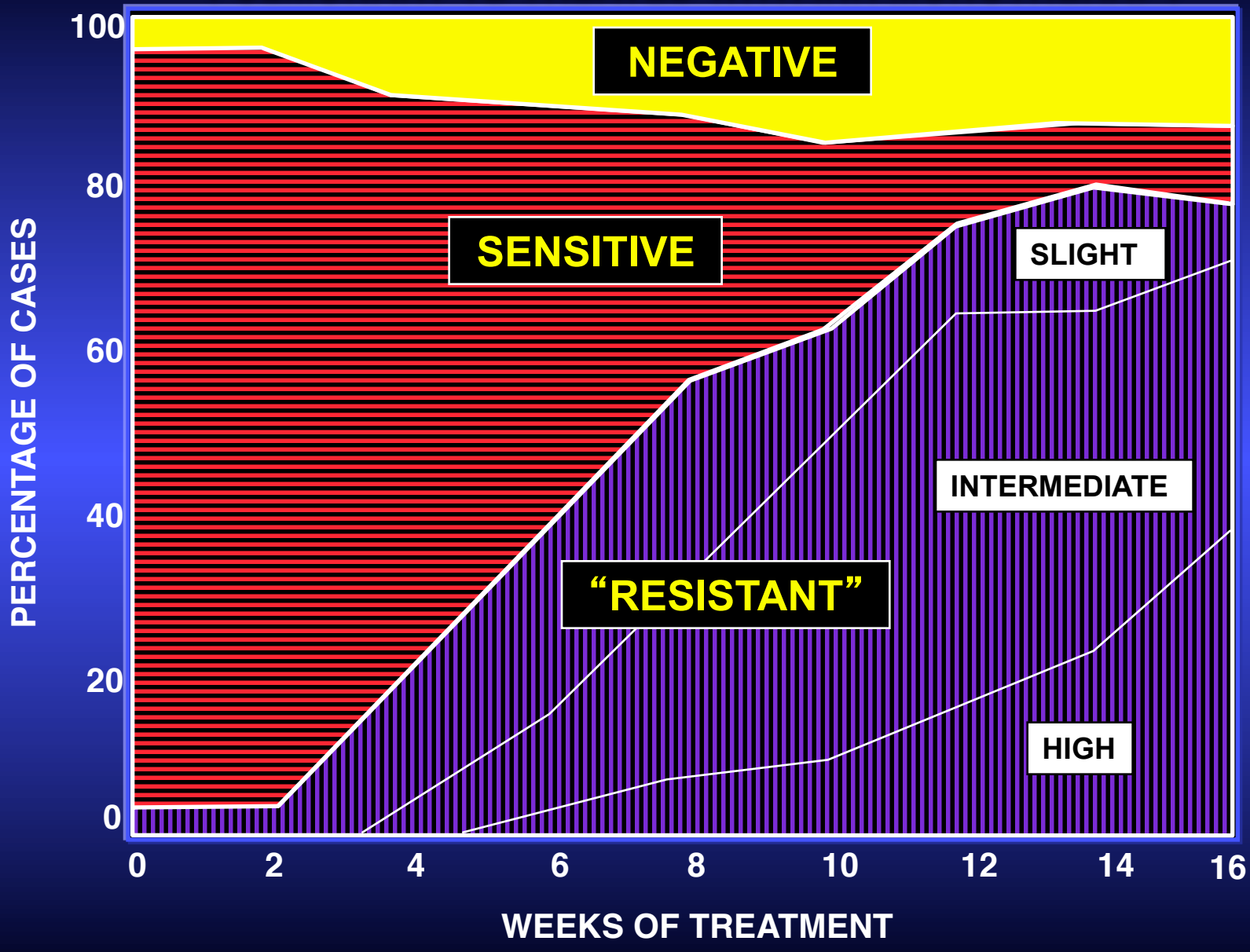
CLINICAL DATA DURING SIXTEEN WEEKS OF INH THERAPY



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

- **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.**

- **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 ~3×10^{-5} nucleotides/ replication cycle.
- ~10^{11} virions are generated by 10^7 - 10^8 rounds of replication each day.

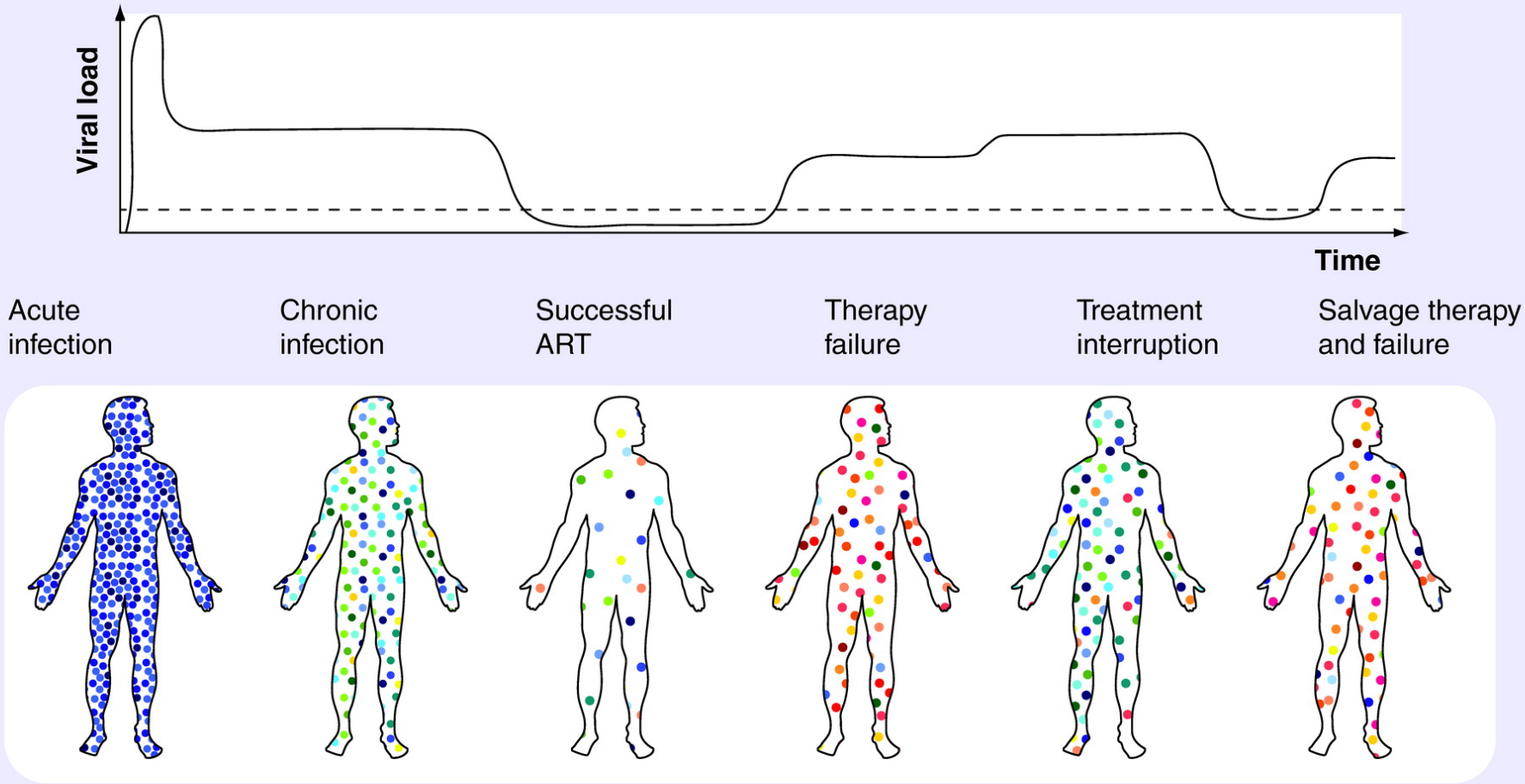
Preexisting Drug Resistance Mutations

- Single mutants produced daily
  - Isolated from treatment-naive patients or those infected before antiretroviral drug availability
- Double mutants less common
- 3 or more specific resistance mutations in the same genome rare

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

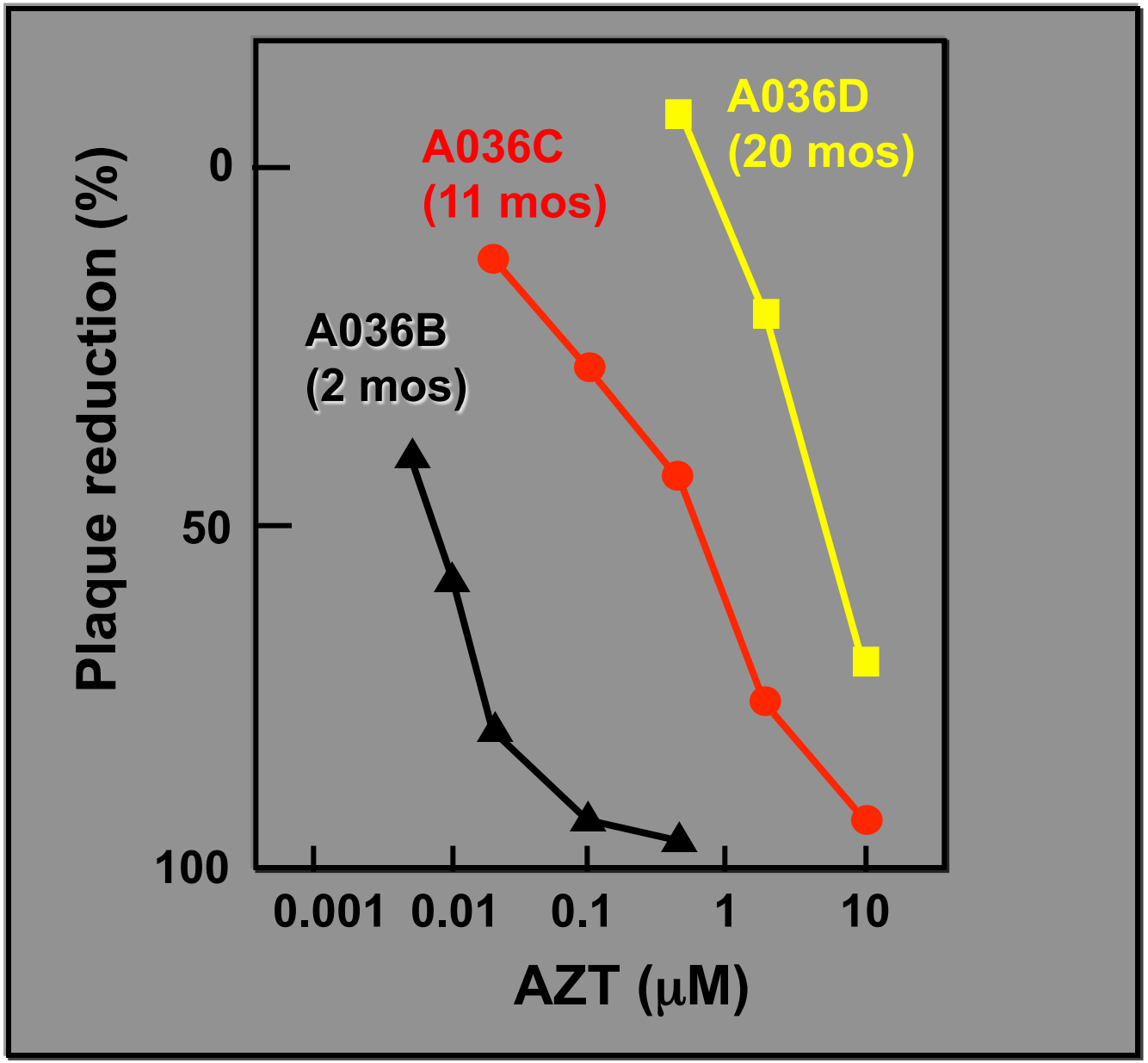
HIV drug resistance is generated by one of two major mechanisms

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

- **Transmitted resistance**
  (primary resistance)

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

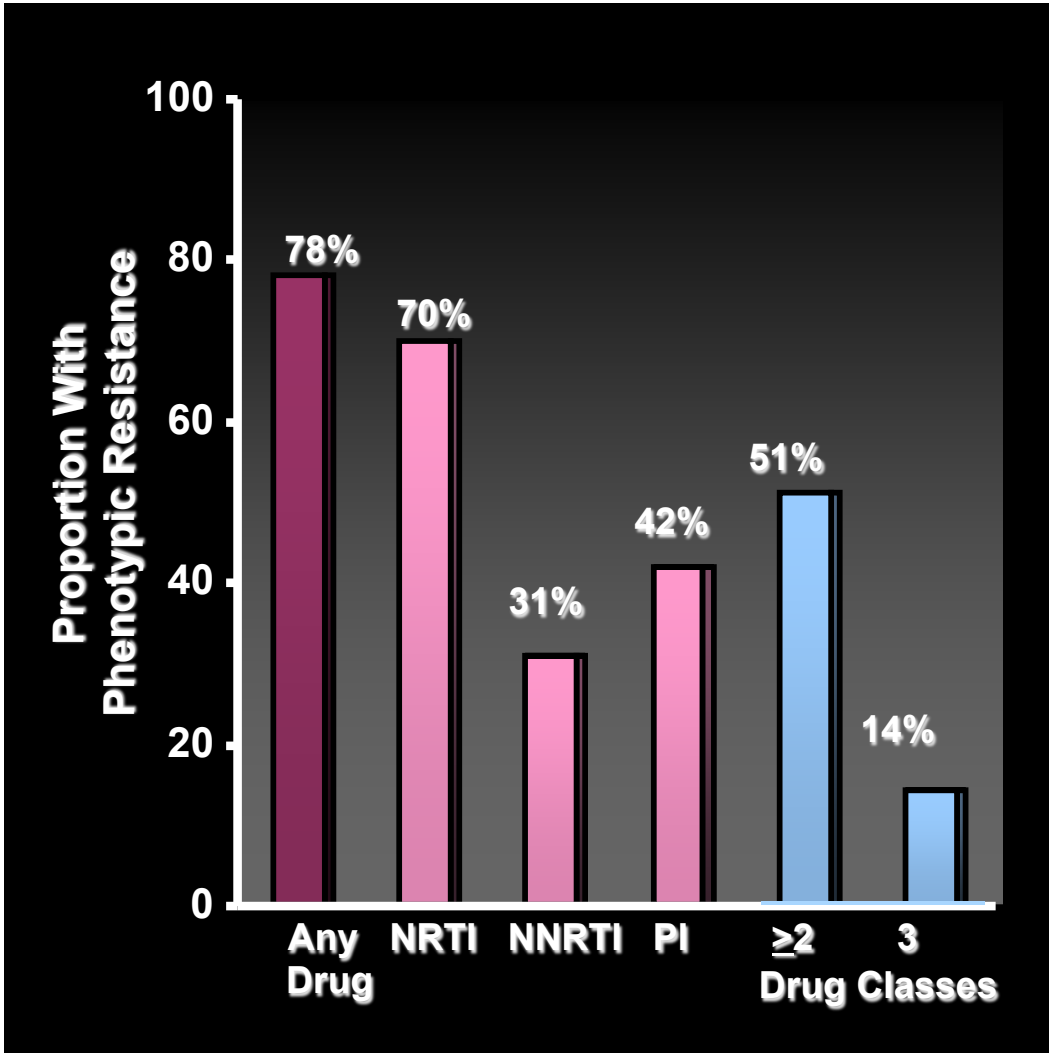
AZT Susceptibility of Sequential Isolates of HIV-1 From a Patient Administered AZT



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

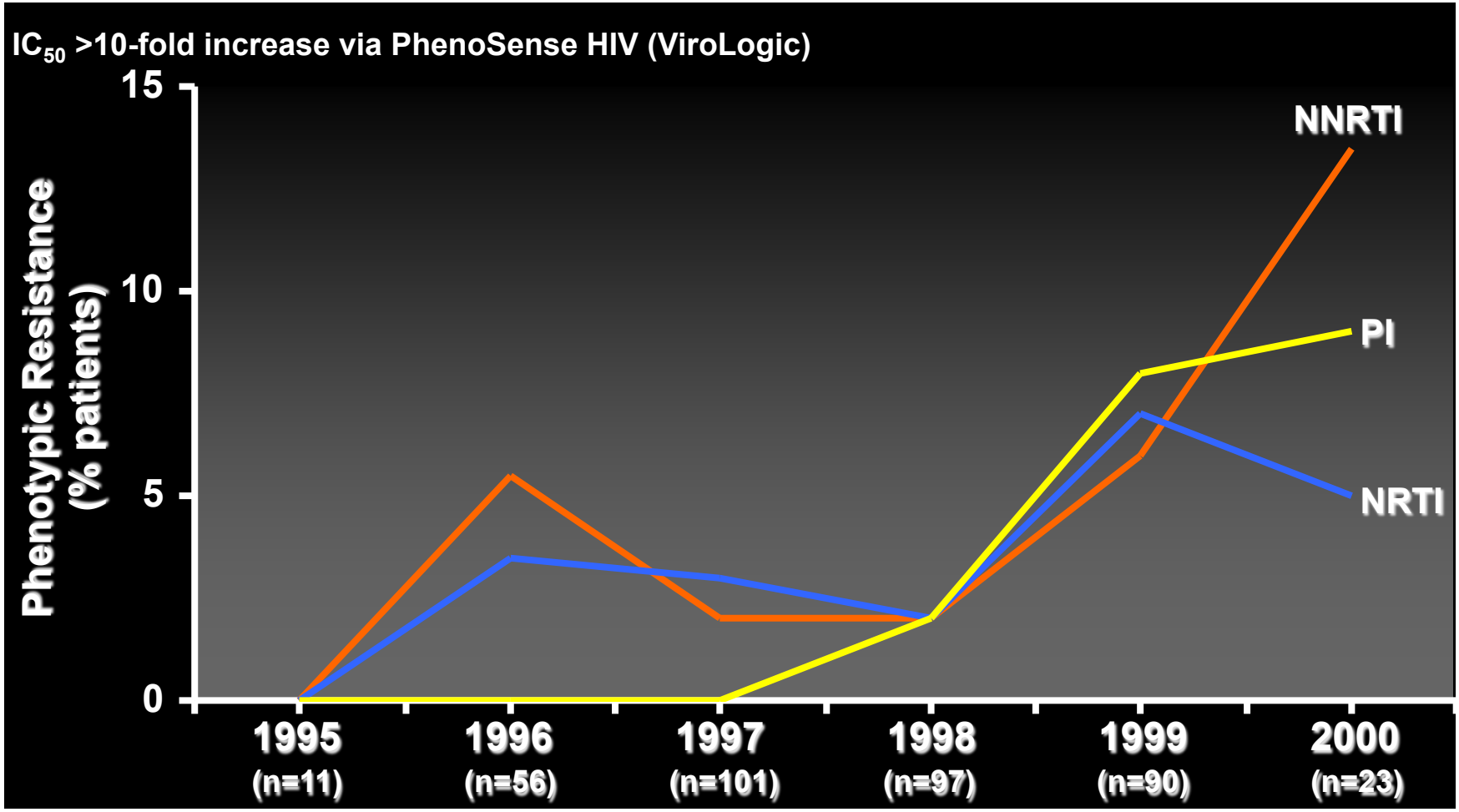
HCSUS: Prevalence of HIV Drug Resistance

- 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



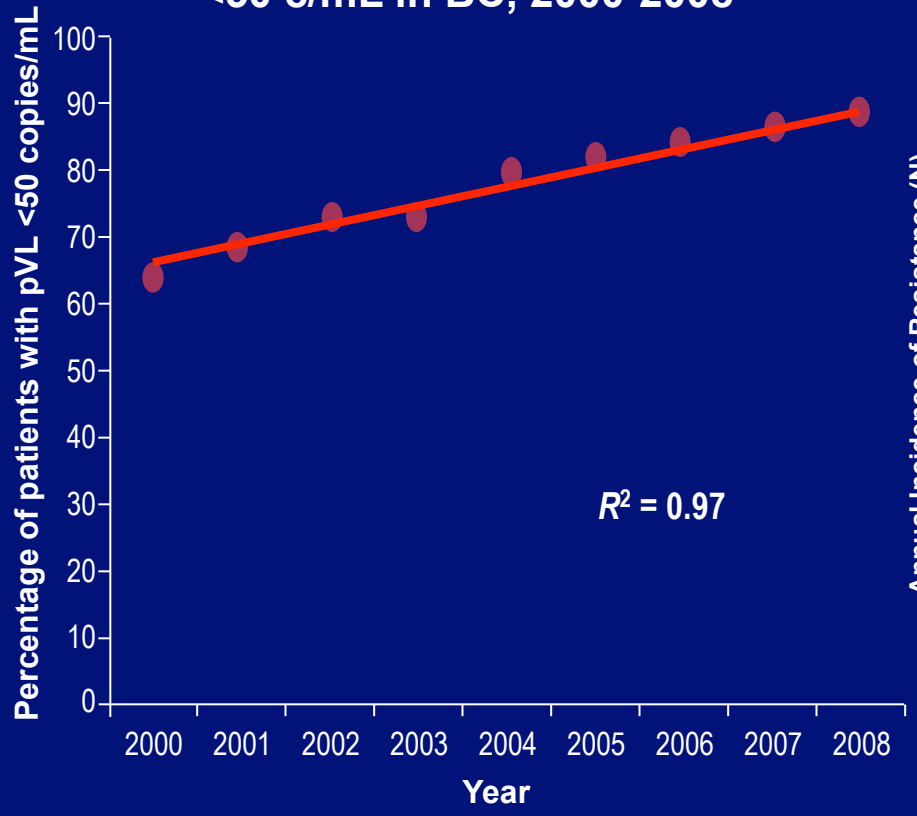
Little SJ, et al. *N Engl J Med.* 2002;347:385-394

The Good News

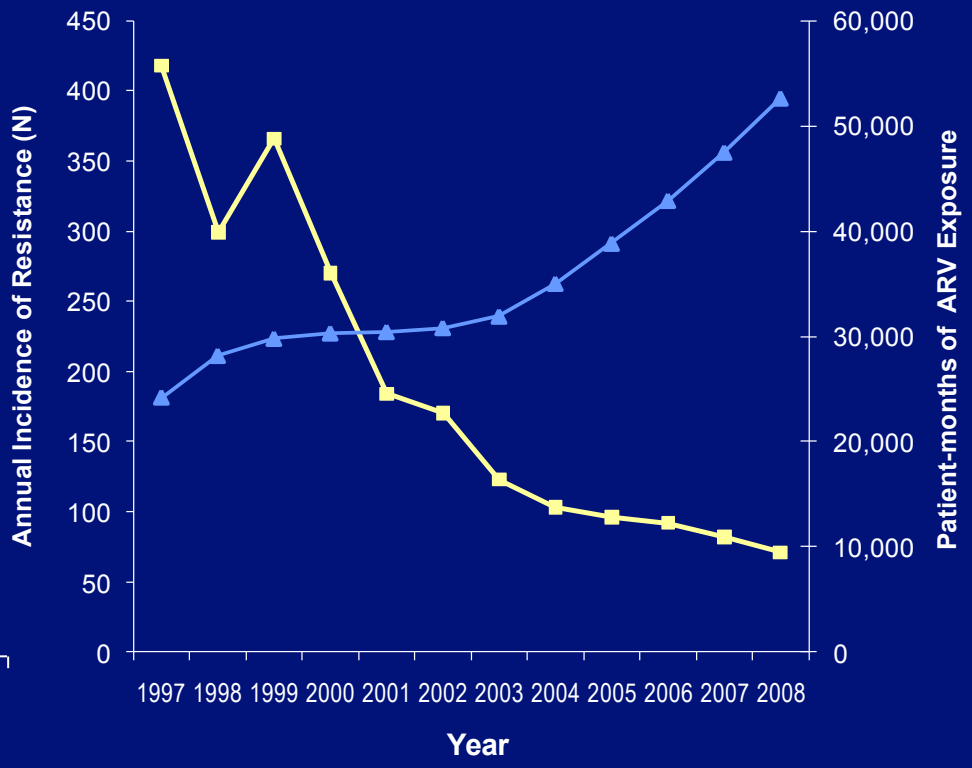
- HIV drug resistance is not maintained in the environment or transmitted by fomites.
- HIV drug resistance is not selected for or maintained in animal reservoirs.
- HIV drug resistance is not maintained or spread on plasmids or other genetic exchange mechanisms, as for antibiotics.
- Better antiretroviral drugs have reduced HIV drug resistance in resource-rich countries.

Improved Virologic Outcomes Concomitant with Decreasing Incidence of Drug Resistance

Increasing proportion of VL levels <50 c/mL in BC, 2000-2008



Decreasing resistance despite increased ARV exposure in BC, 1997-2008



Gill VS, et al. *CID (2010) 50:98-105*

How did this reduction in resistance 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**

The Bad News

- **With the roll-out of antiretroviral drug treatment in low and middle income countries which has proven to be a dramatic accomplishment, the mistakes made in rich countries have been recapitulated.**

GENEVA/DAKAR, 12 DECEMBER 2002 - HIV Treatment Access Coalition (ITAC)

Aimed to boost efforts to provide access to antiretroviral drugs that have saved hundreds of thousands of lives in Europe and the US to the growing number of people with HIV/AIDS in low and middle income countries who need them.

Joep Lange the then president of the IAS:

"if we can get cold Coca Cola to every remote corner of Africa, it should not be impossible to do the same with drugs"

Acquired Drug Resistance

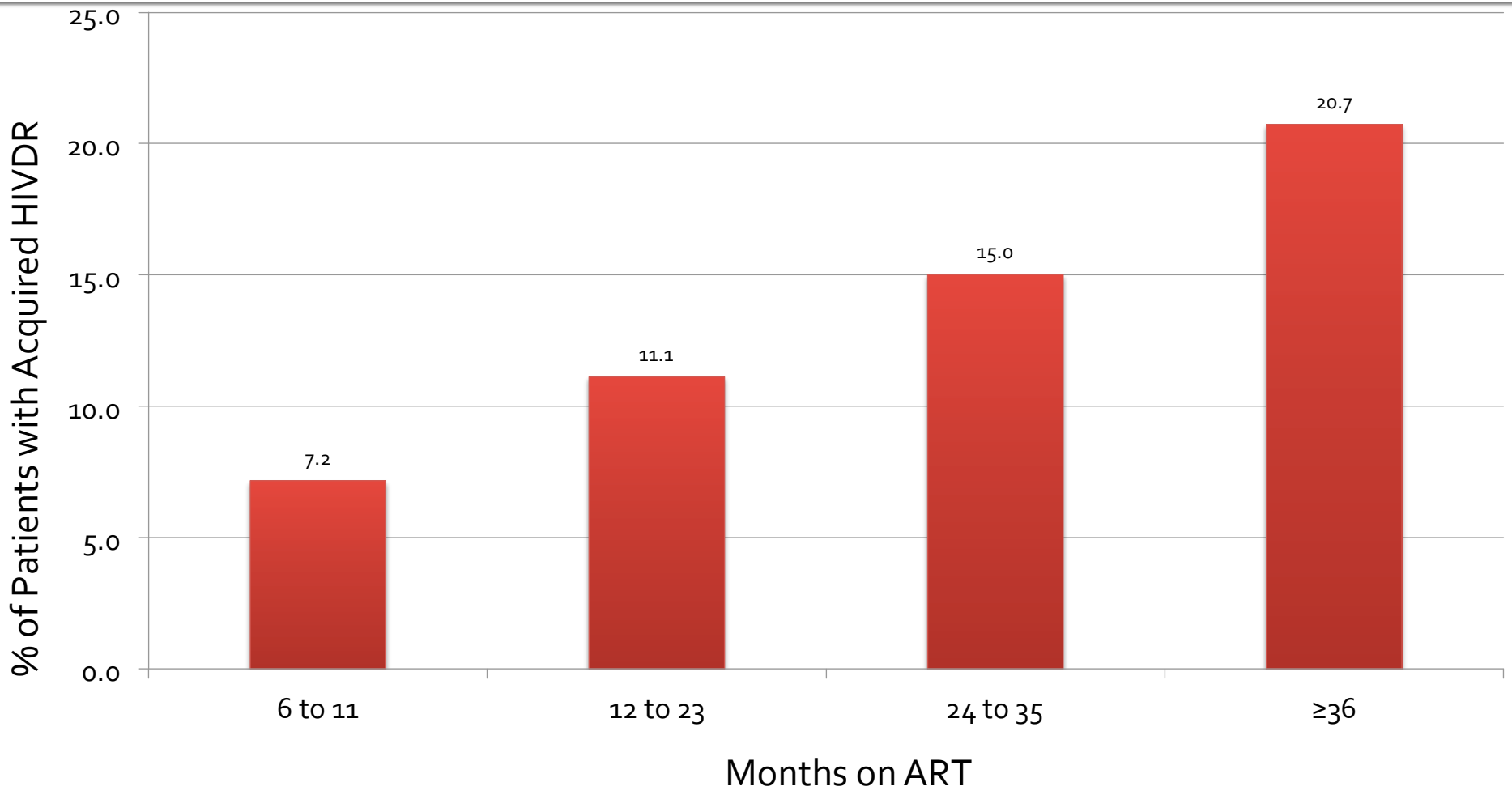


Figure 1. Changes in rates of acquired HIVDR to any drug class according duration of treatment. HIVDR=human immunodeficiency virus drug resistance. ART=antiretroviral therapy.

Stadeli and Richman, Antiviral Therapy 18(1):115-23, 2013

Acquired Drug Resistance

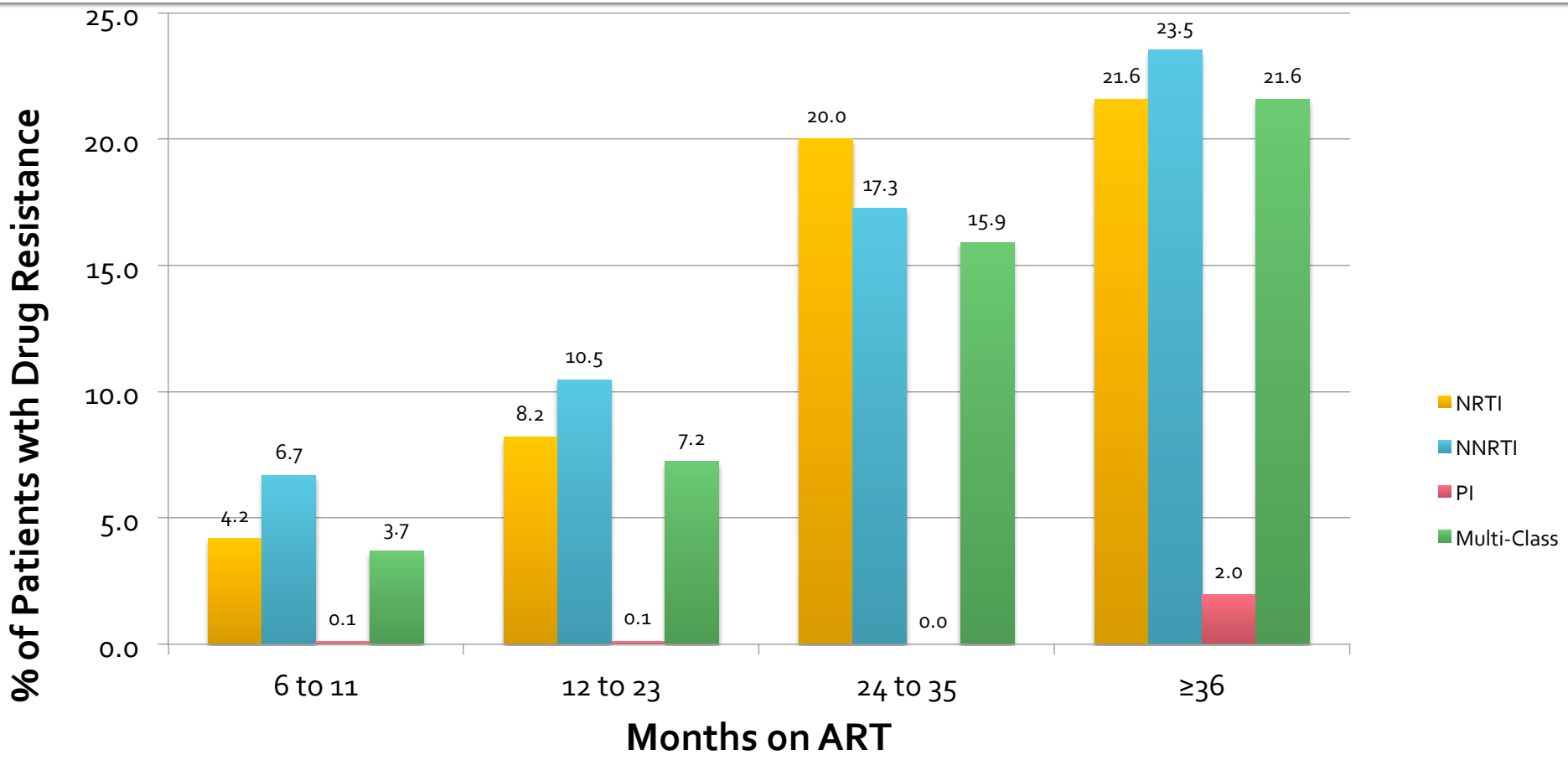


Figure 2. Distribution of acquired HIVDR to individual drug classes according to time on antiretroviral therapy

Stadeli and Richman, Antiviral Therapy 18(1):115-23, 2013

Transmitted Drug Resistance

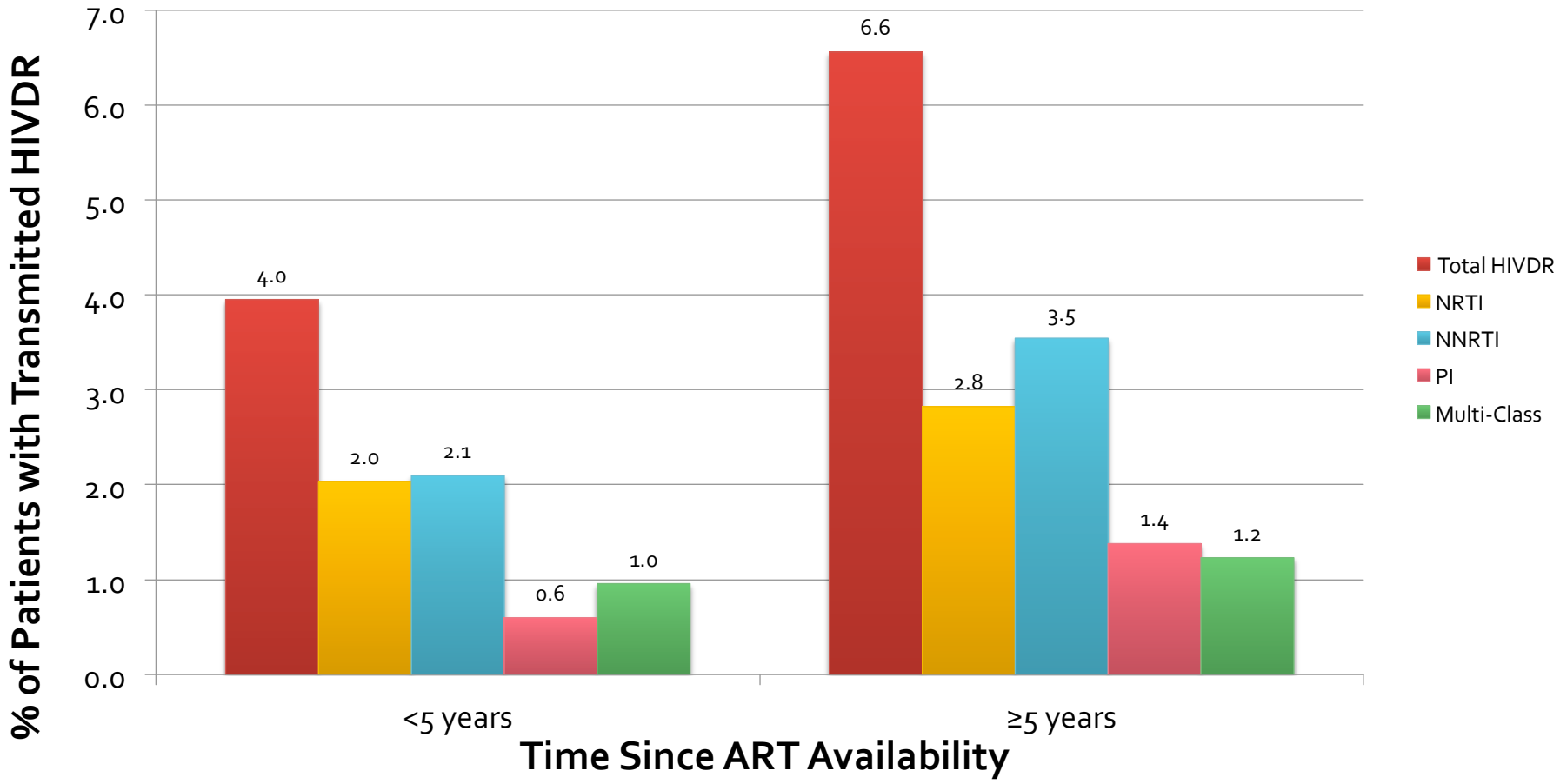
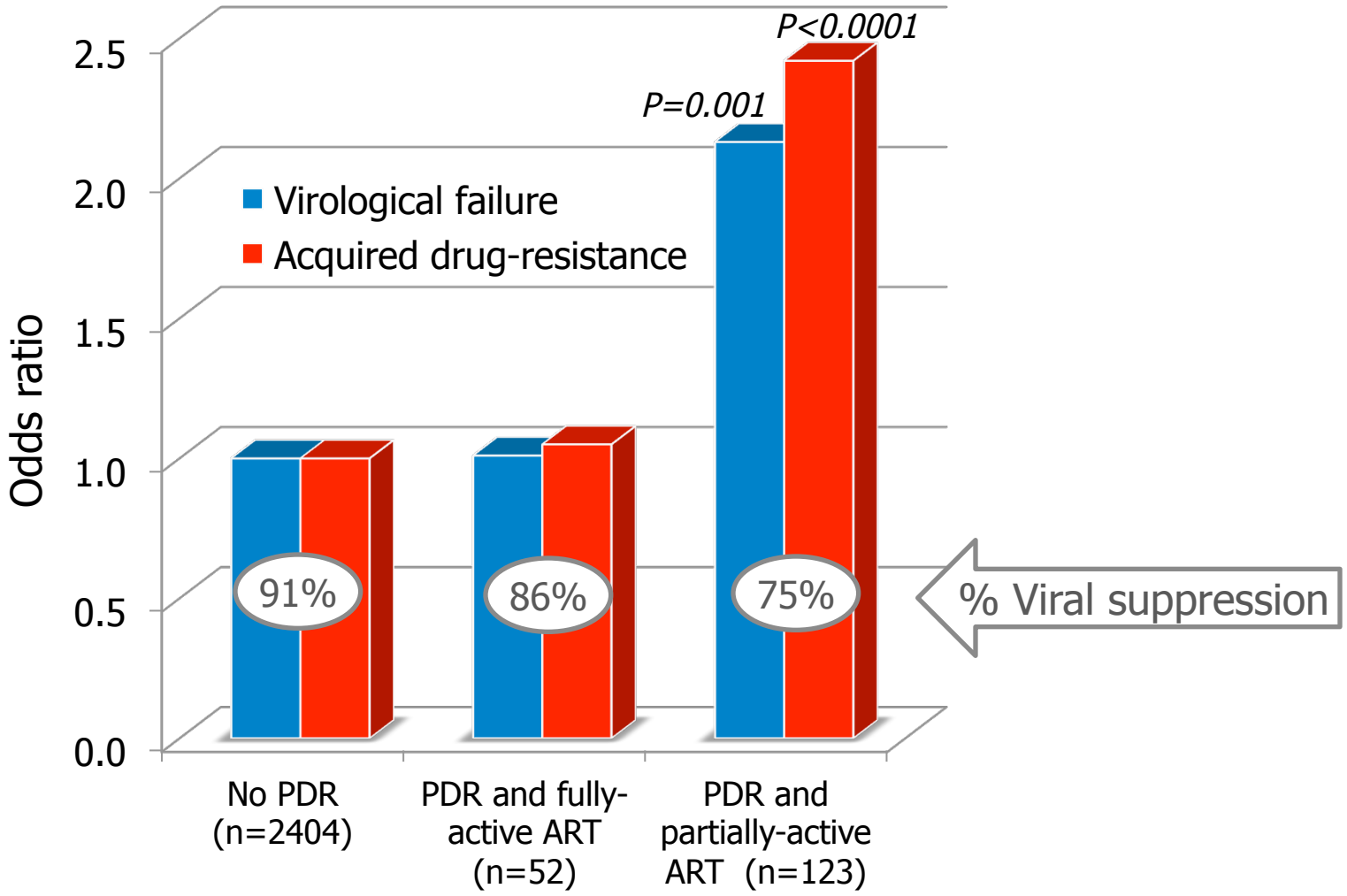


Figure 3. Changes in rates of transmitted HIVDR according to time since ART availability

Stadeli and Richman, Antiviral Therapy 18(1):115-23, 2013

PDR increases risk of VF and acquired DR
Multi-country cohort Africa

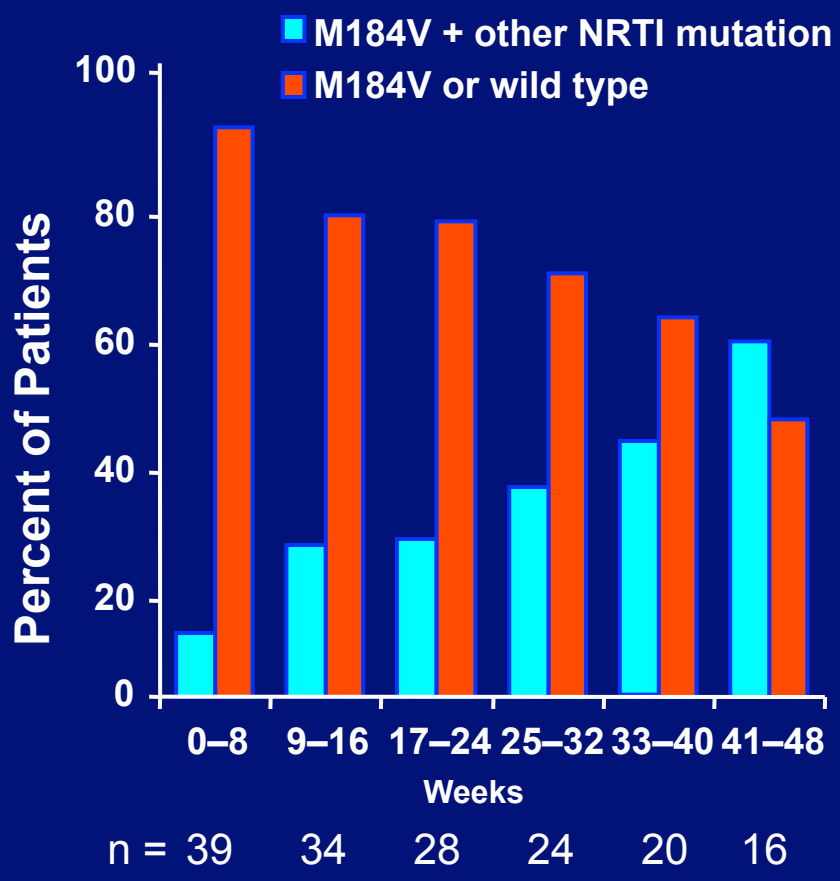


Multivariate analysis

Pretherapy drug resistance (PDR) defined using IAS-USA list and Stanford hivdb algorithm

Hamers, PASER, Lancet Inf Dis 2012

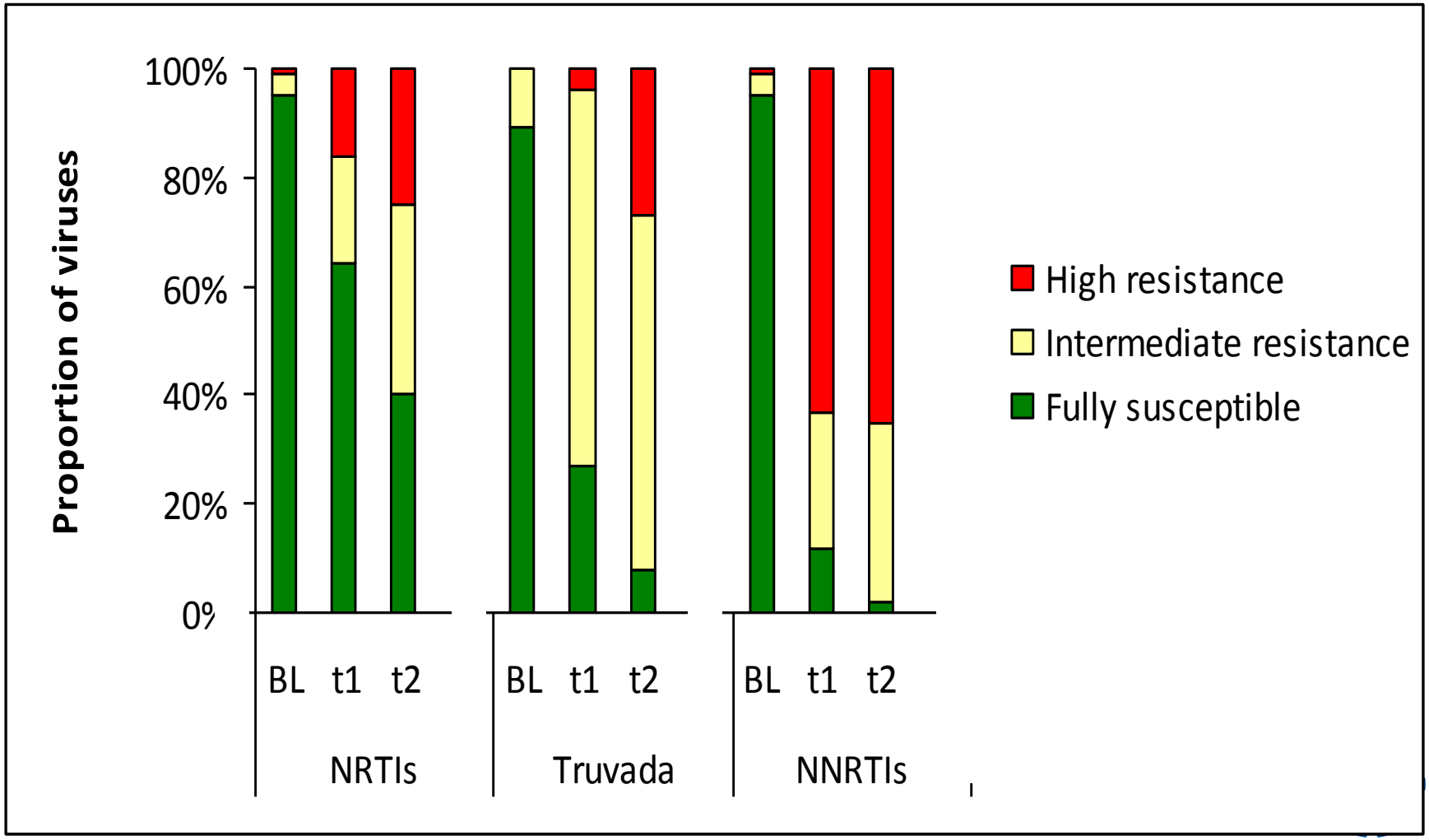
Cost of continuing a regimen failing as defined by virologic criteria



- 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

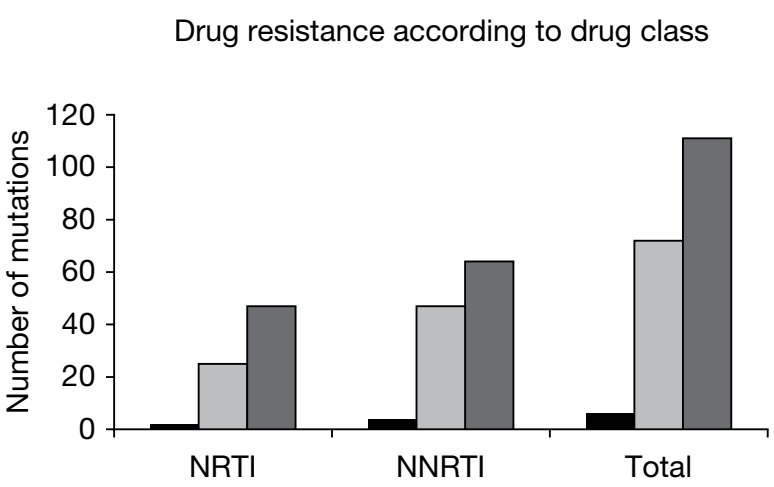
Melby T, et al. 8th CROI; 2001; Chicago, Ill. Abstract 448

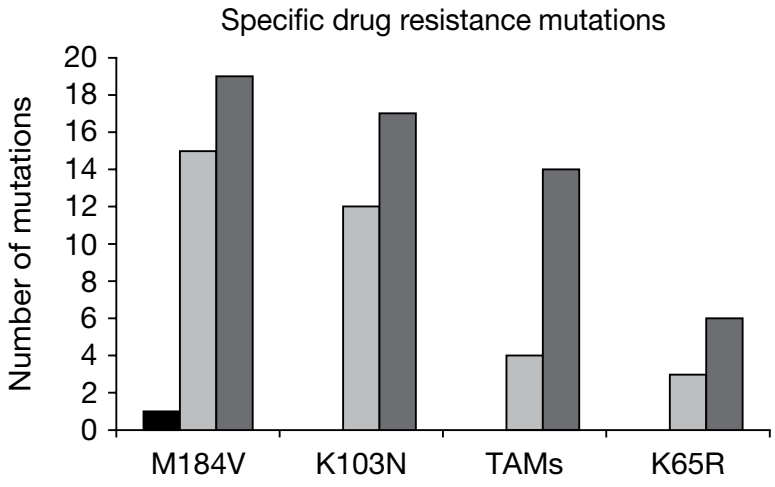
Predicted viral drug susceptibility



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

How much will resistance impact the benefits of the antiretroviral rollout in resource-limited countries?

Access to antiretroviral therapy has been a remarkable achievement with a dramatic impact on almost 12 million individuals in resource-limited countries; however,

- **We have been using suboptimal regimens for treatment and for MTCT.**
- **We are assessing failure by clinical or CD4 endpoints.**
- **We are not optimally monitoring virologic failure in individuals or resistance in populations (both acquired and transmitted).**

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

Additional factors specific to LMIC that contribute to the emergence of HIV drug resistance

- Suboptimal Regimens
  - Thymidine analogues
  - Insufficient second-line and salvage regimens
- Failure of methods and resources to monitor viral loads
- Drug distribution (stock-outs)
- Perinatal PMTC rather than treating pregnant women with ART (option B+)

Summary

- The principles of HIV drug resistance are well established (Darwinian evolution).
- The mistakes and lessons learned in the developed world are being recapitulated in low and middle income countries.
- Prevention of further increases in drug resistance
  - Better regimens
  - Avoid stockouts
  - Monitor viral load
  - Interventions to improve adherence and reduced risk behaviors