Dr Charles Boucher

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COMPETING INTEREST OF FINANCIAL VALUE > £1,000:	
Speaker Name	**Statement**
Dr Charles Boucher	Dr Boucher acts in a Consultancy capacity for **(Merck, Abbvie, Viiv)** and as a speaker at company-sponsored events for **(BMS)**. He has (also) received personal grants for attending conferences from **(Janssen)** end/or has received a personal grant for research from **(Merck, Roche)**.
Date	**April 2013**

HIV drug resistance in the future : a clinical virologist's perspective

Charles Boucher
Erasmus Medical Center
Rotterdam, The Netherlands

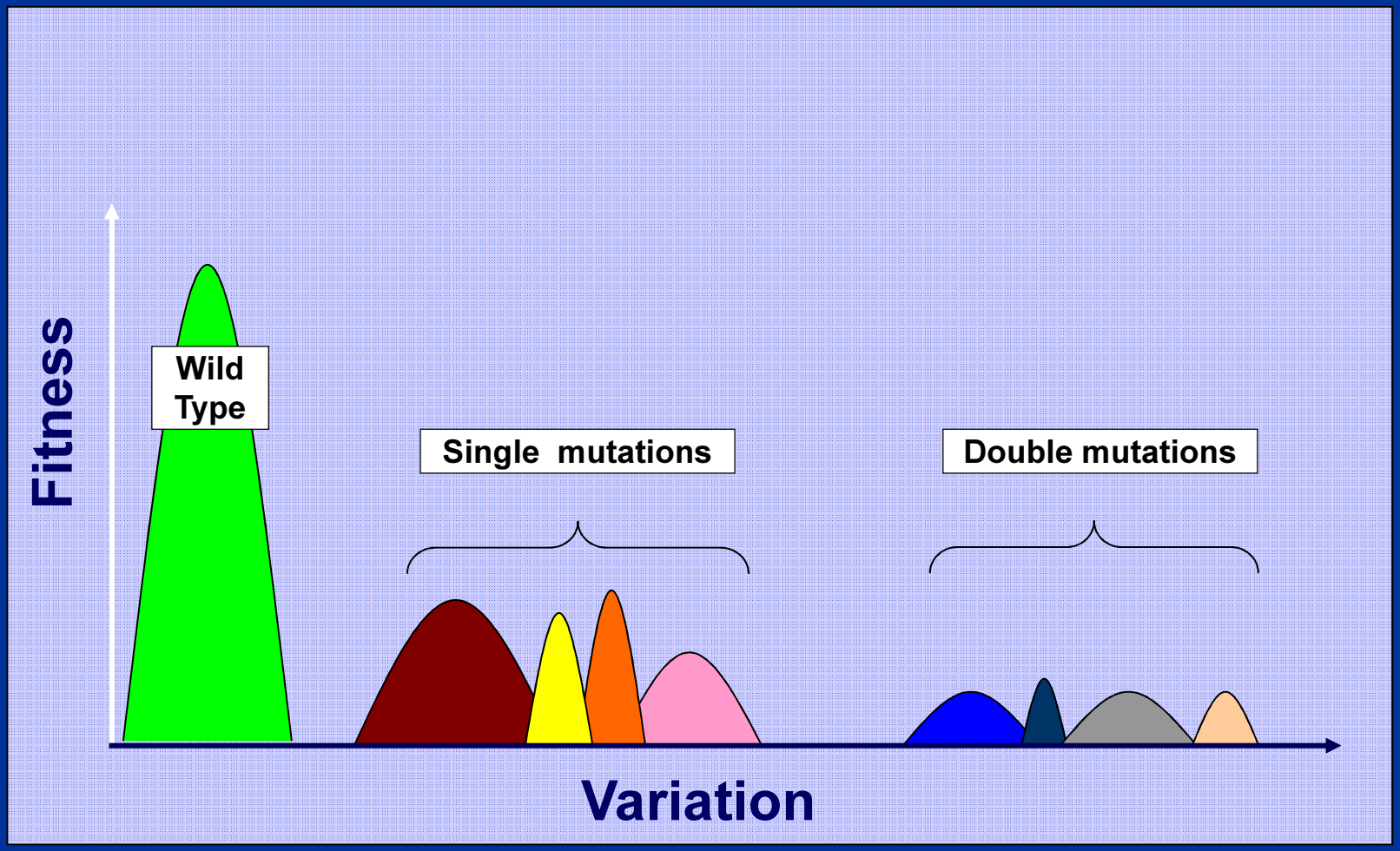
Predicting the future

- Biological factors driving the emergence, persistence and transmission of drug resistant viruses
- The current situation
- Prediction by models

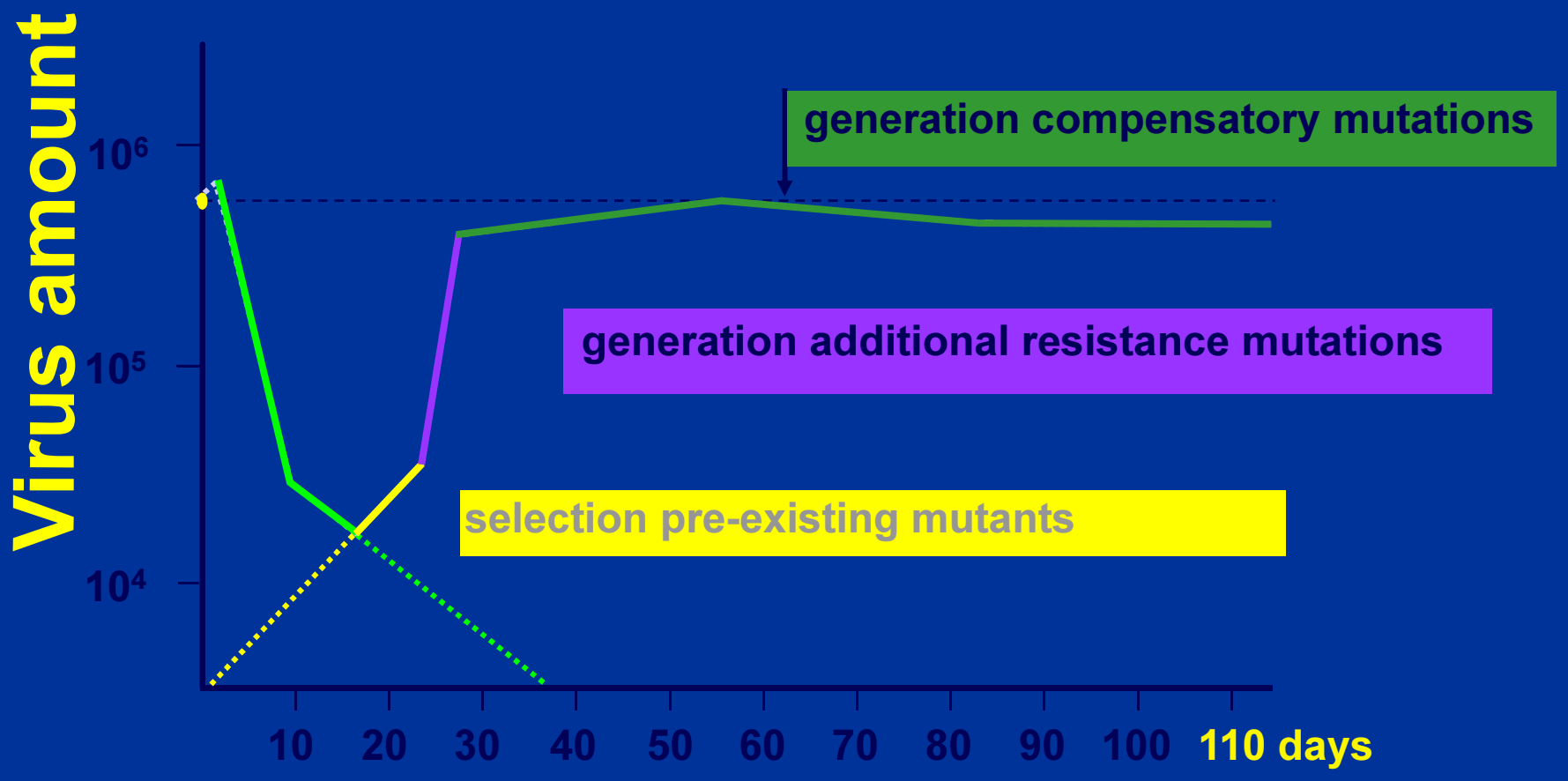
Worse case scenario

A truly (multi-class) drug resistant virus will be generated, which is as transmissible (or even more) and dominates the epidemic.

Viral quasispecies



Continuous genetic evolution

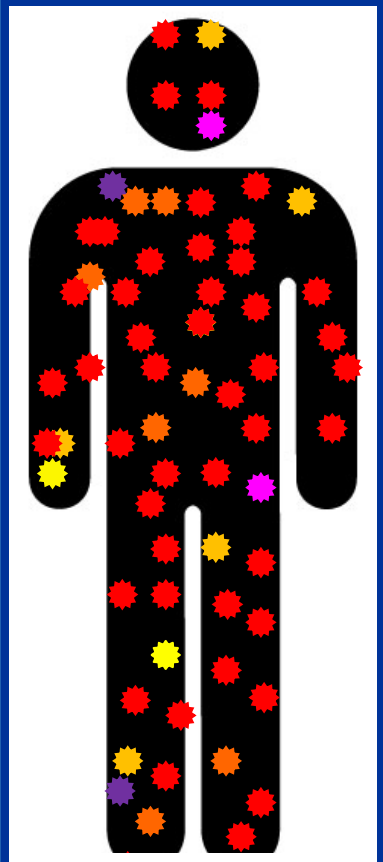


non suppressive therapy

Worse case scenario

A truly (multi-class) drug resistant virus will be generated, which is as transmissible (or even more) and dominates the epidemic.

Transmission of HIV drug resistance mutations



Treated patient
Multiple mutants

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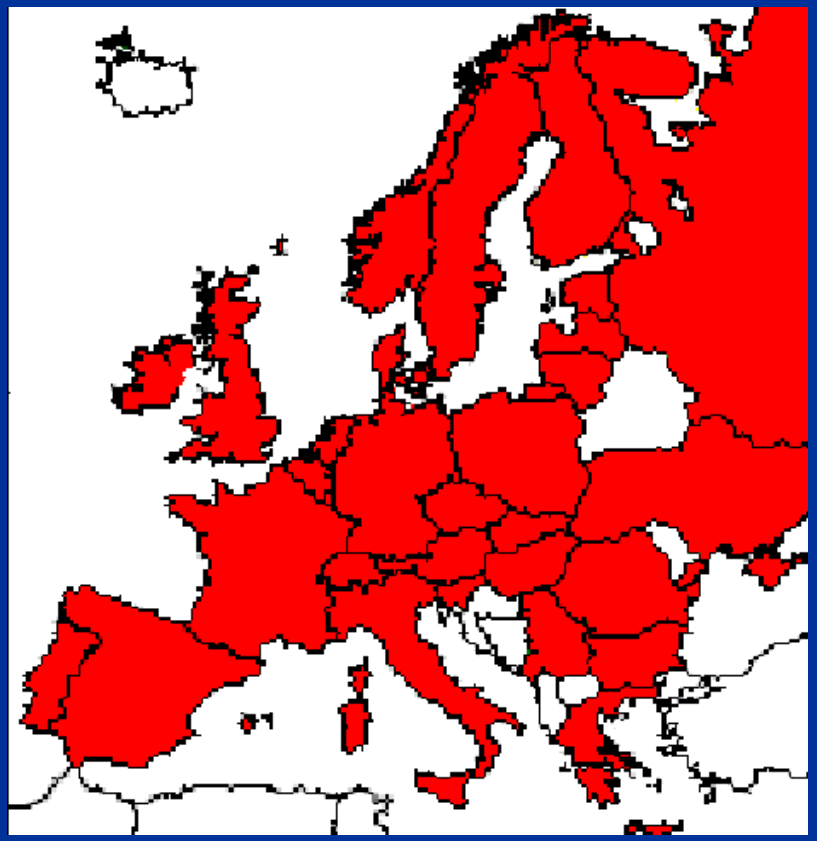
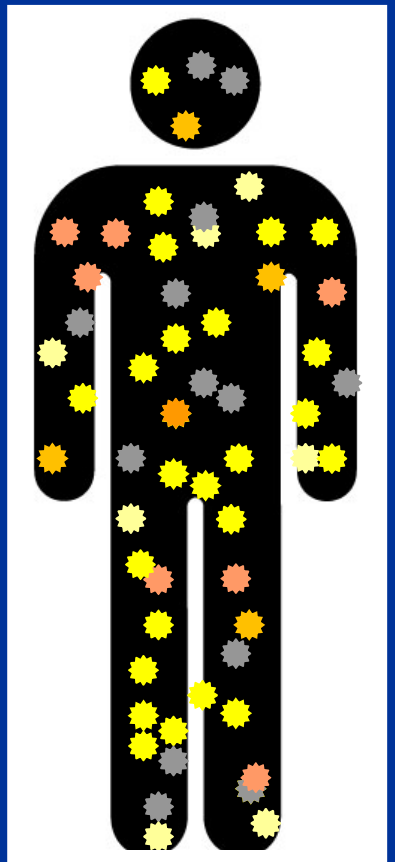
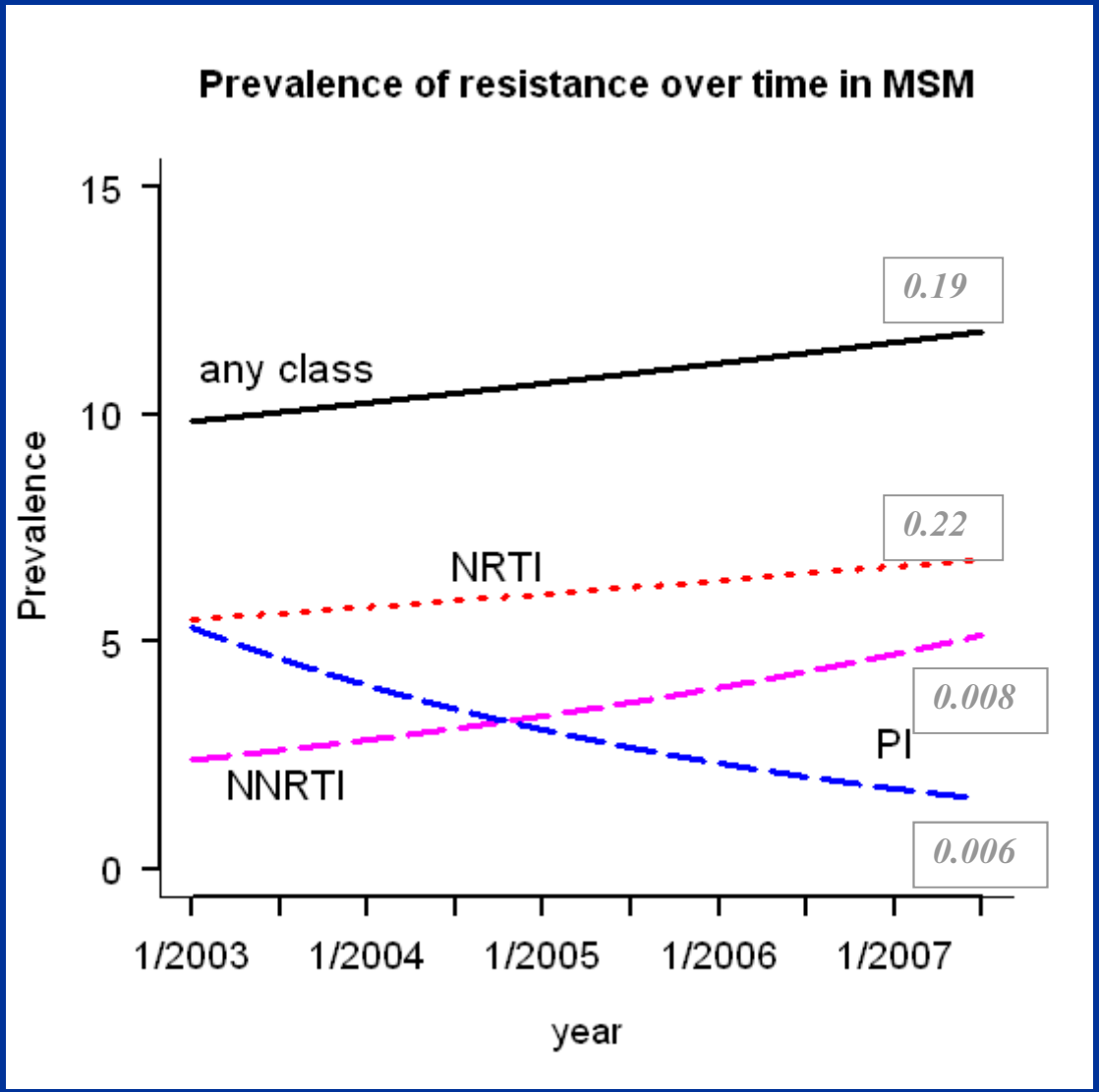




Diagnosed patient
Limited profile

Trends over time in MSM



TDRM patterns

	n (%)
NRTI-related mutations	
M41L	**73 (1.7)**
D67N	**16 (0.4)**
L210W	**27 (0.6)**
T215Y	**14 (0.3)**
T215rev	**118 (2.7)**
K219Q	**24 (0.6)**
NNRTI-related mutations	
K103N	**72 (1.7)**
G190A	**21 (0.5)**
PI –related mutations	
L90M	**10 (0.6)**

Paradox of transmitted drug resistant viruses

- Continous circulation/transmission of viruses with drug resistance mutations , which have been repoted to reduce viral replication. (transmission)

- Drug resistance mutations found in new patients have not been selected by the use of modern HAART regimens (represent onwards transmission)

Persist study

33 patients:

- 4 countries: the Netherlands, Belgium, Slovenia, Greece
- 57 resistance mutations (IAS list)
- Diagnosed: 2001-2008
- HIV-RNA: 4.6log (SPREAD: 4.8log)
- CD4 count: 617 cells/mm^3 (SPREAD: 343)

M. Pingen et al, preliminary data.

Transmitted drug resistance profiles – one year

NRTI	NNRTI	PI
M41L (3x)	K103N (2x)	M46L (5x)
T69TP	K103Q	L90M
L210LS	V179I	
T215D (2x)	Y181C	
T215S	G190A	
T215IT		
K219N	Complex	
D67N T215C	RT: D67G **Y181CY** T215C K219E	
D67G T215C K219E (3x)	PR: **G73S** L90M RT: K103N	
M41L T69S T210E T215ST (2x)	PR: **F53FL** I54V V82A L90M RT: M41L D67N L210W T215D	

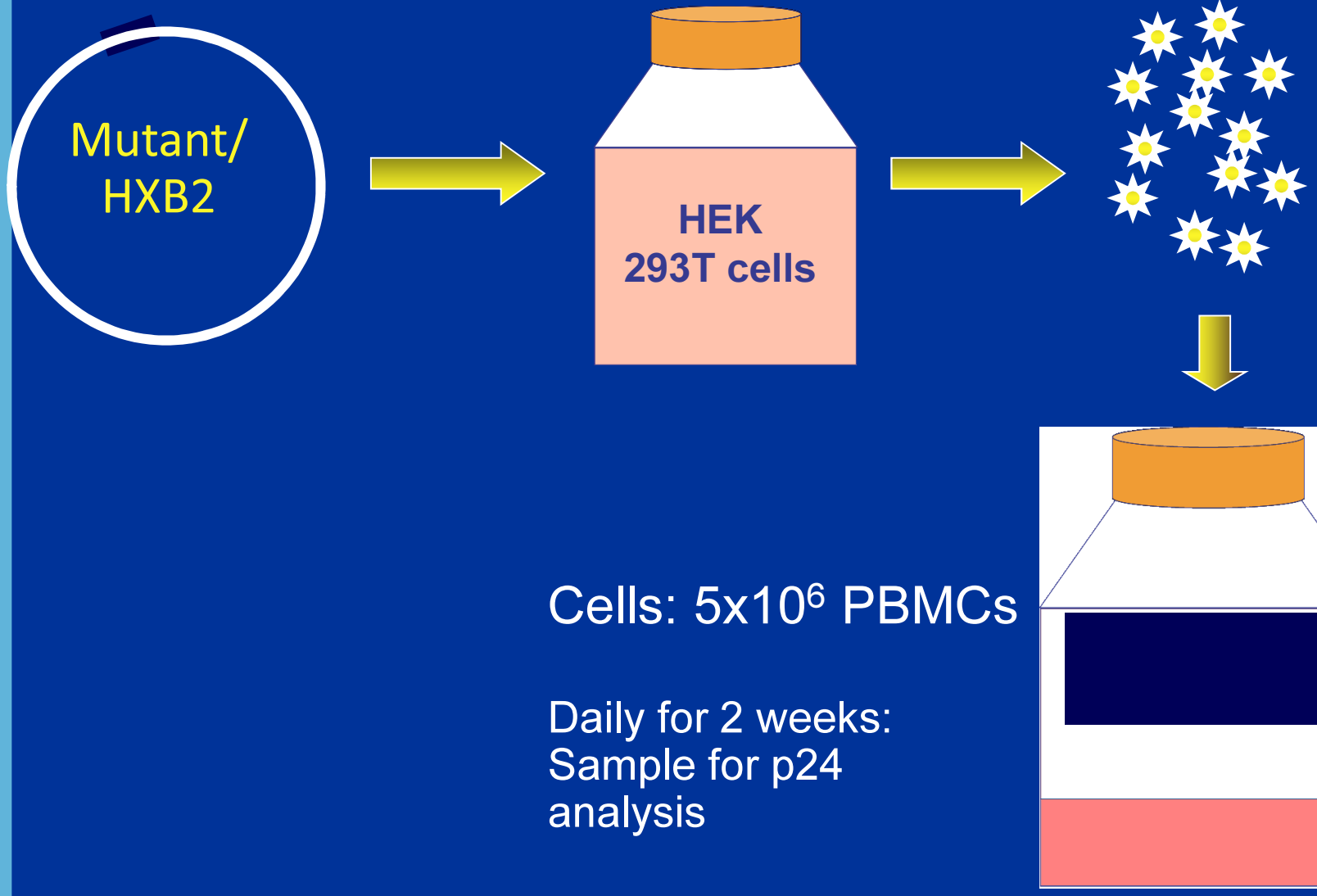
M. Pingen et al, preliminary data.

Virus panels

Site-directed mutants	Patient-derived virus
HXB2wt	
M184V	
M184I	
M184T	
M41L	pM41L pM41L-T69S-L210W-T215S
K103N	pK103N
M46L	pM46L
M46I	pM46I
L90M	pL90M pI54V-V82A-L90M

M. Pingen et al

Materials & Methods



Cells: $5x10^6$ PBMCs

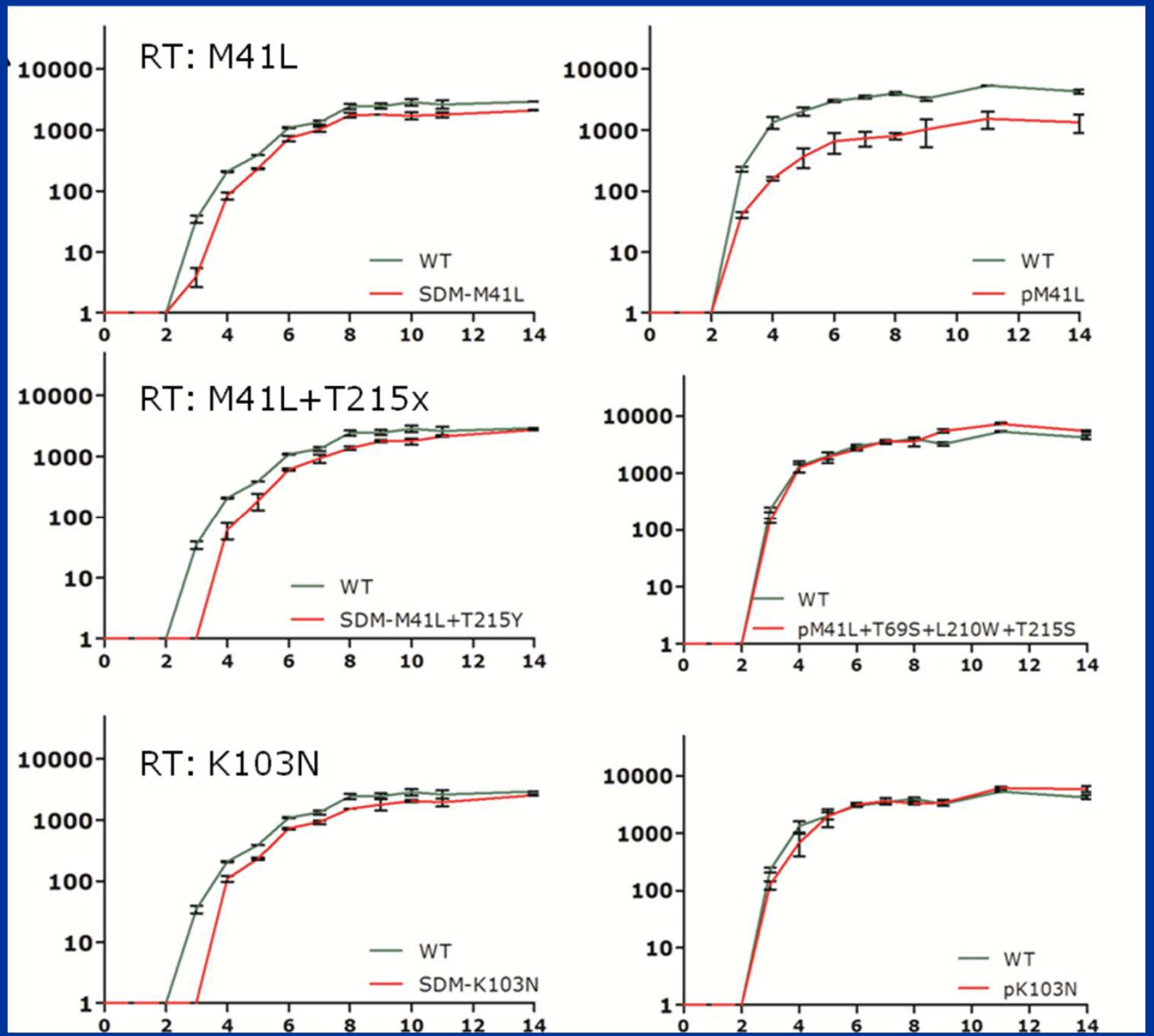
Daily for 2 weeks:
Sample for p24
analysis

M. Pingen et al, preliminary data.


10.
11.
dnRT
12.
dnRT
13.
14.
15.
Hxb2 nR
16.
P103N
Hxb2 nRT
17.
103N
18.
Hxb2 nRT

SDM viruses

Patient derived virus

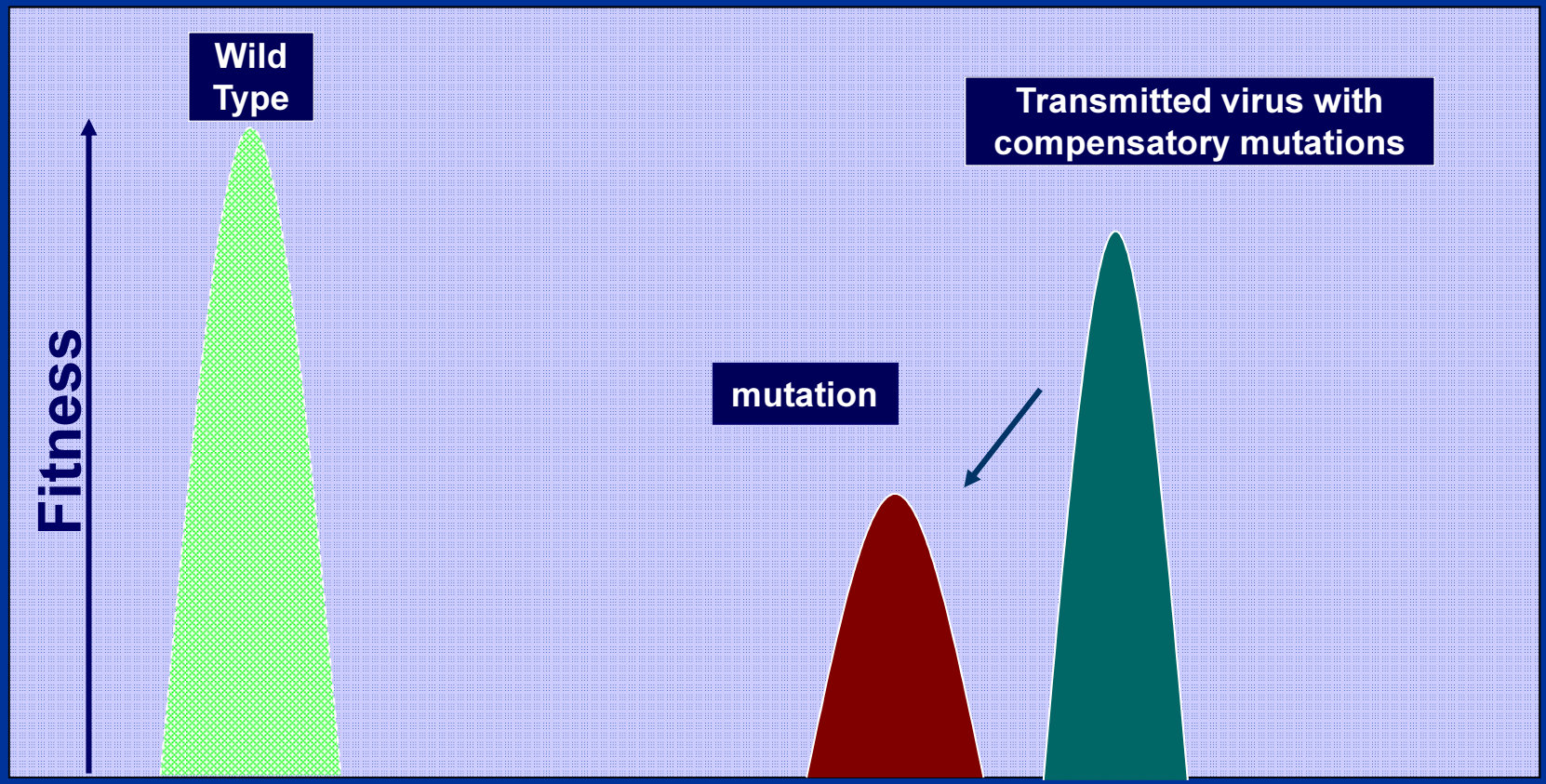


Ng P24/ml

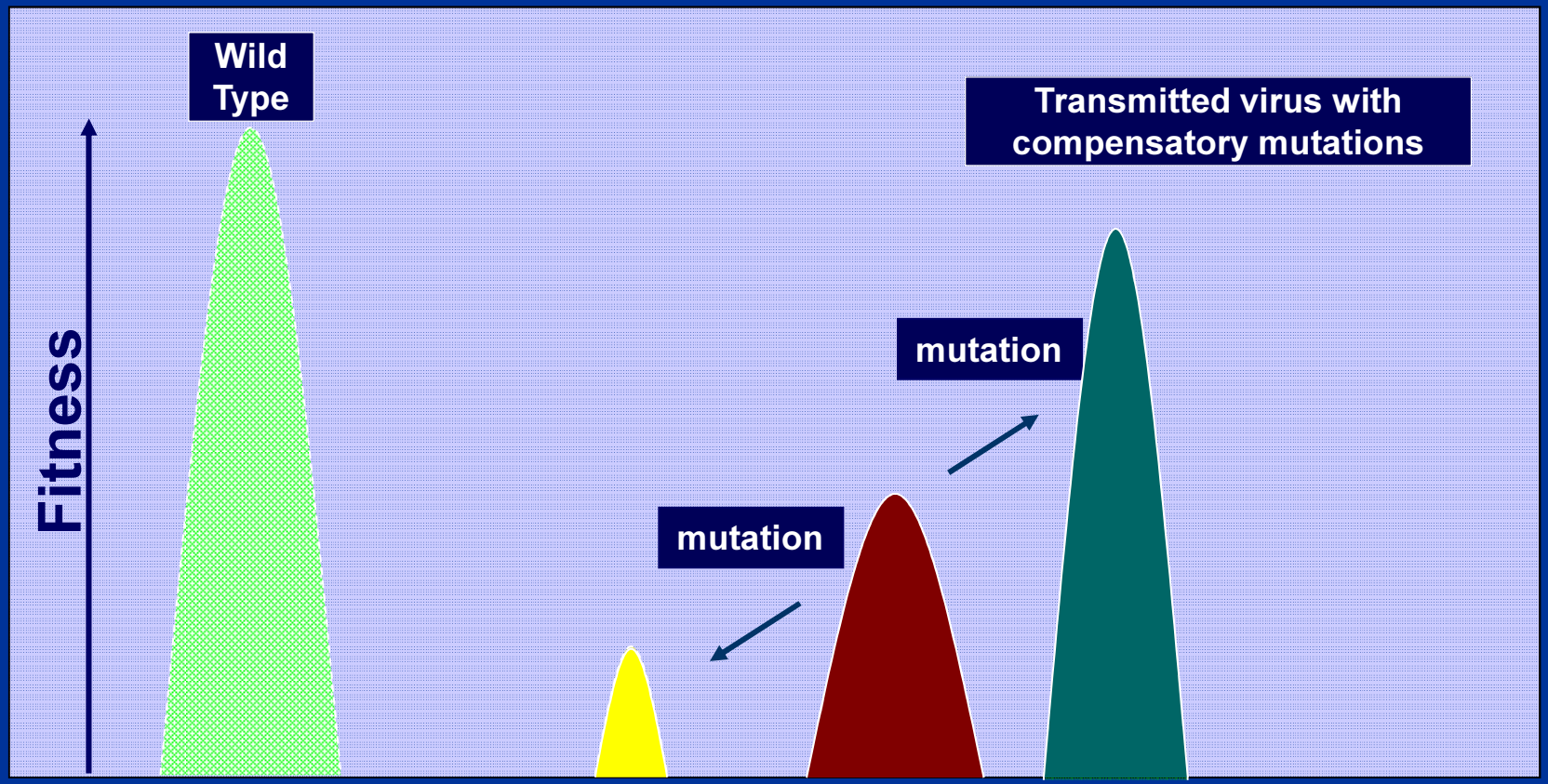
Days post infection

M. Pingen et al, preliminary data.

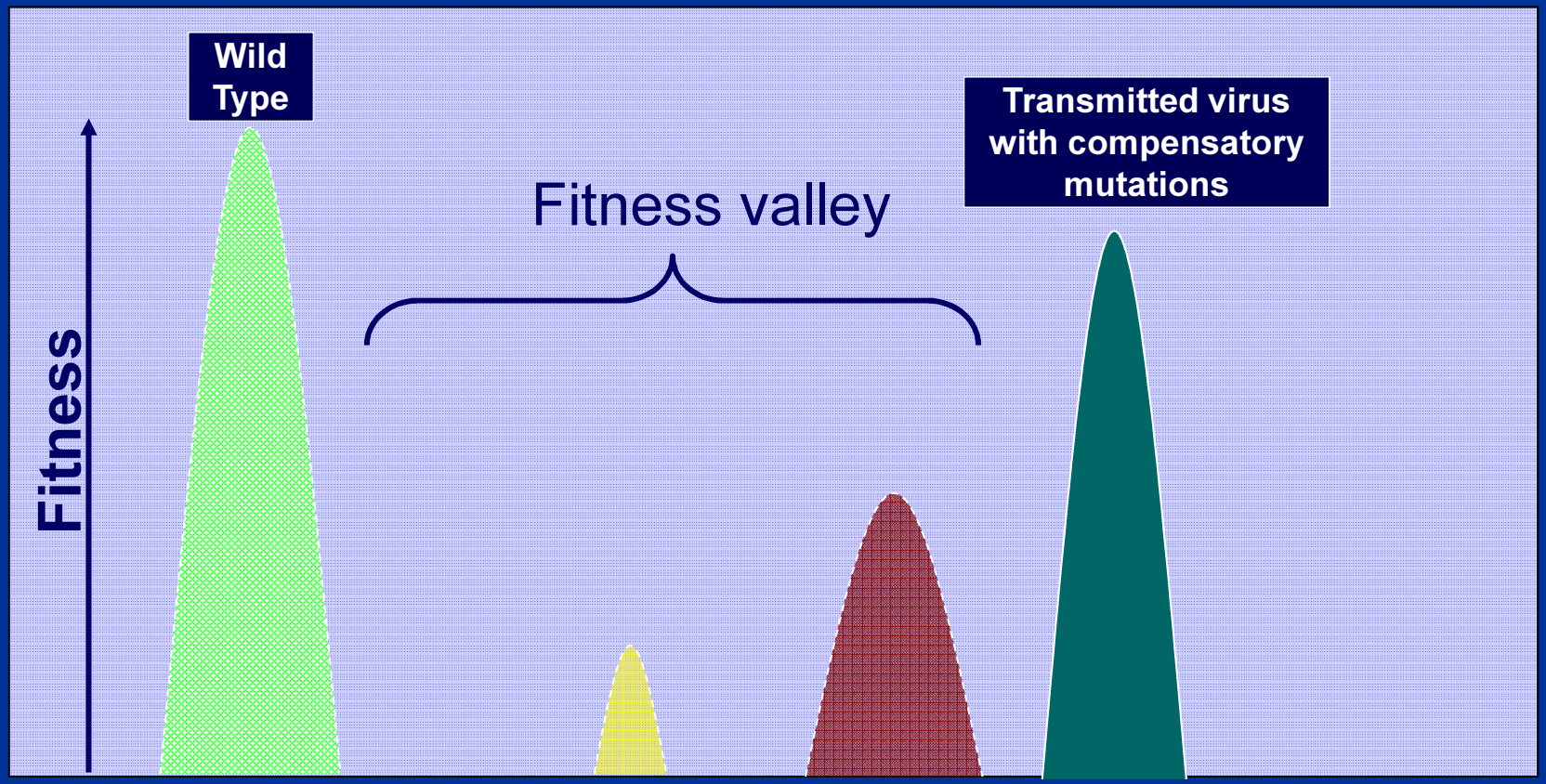
Compensatory fixation: a fitness valley blocks reversion to wild type



Compensatory fixation: a fitness valley blocks reversion to wild type



Compensatory fixation: a fitness valley blocks reversion to wild type



Continuous replication of HIV under non-suppressive therapy can generate drug resistant viruses with a compensated fenotype resulting in wild type level replication (transmission) and (compensatory) fixation leading to onwards transmission and thus fixation in (a proportion of) the epidemic

Worse case scenario

A truly (multi-class) drug resistant virus will be generated, which is as transmissible (or even more) and dominates the epidemic.

Should we fear a dramatic increase in HIVDR?

VIEWPOINT

Preventing antiretroviral anarchy in sub-Saharan Africa

A D Harries, D S Nyangulu, N J Hargreaves, O Kaluwa, F M Salaniponi

Combination antiretroviral therapy has dramatically improved the survival of patients living with HIV and AIDS in industrialised countries of the world. Despite this enormous benefit, there are some major problems and obstacles to be overcome.[1] Treatment of HIV-infection is likely to be lifelong.[2] Unfortunately, many HIV-infected individuals cannot tolerate the toxic effects of the drugs, or have difficulty complying with treatment which involves large numbers of pills and complicated dosing schedules. Poor adherence to treatment leads to the emergence of drug-resistant viral strains that need new combinations of drugs or new drugs altogether.

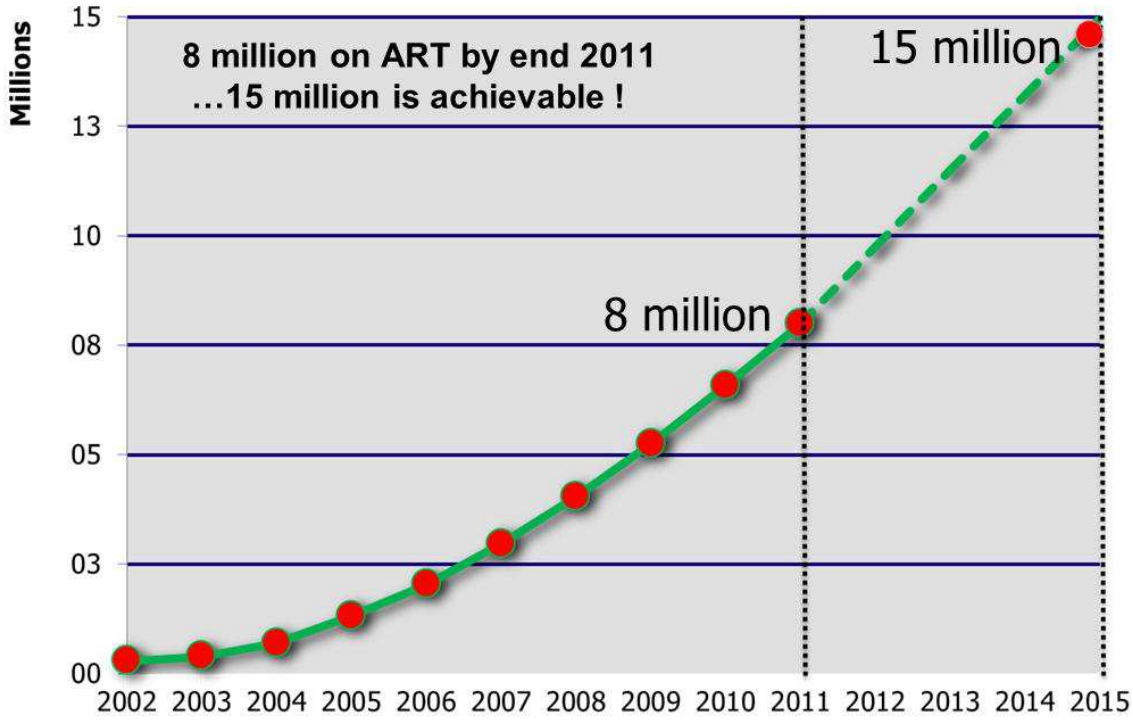
"Widespread, unregulated access to ARV drugs in sub-Saharan Africa could lead to the rapid emergence of resistant viral strains, spelling doom for the individual, curtailing future treatment options, and leading to transmission of resistant virus."

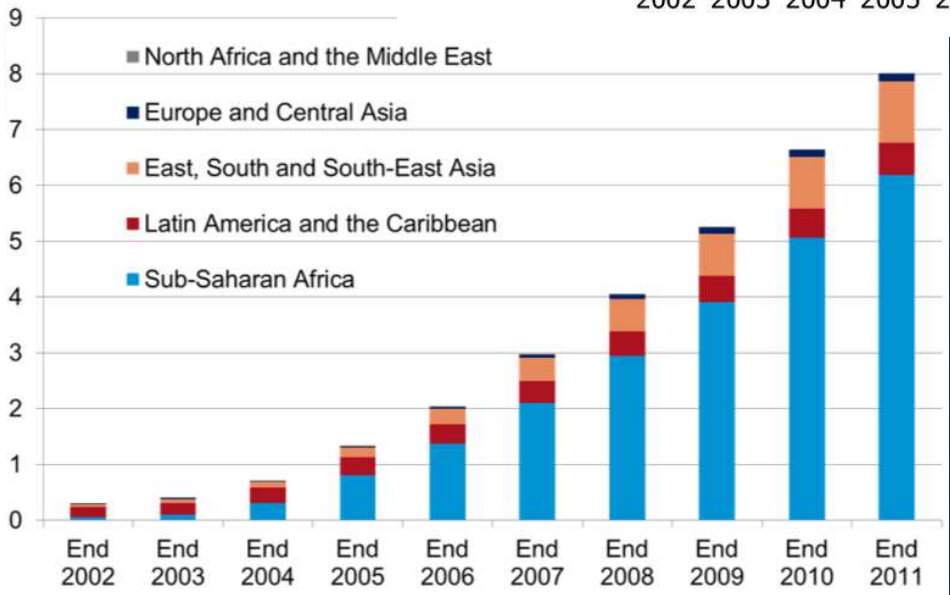
*"If compliance and careful follow-up of patients is not achieved, **we will see a dramatic increase in multidrug-resistant HIV mutants…**"*

Robert C. Gallo and Luc Montagnier. Prospects for the Future. Science 2002

Global scale-up of ART

WHO public health model

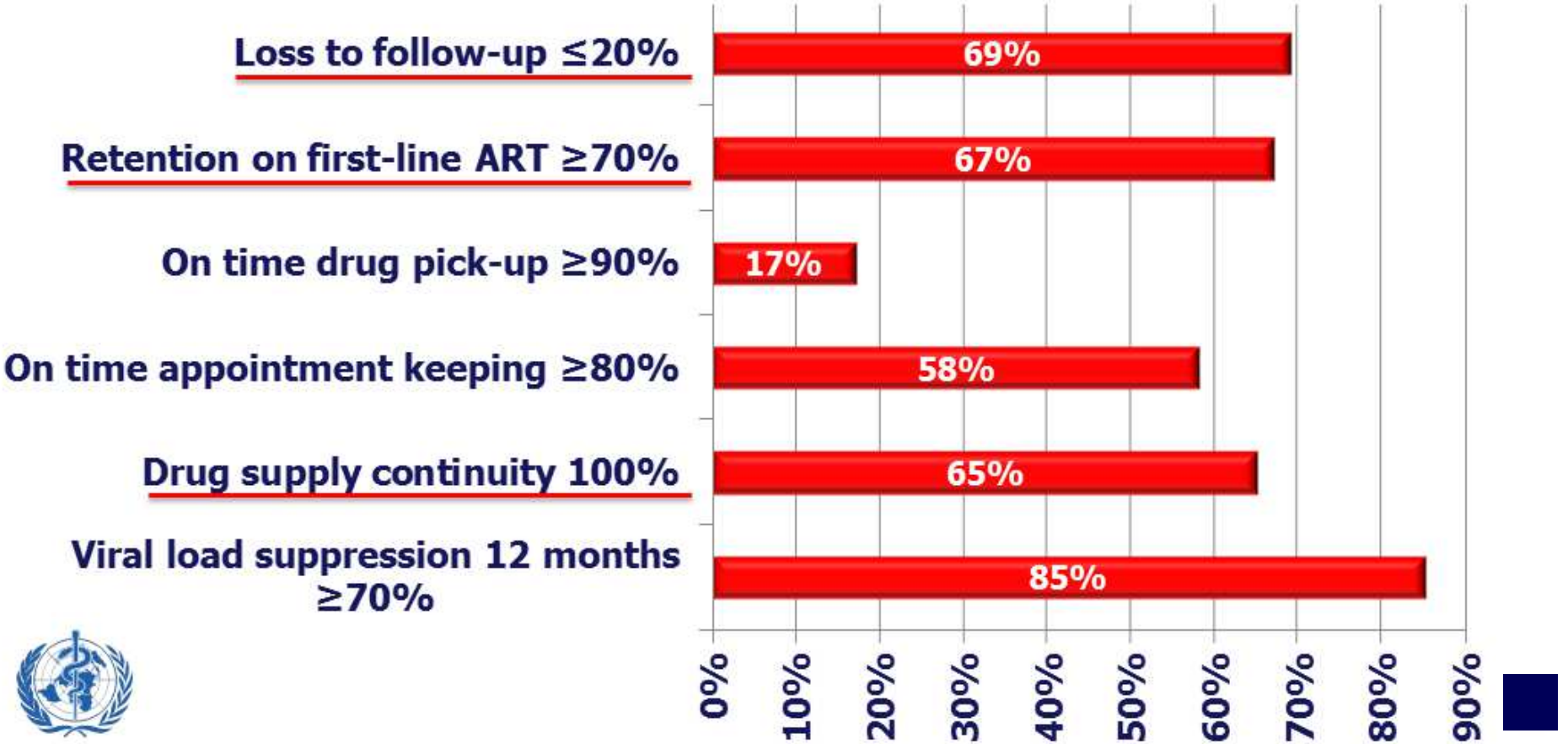




- Standard ART regimens
- Restricted drug options
- Limited lab monitoring
- Decentralized service delivery and task shifting

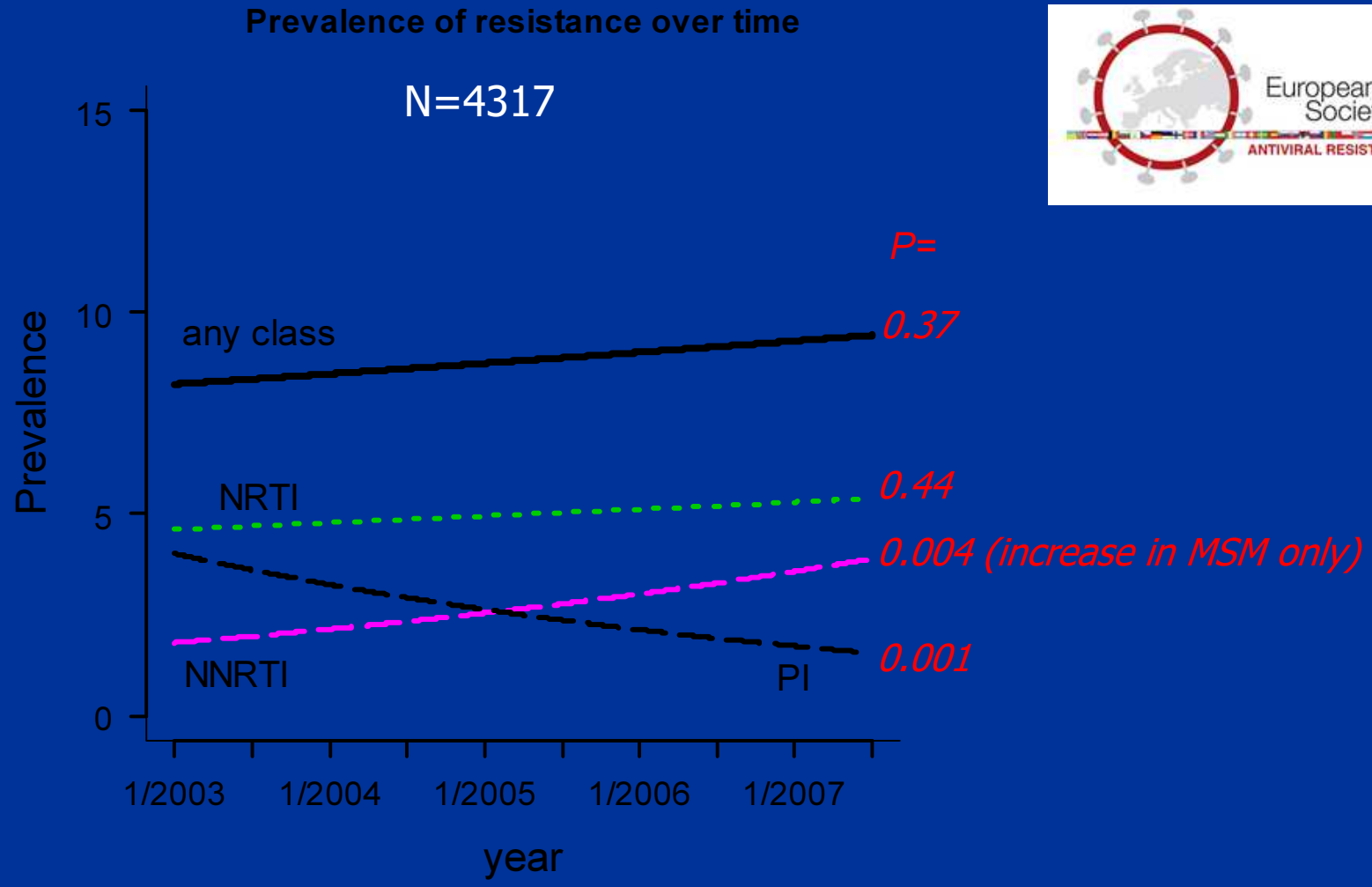
HIVDR early Warning Indicators (EWI) Proportion of Clinics Achieving WHO-Recommended Targets

2107 clinics (2004-2009), >131,000 people, >50 countries



WHO HIV Drug Resistance Report 2012

Transmitted HIVDR in MSM and HSX is stabilizing in Europe



European Society for ANTIVIRAL RESISTANCE

WHO 2009 Surveillance Drug Resistance Mutation list

Wensing, on behalf of SPREAD
eacs-conference Oct 2011

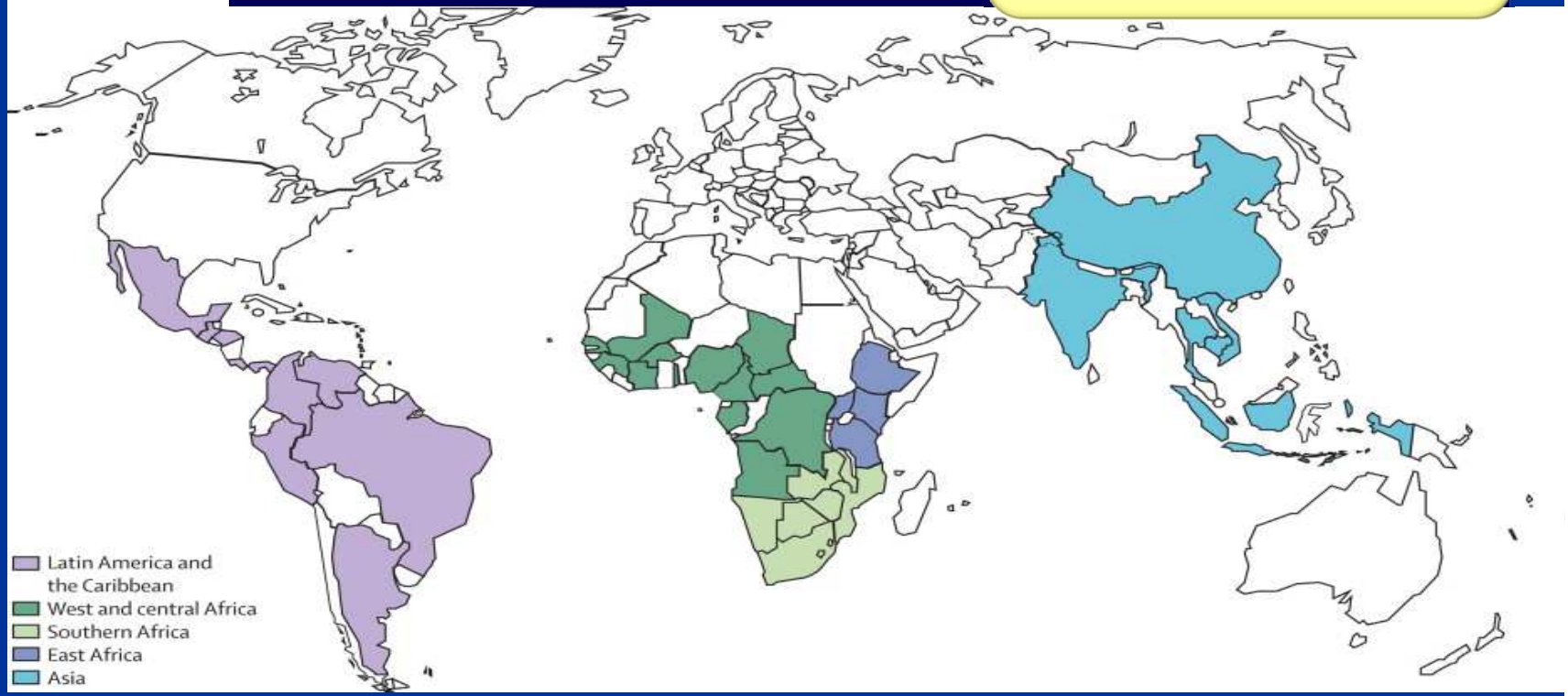
Global trends in antiretroviral resistance in treatment-naive individuals with HIV after rollout of antiretroviral treatment in resource-limited settings: a global collaborative study and meta-regression analysis

Ravindra K Gupta, Michael R Jordan, Binta J Sultan, Andrew Hill, Daniel H J Davis, John Gregson, Anthony W Sawyer, Raph L Hamers, Nicaise Ndembi, Deenan Pillay, Silvia Bertagnolio

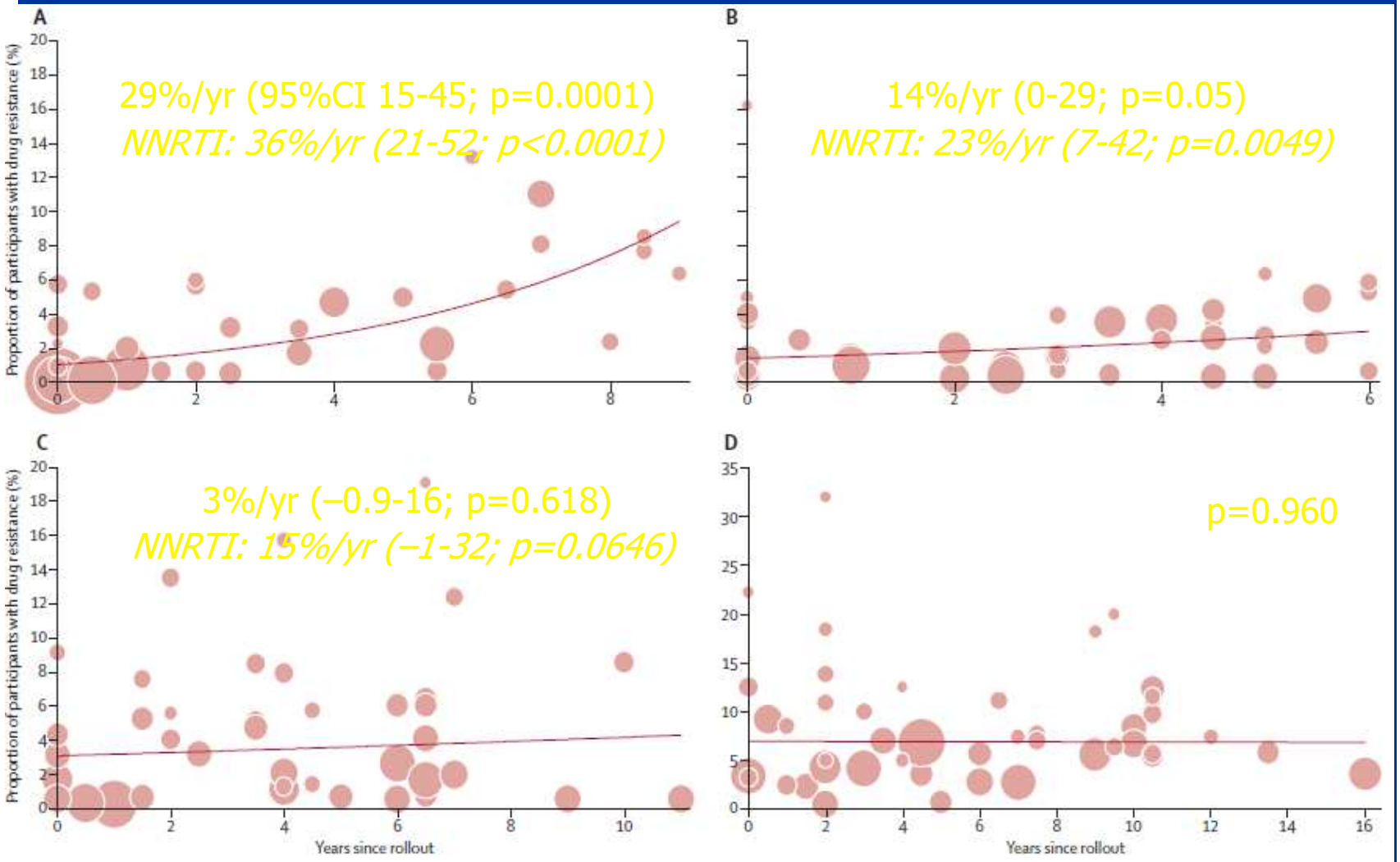
Lancet 2012; 380: 1250–58

Published Online
July 23, 2012
http://dx.doi.org/10.1016/S0140-6736(12)61038-1

26,102 patients from 191 datasets from 42 countries in Africa, Asia, Latin America



Prevalence of HIVDR in ARV-naïve individuals, by time since ARV rollout



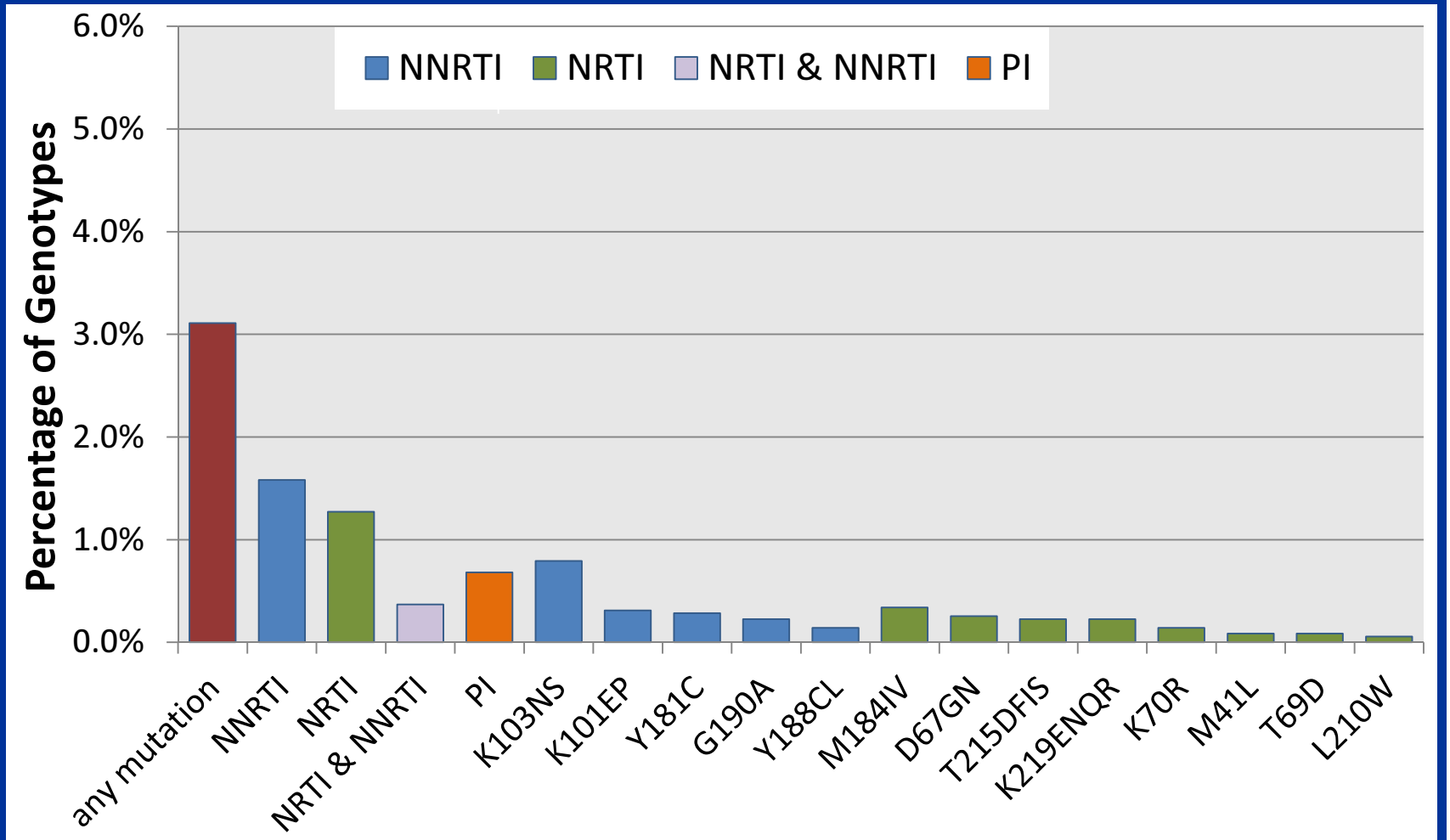
Every circle is a study and the size of the circle is proportional to the precision of the estimate from the individual study

Gupta et al. Lancet 2012

WHO transmitted HIVDR surveys

Mutation Prevalence

n=3588, pooled analysis from 82 surveys

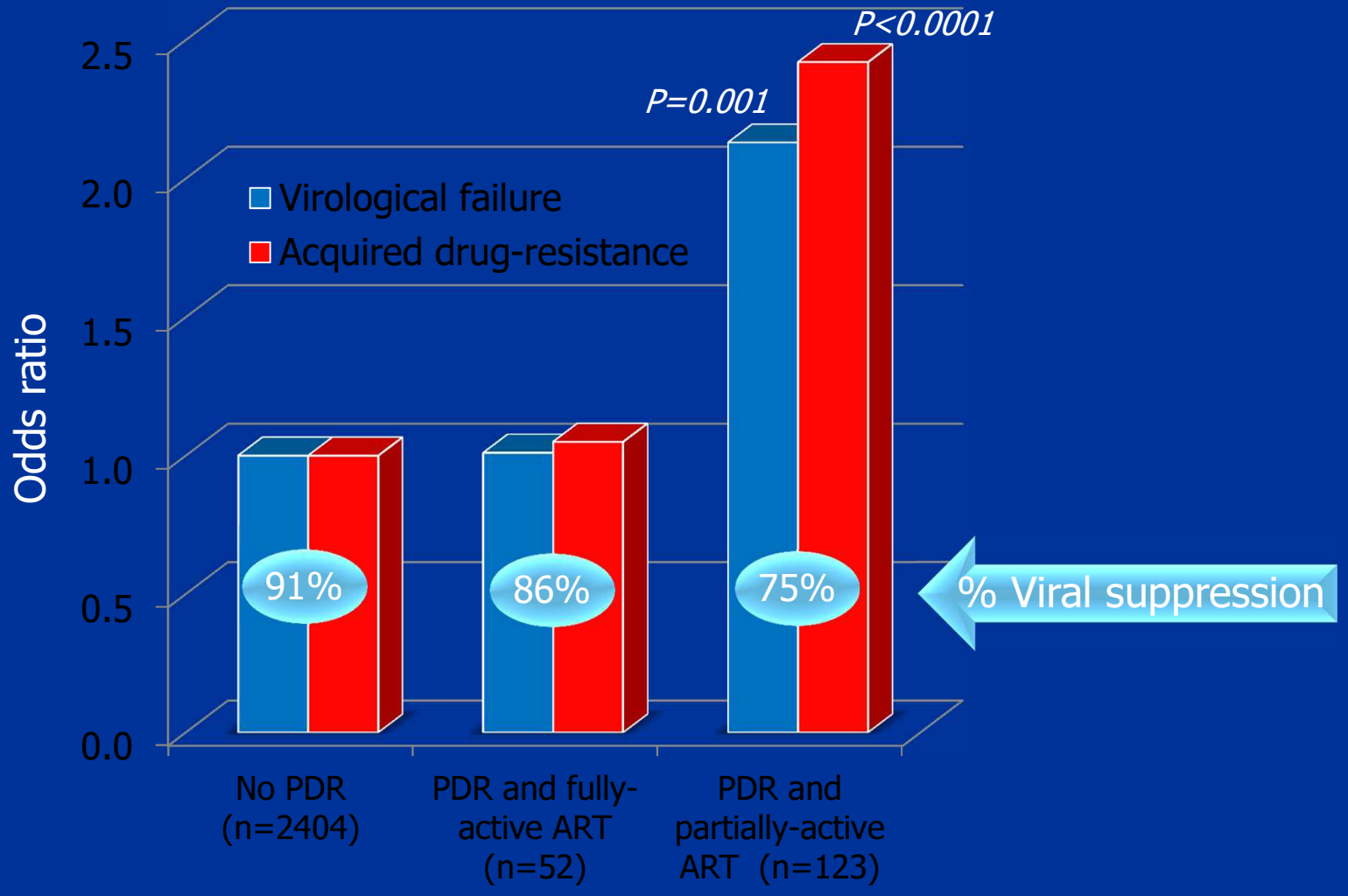


WHO 2009 Surveillance Drug Resistance Mutation list

WHO HIV Drug Resistance Report 2012

Pretherapy HIVDR doubles 1st year risk of VF and acquired HIVDR

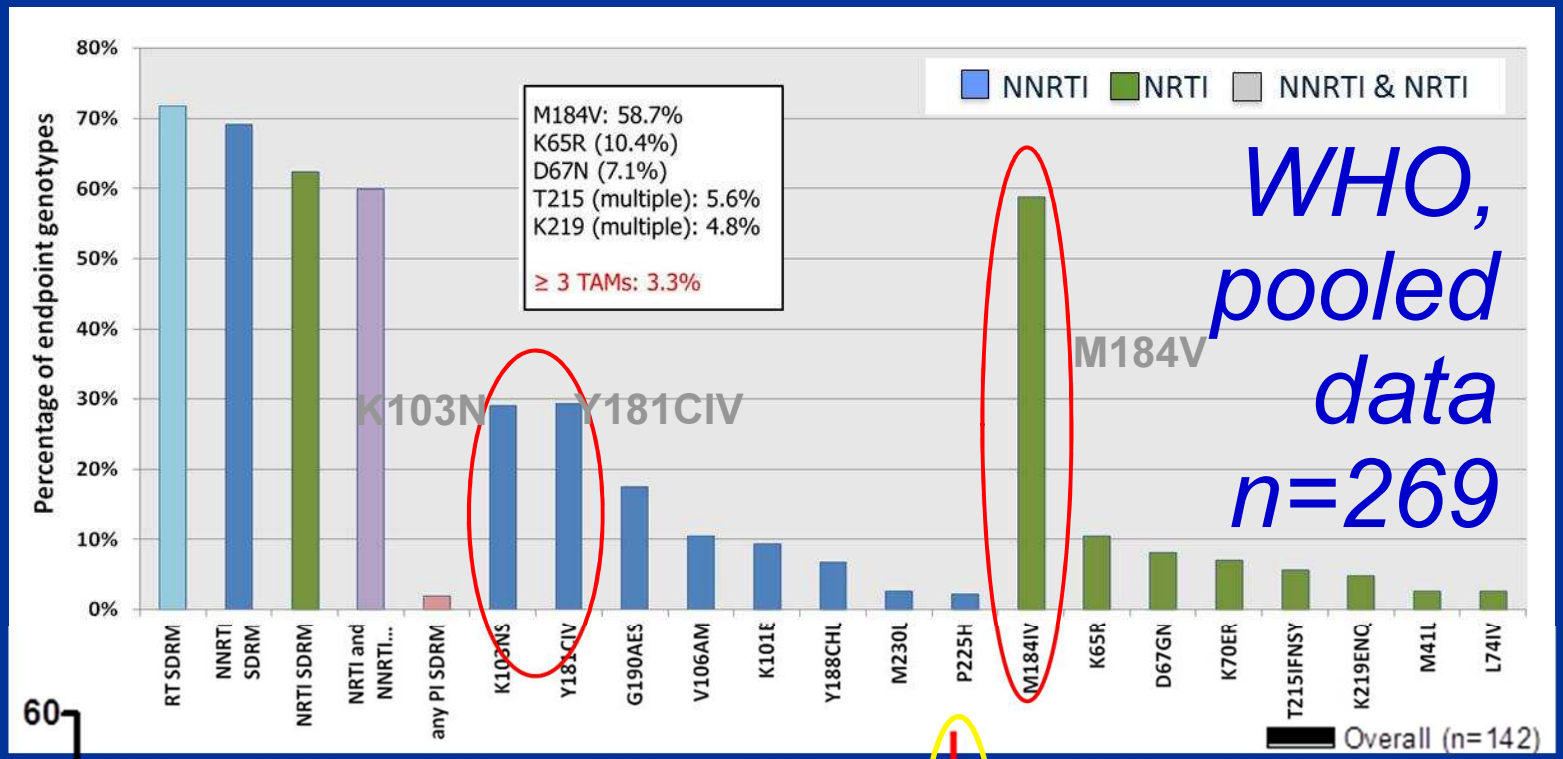
PASER-M cohort in 6 African countries

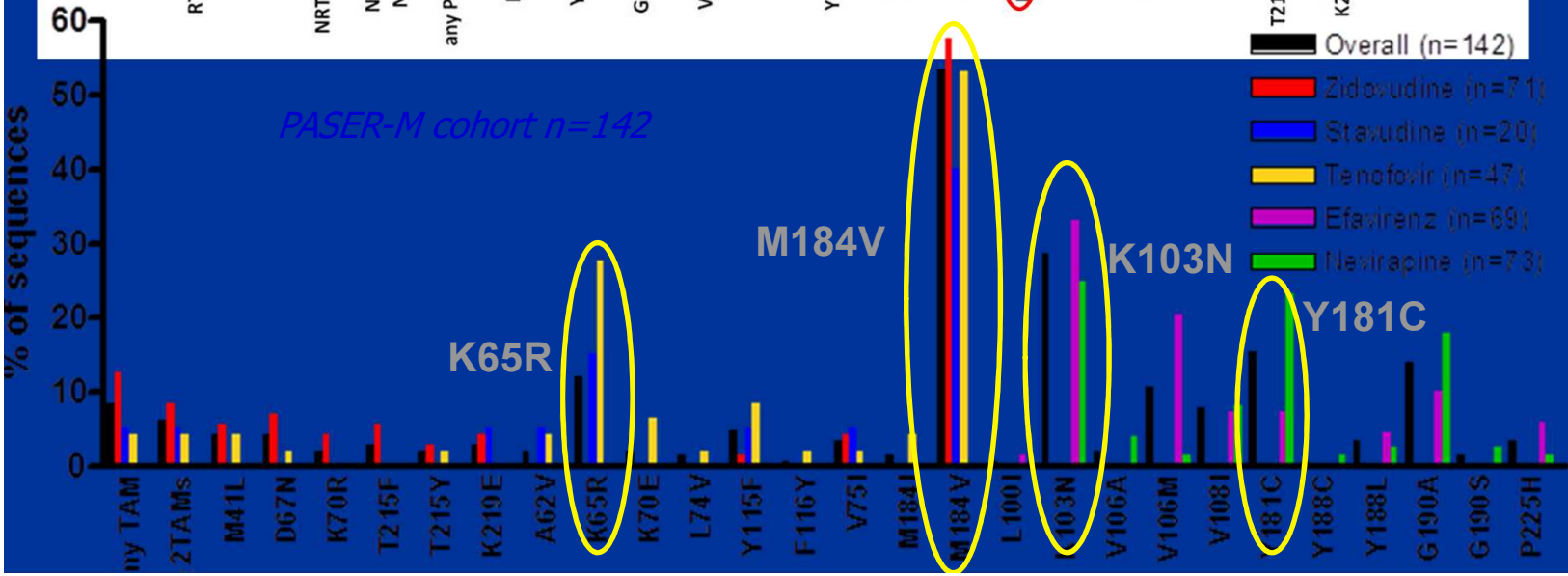


Multivariate analysis adjusted for sex, age, calendar year, WHO clinical stage, BMI, pretherapy HIVRNA and CD4, prior ARV use, type of NRTI and NNRTI.

Hamers et al. Lancet Inf Dis 2012

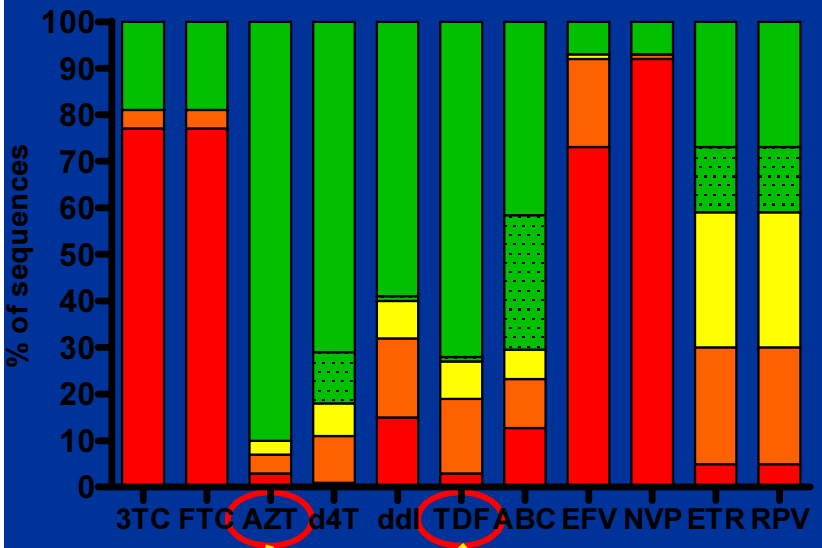
Acquired HIVDR mutations in people failing ART at 12 Months from LMIC

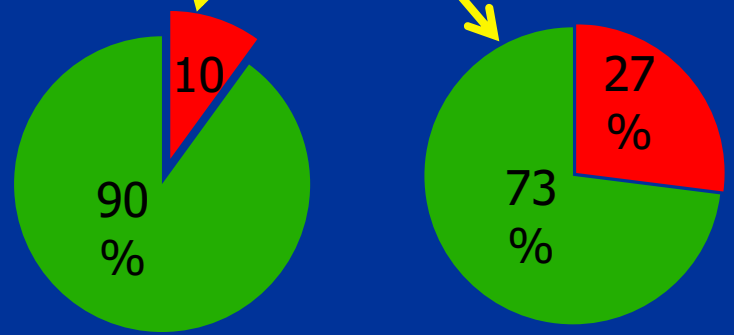




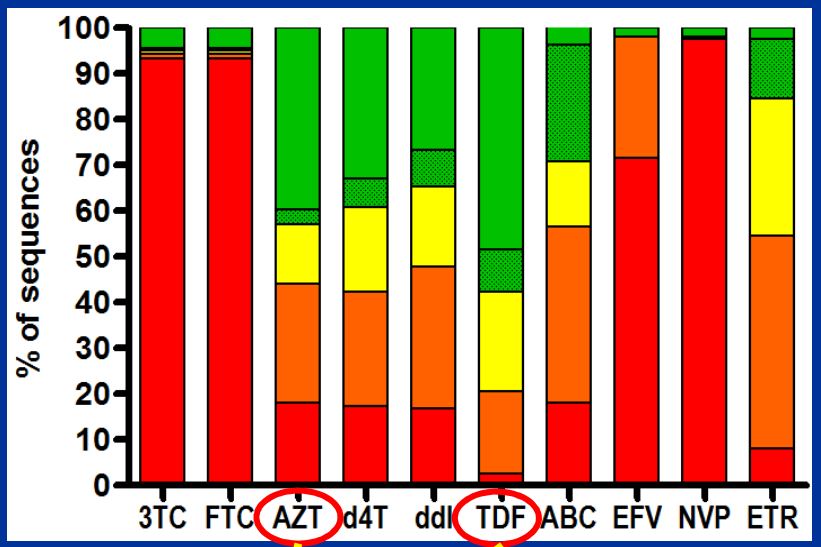
Lack of VL monitoring leads to loss of drug susceptibility

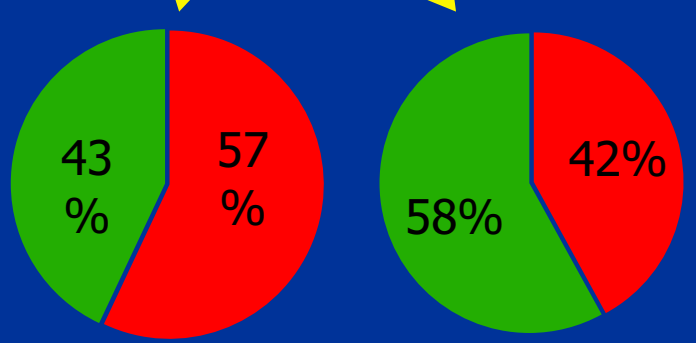
Cohort 1 (n=100)
Virological failure by routine pVL test, 12 mo ART





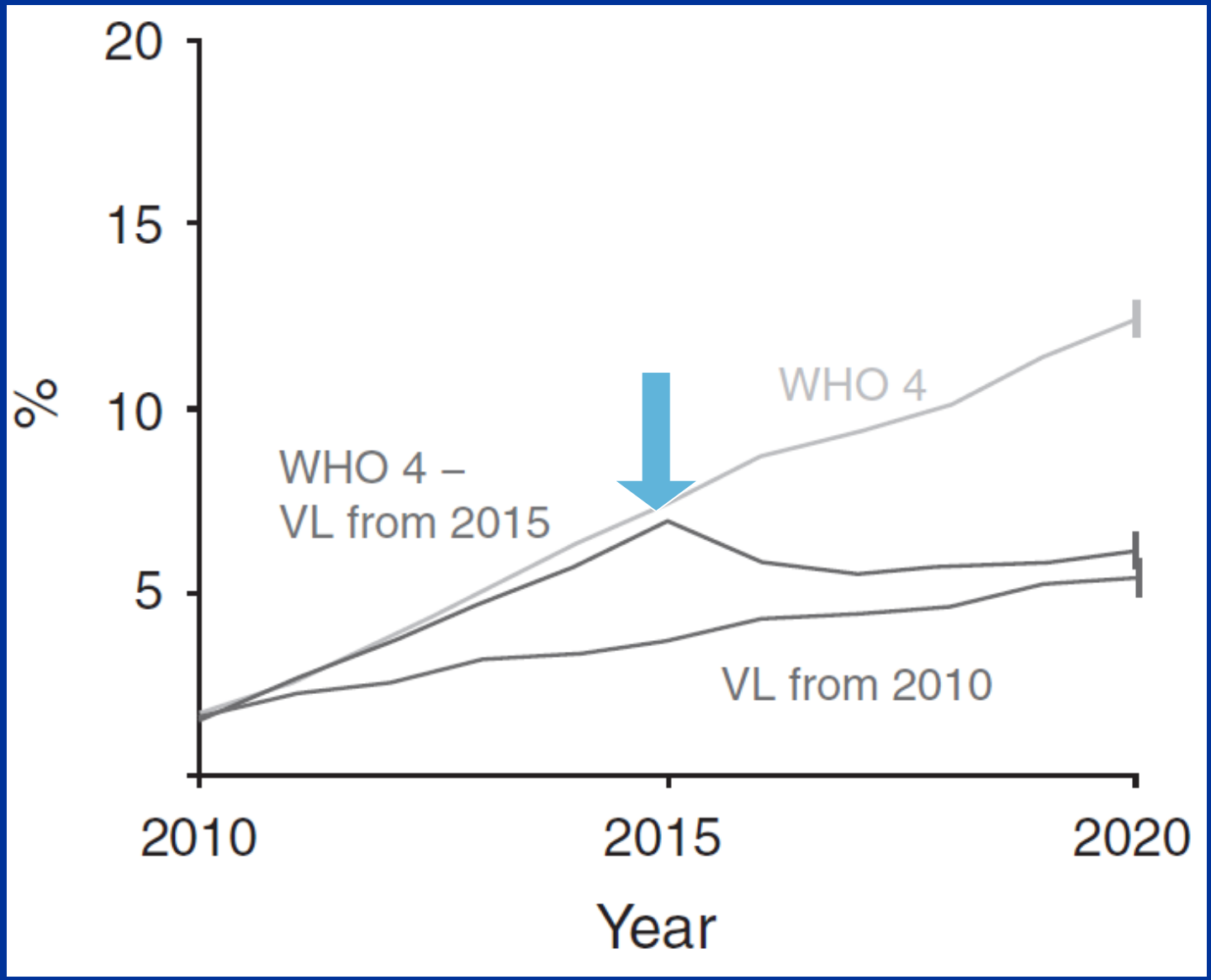
Cohort 2 (n=161)
Clinico-immunological failure, 26 mo ART





Hamers CID12; Sigaloff JID12

TDR reduced by implementing routine pVL monitoring to guide switches



Phillips A et al. AIDS 2011

Earlier treatment of HIV and transmitted HIV drug resistance in Sub-Saharan Africa

Brooke Nichols
Department of Virology
Erasmus MC
Rotterdam, The Netherlands

HIVLimited availability treatment

- Treating with three different drugs from two different classes is necessary, else resistance will develop
- In sub-Saharan Africa, limited HIV treatment regimens are available
  - Zidovudine-based (+lamivudine +NNRTI)
  - Tenofovir-based (+lamivudine +NNRTI)
  - A boosted protease inhibitor + 2 NRTIs

Potential issues with earlier treatment

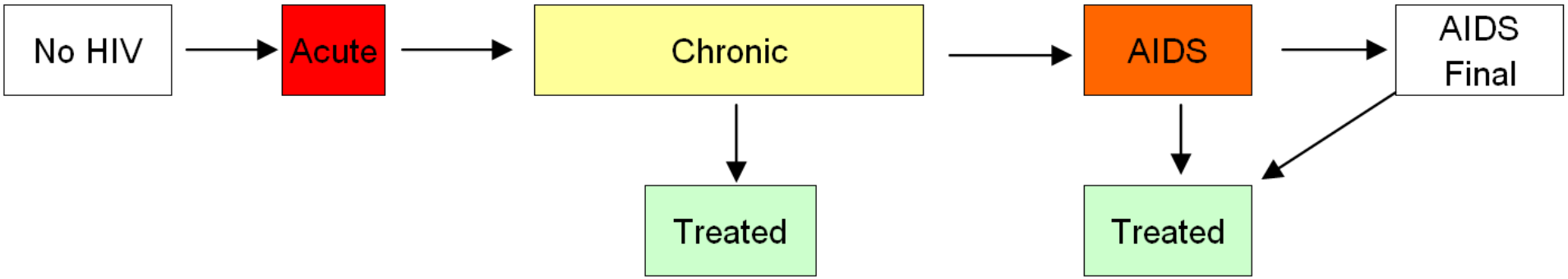
- Resource limited settings
  - Already stretched thin, let alone with additional monitoring tests to detect drug resistance
- Viral load assays frequently not available
  - Expensive!
  - Without viral load assays, resistance emerges more quickly (Nichols J Intern Med 2011)
- Earlier treatment may also have adherence issues
  - Therefore- more resistance?

Kampala, Uganda

- Urban, government clinic
- PASER-S: Surveillance 2010
  - Transmitted drug resistance prevalence: 8.6%

- PASER-M: Monitoring 2007-8 enrollment
  - 10% acquired drug resistance after 12 months on zidovudine-based regimen
  - 6% acquired drug resistance after 12 months on tenofovir-based regimen
    - 40% of patients on tenofovir-based regimen

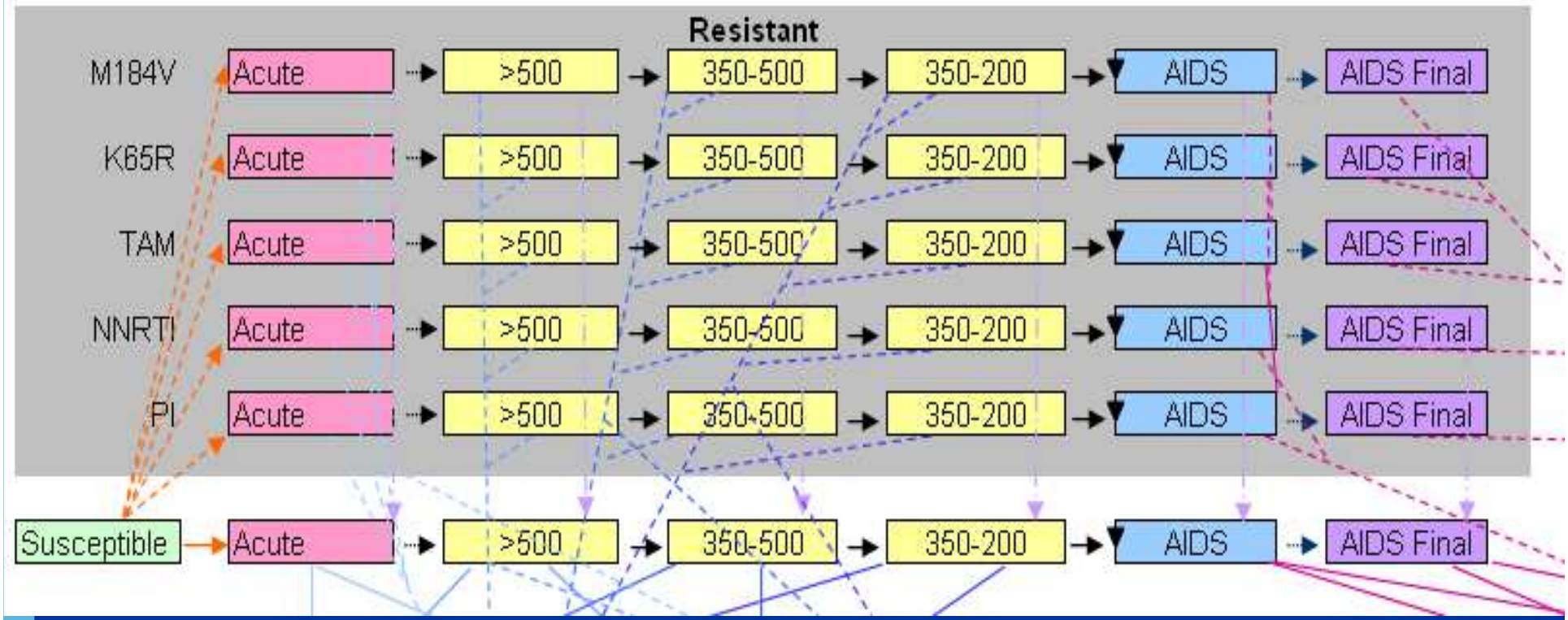
The Model: Simplified



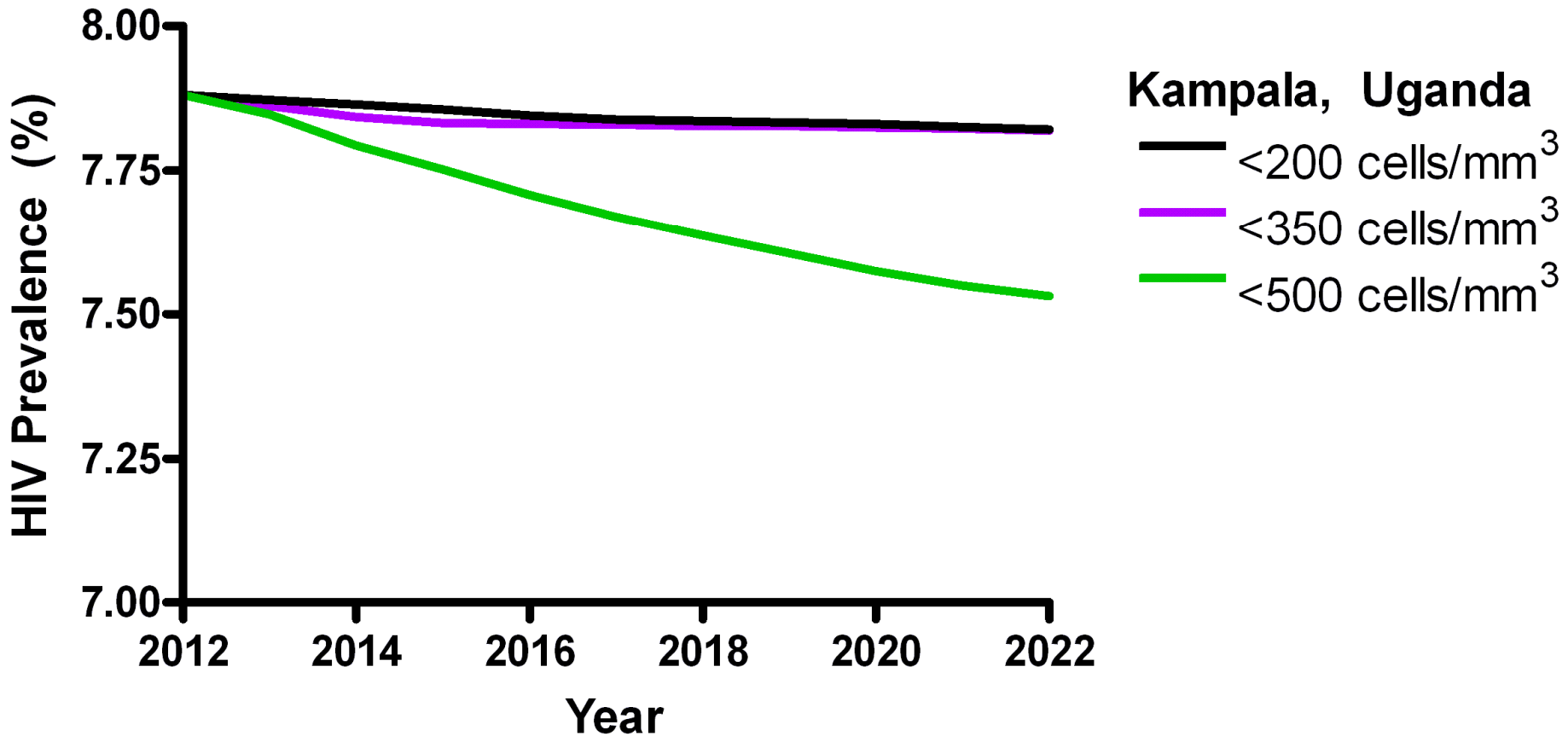
Model calibrated to Kampala epidemic & Mombasa epidemic separately

Key model features

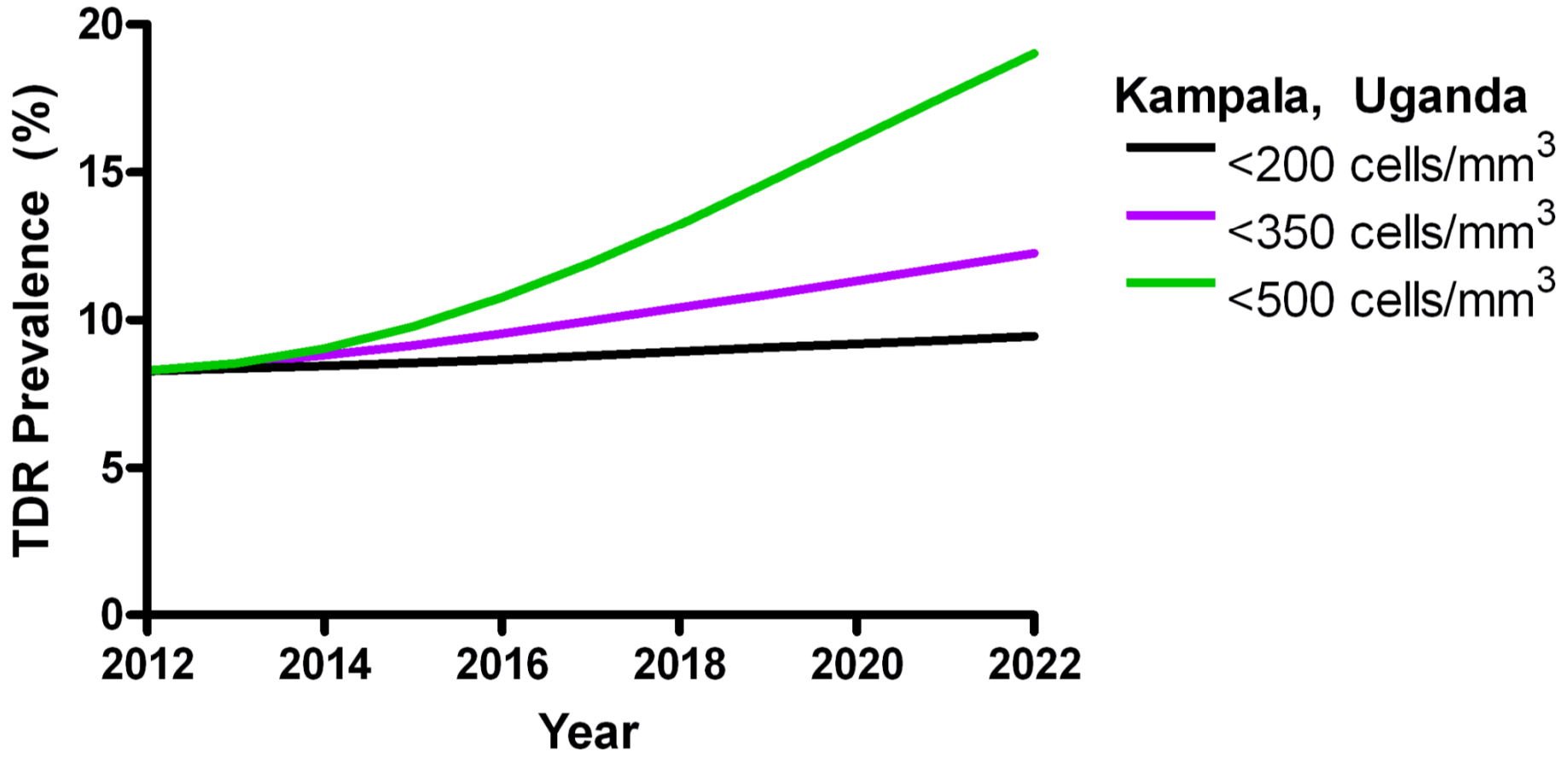
- Drug resistance by mutation or class- individuals can be infected with:



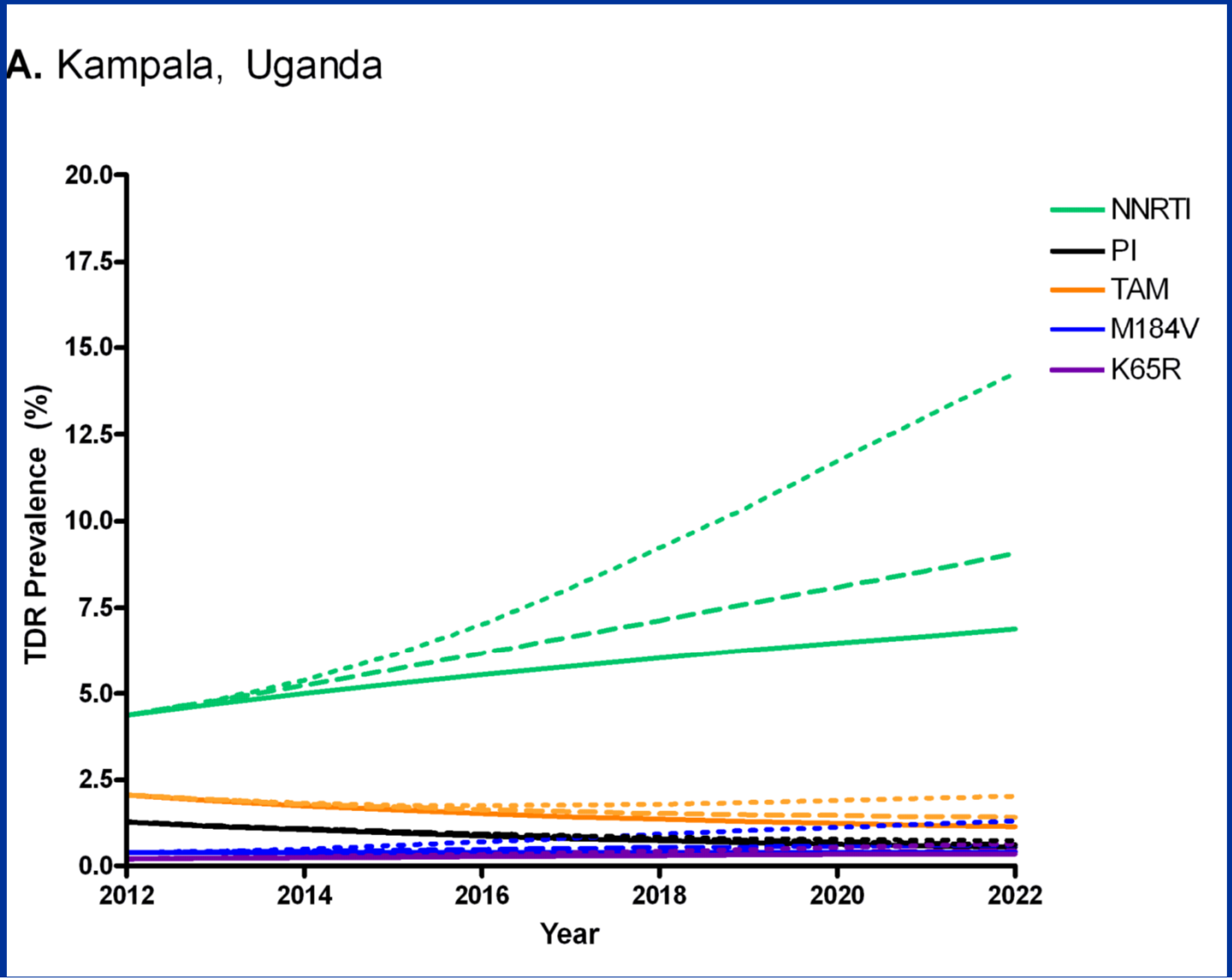
HIV Prevalence



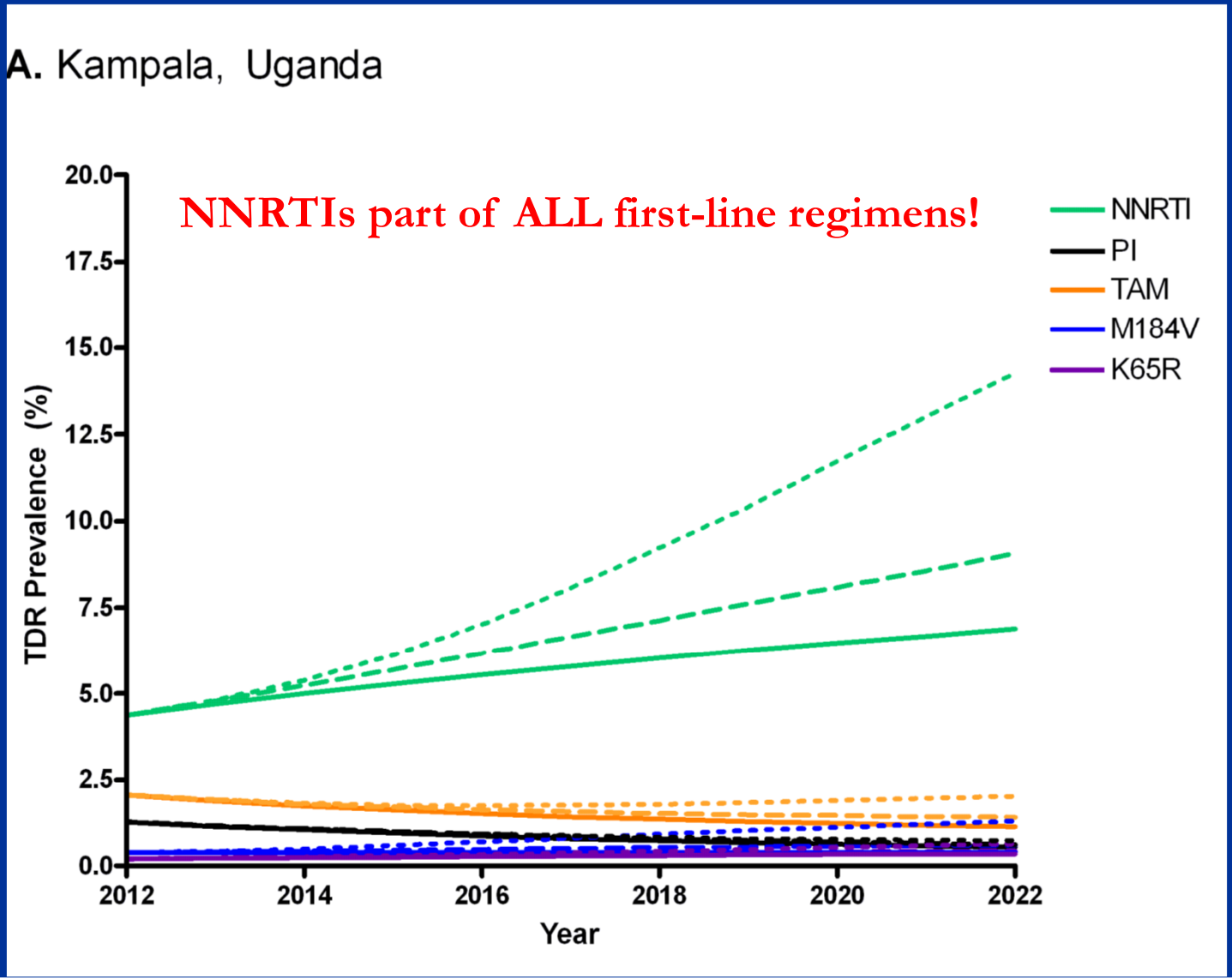
Transmitted Drug Resistance Prevalence



Transmitted drug resistance by drug class or mutation



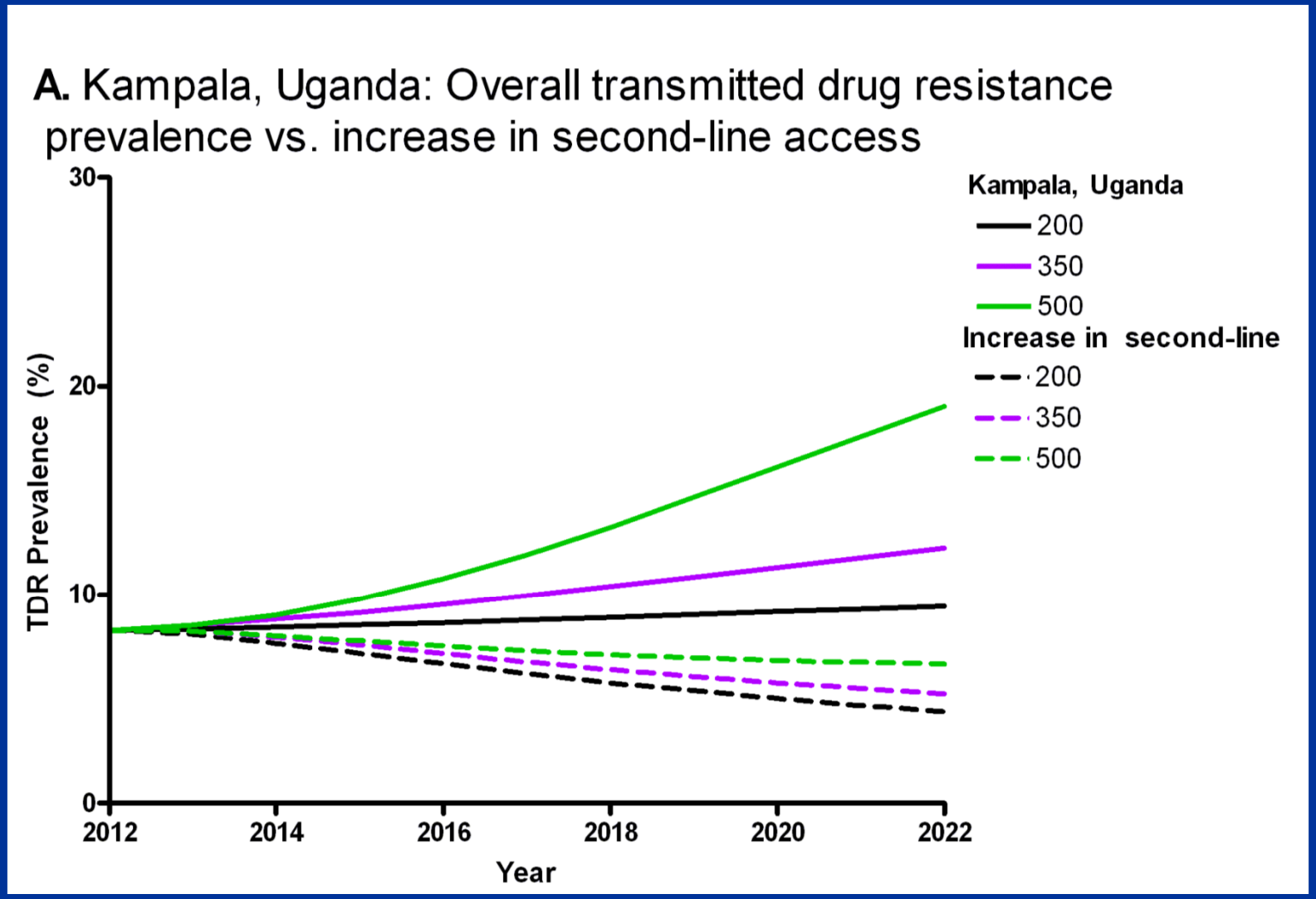
Transmitted drug resistance by drug class or mutation



Where is it possible to intervene?

- Increase access to second-line!
  - Only 33-50% of patients with continued failure on first-line make it onto second line
  - Increase to 80-100%?

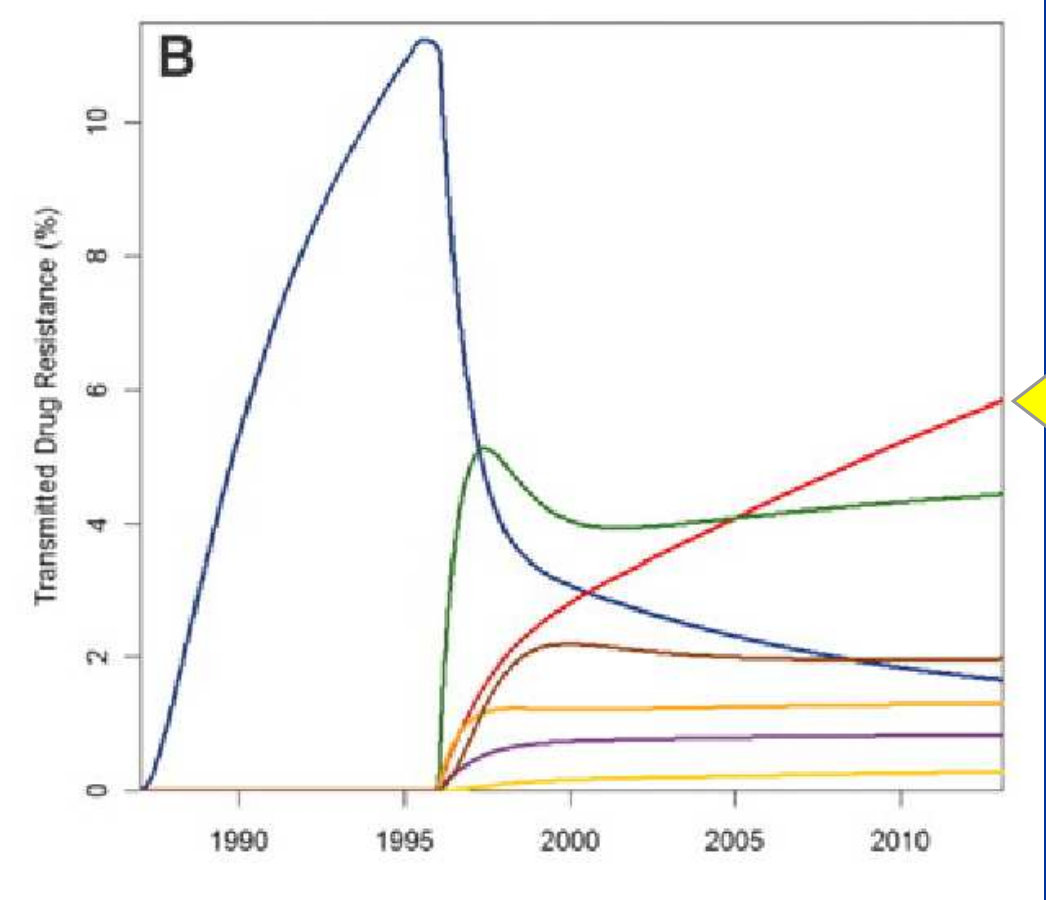
Increasing access to second-line



Prevention of new infections vs. increase of transmitted drug resistance

- Kampala:
  - Treatment increase to CD4 <350: 18 infections averted for every additional case infected with a drug-resistant virus
  - When treatment at CD4 <500: 22 infections averted for every additional case infected with a drug-resistant virus

Discussion



Smith, *Science* 2010

Previous papers have only shown the potential harms of increasing treatment and the issues with drug resistance

Not the benefits of averting new infections!

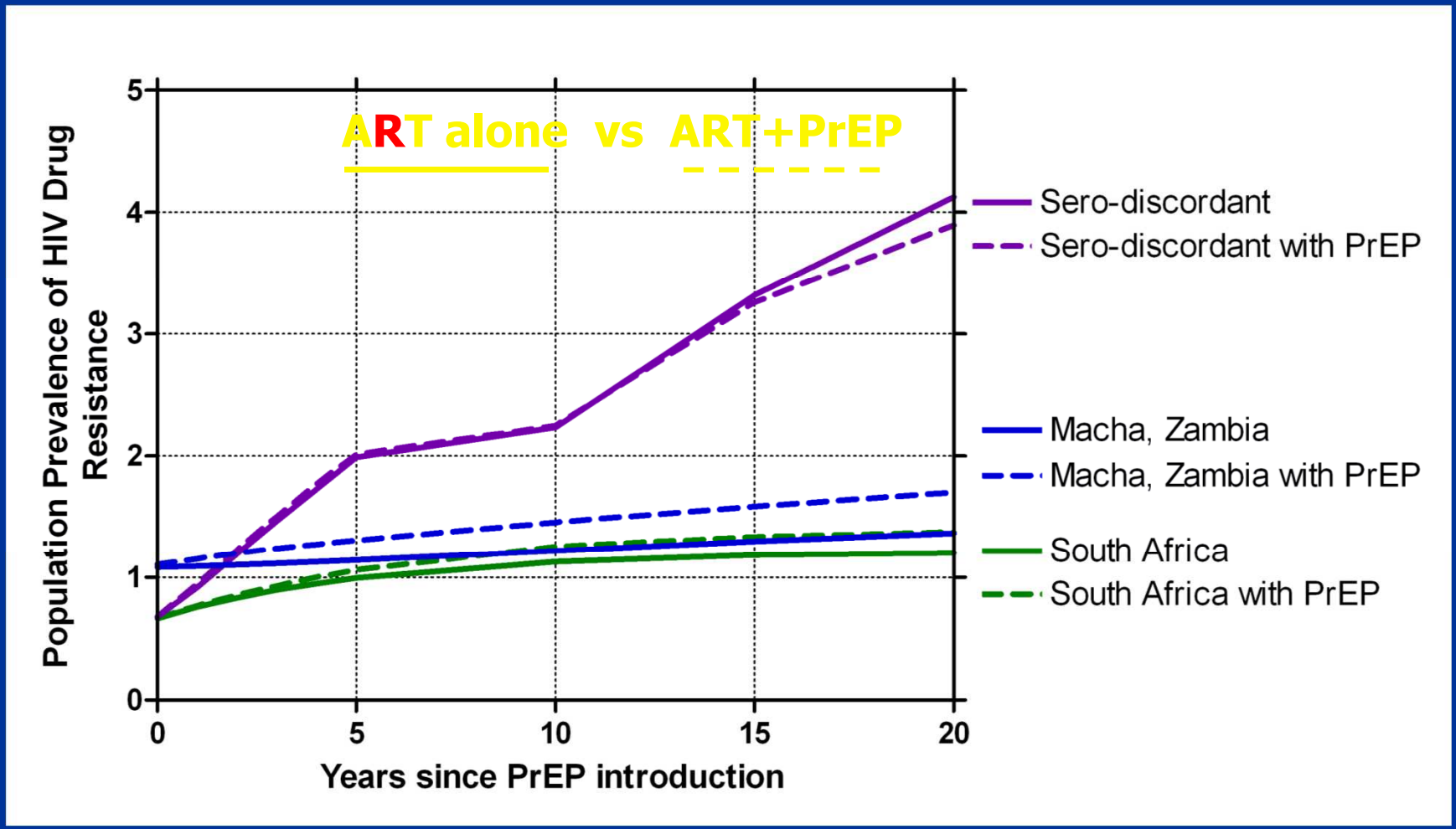
We have shown that the benefits of earlier treatment outweigh the risks associated with resistance!
Starting second-line in a timely manner can eliminate this altogether!

Conclusions

- Increasing access to ART will increase the prevalence of drug resistant HIV among new infections, particularly NNRTI resistance
- The number of new infections is strongly reduced by increasing ART coverage
  - outweighs the risk of increased TDR
- Timely switching to second-line boosted PI regimens can actually *reduce* TDR over time

Pre-exposure profylaxis (PREP) ?

Limited impact on HIVDR prevalence in sub-Saharan Africa



van de Vijver, Nichols, et al. Int AIDS Conference 2012 FRLBX04

Conclusions – 1

- A possibilities that transmissible multidrug resistance will be generated

- Available evidence suggests that ART scale-up is driving TDR (NNRTIs) in east and southern Africa, which compromises response to first-line NNRTI-based ART
  - Of concern, but not at unexpected levels and rates
  - Lack of routine HIVDR surveillance data

- Current standard 1st and 2nd line regimens still effective for the majority of patients

Conclusions - 2

- Mathemathical modelling predicts that:
  - Early ART initiation drives TDR, but outweighed by new infections averted
  - TDR can be eliminated by early failure detection and timely switch
  - HIVDR from treatment scale-up is expected to far exceed that from PrEP
- As novel ART strategies are being implemented, operational research needed to assess their impact in terms of adherence, retention and HIVDR development

Conclusions – 3

- HIVDR is a possible, but manageable, future threat to the success of the global HIV/AIDS control.

Acknowledgements

- *Erasmus MC, Rotterdam*
  - Brooke Nichols, Marieke Pingen , David van de Vijver
- *PharmAccess, Amsterdam*
  - Kim Sigaloff, Raph Hamers, Tobias de Wit

British HIV Association

BHIVA

19th Annual Conference of the British HIV Association (BHIVA)

16–19 April 2013

Manchester Central Convention Complex