Evolution, dynamics and clinical relevance of transmitted drug resistant mutations in HIV

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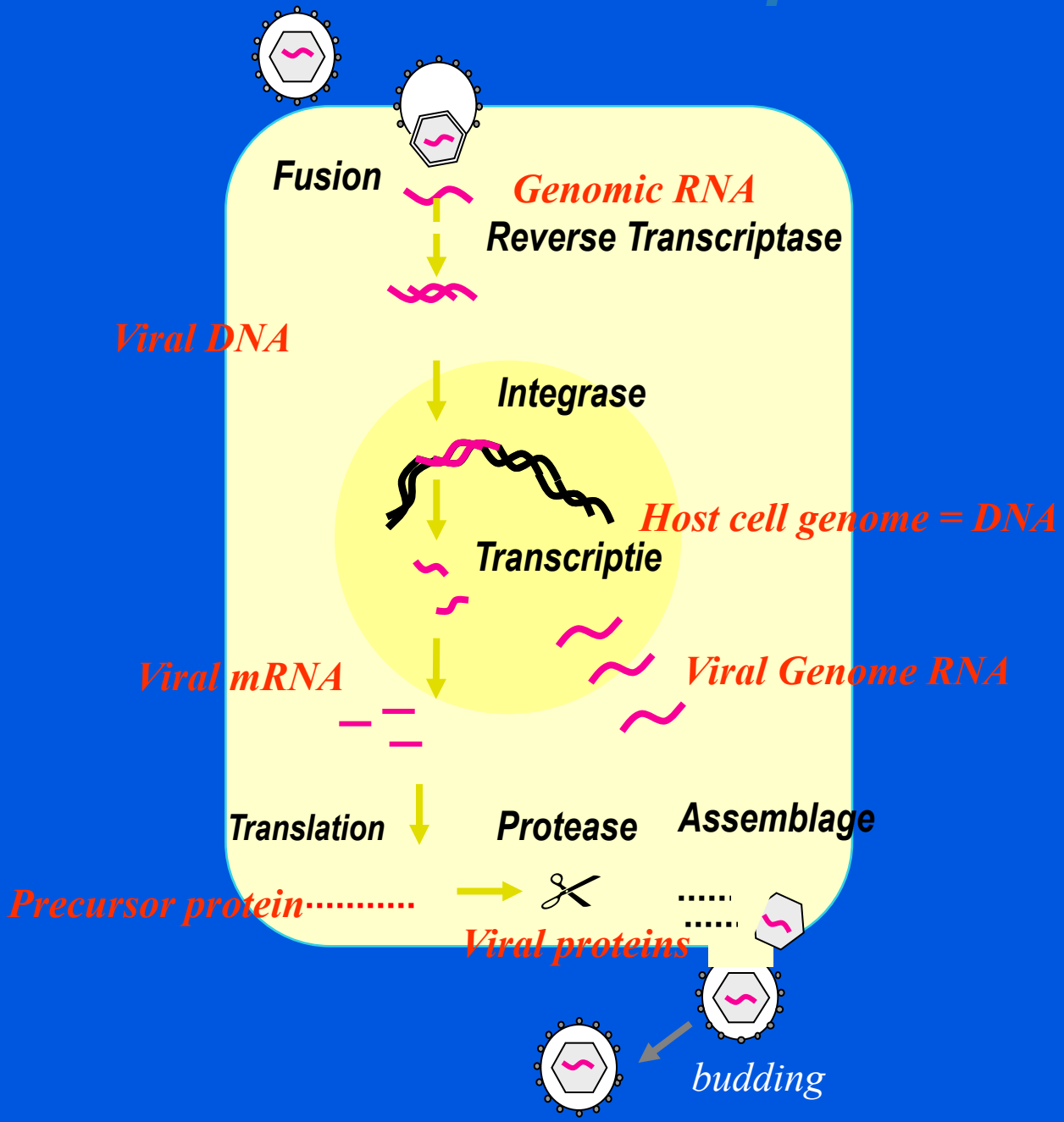
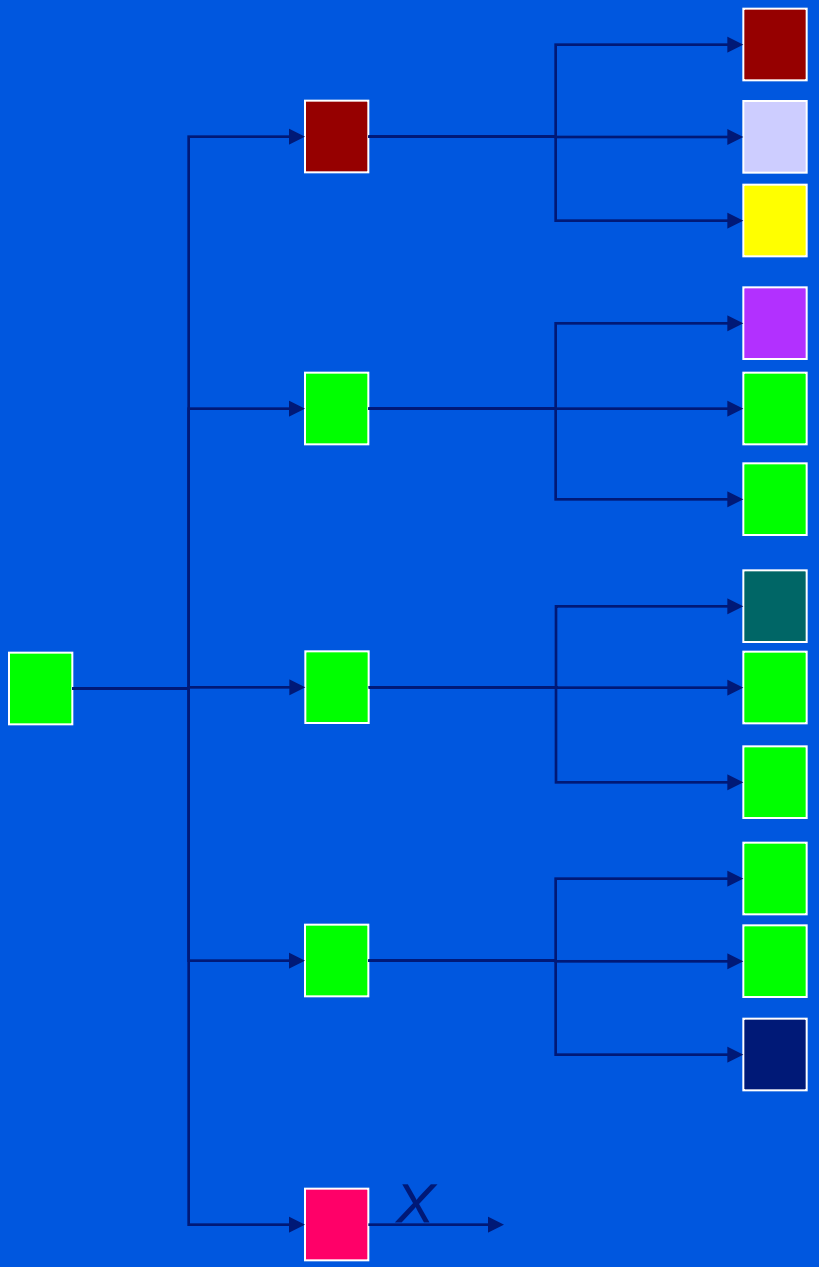
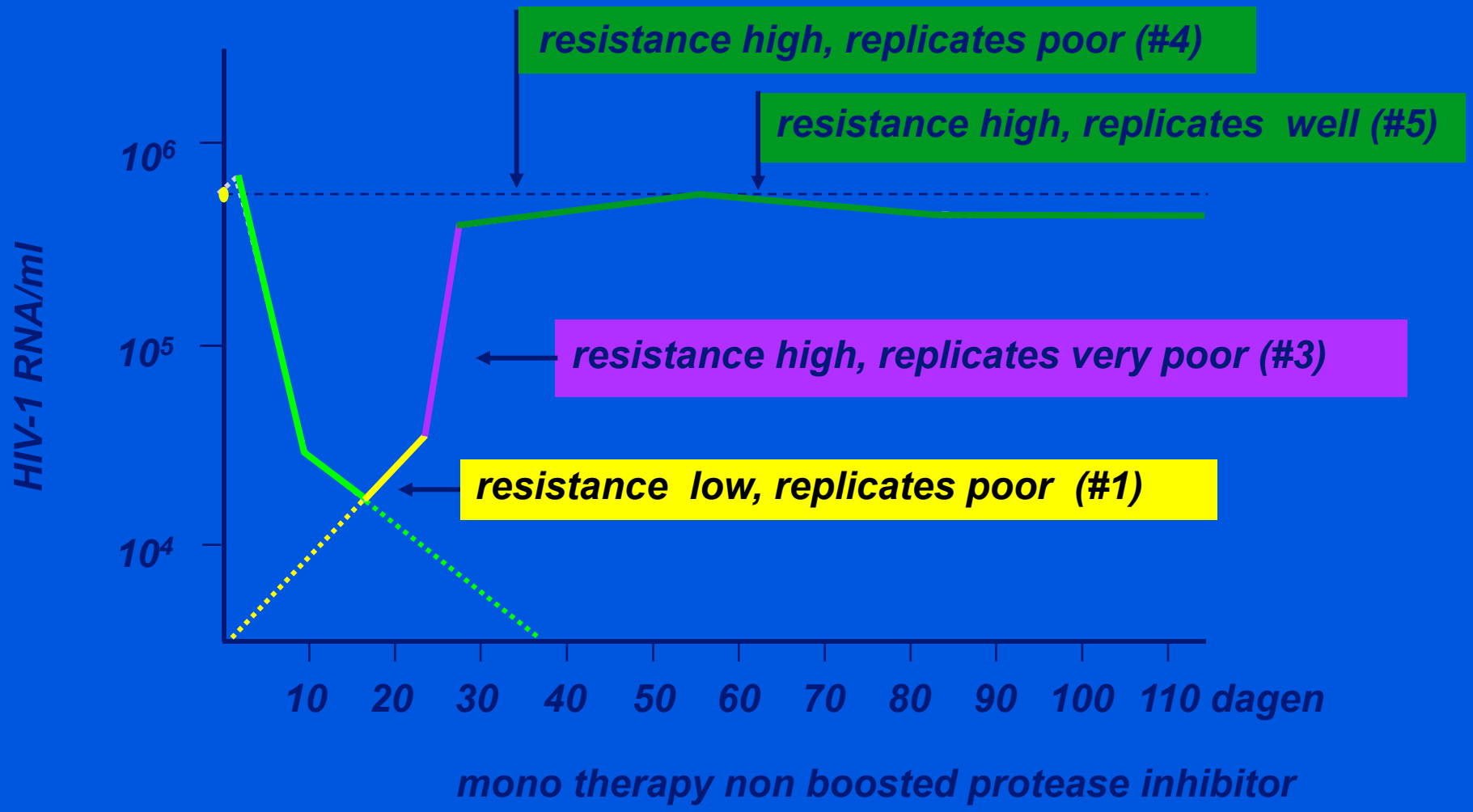
HIV-1 replicatie cyclus



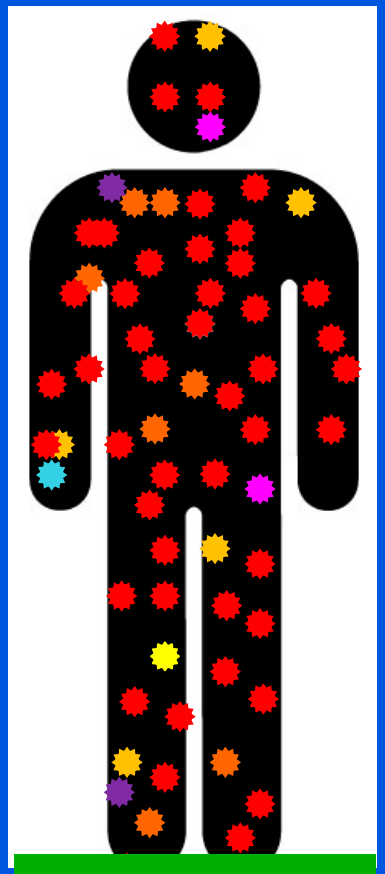
Generation of Mutations

- Error prone RT
  - Important, but # of replication cycles drives diversity
- Large number of HIV-infected, virus producing cells
  - Produce ~10^{11} virions per day
- Large number of viral replication cycles per day
- All single & some double drug-resistant mutants pre-exist but at very low frequency (<10^{-5})
  - Drug-resistant mutants less fit in the absence of drug


X


resistance high, replicates poor (#4)
resistance high, replicates well (#5)
resistance high, replicates very poor (#3)
resistance low, replicates poor (#1)
HIV-1 RNA/ml
10^6
10^5
10^4
10 20 30 40 50 60 70 80 90 100 110 dagen
mono therapy non boosted protease inhibitor

Transmission



Treated patient
Multiple viruses

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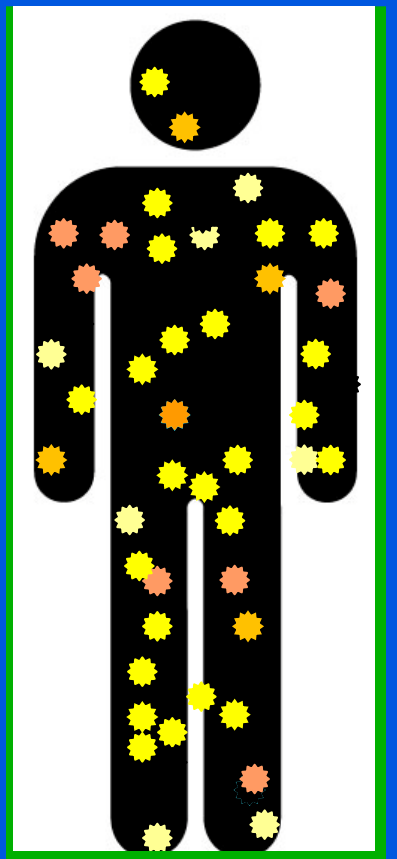
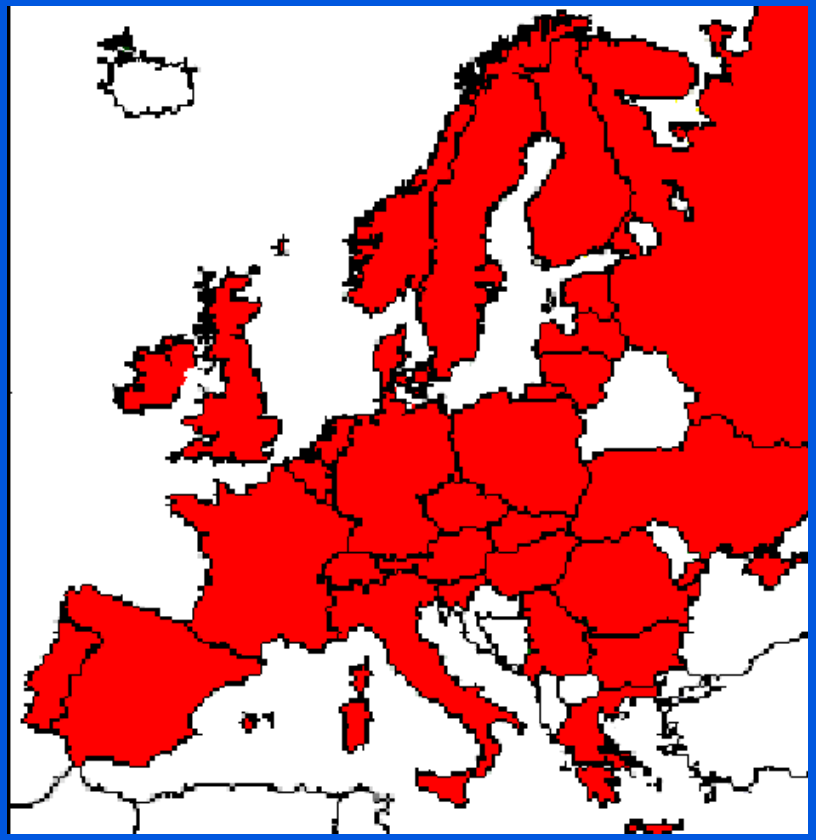


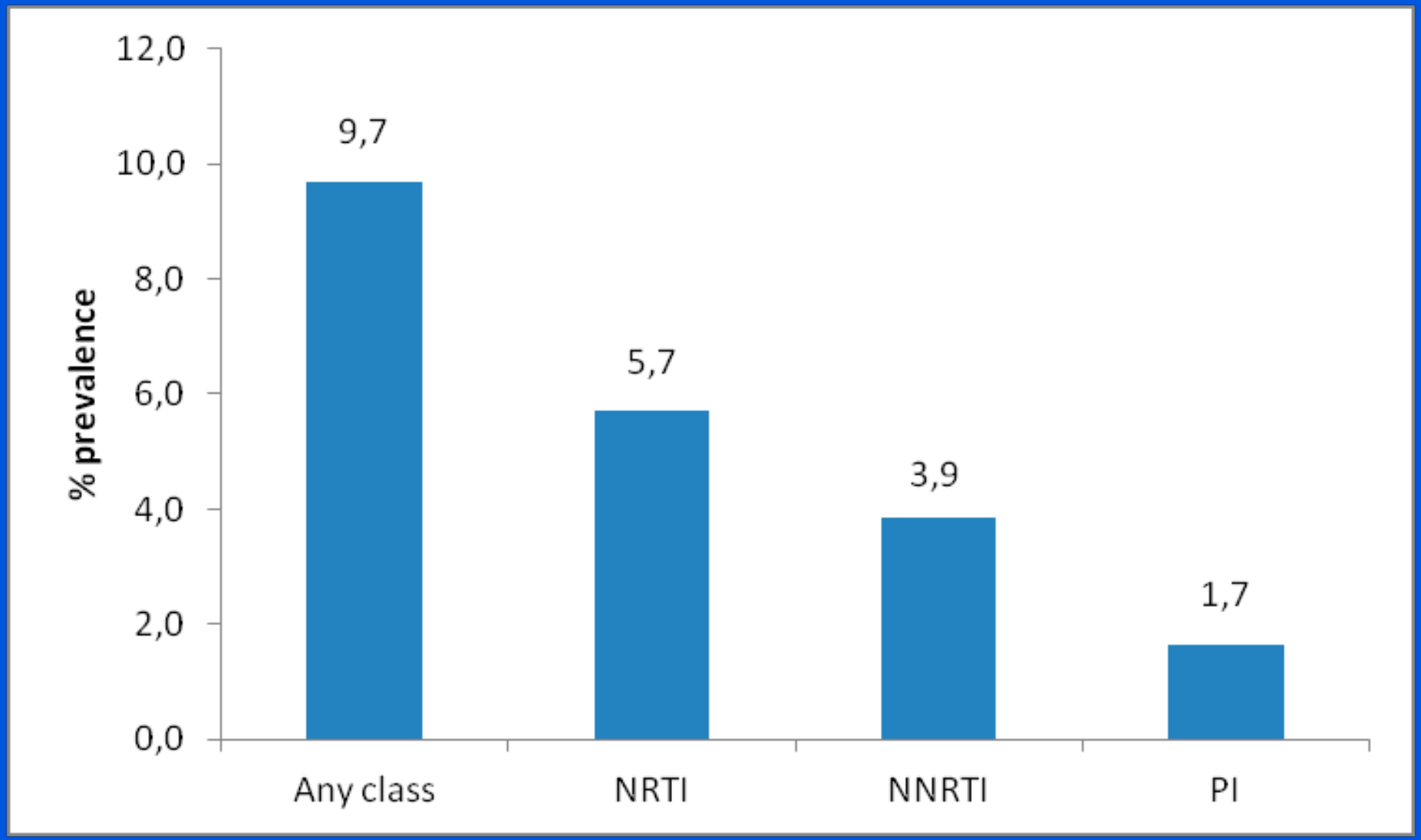
new patient
Limited profile

SPREAD



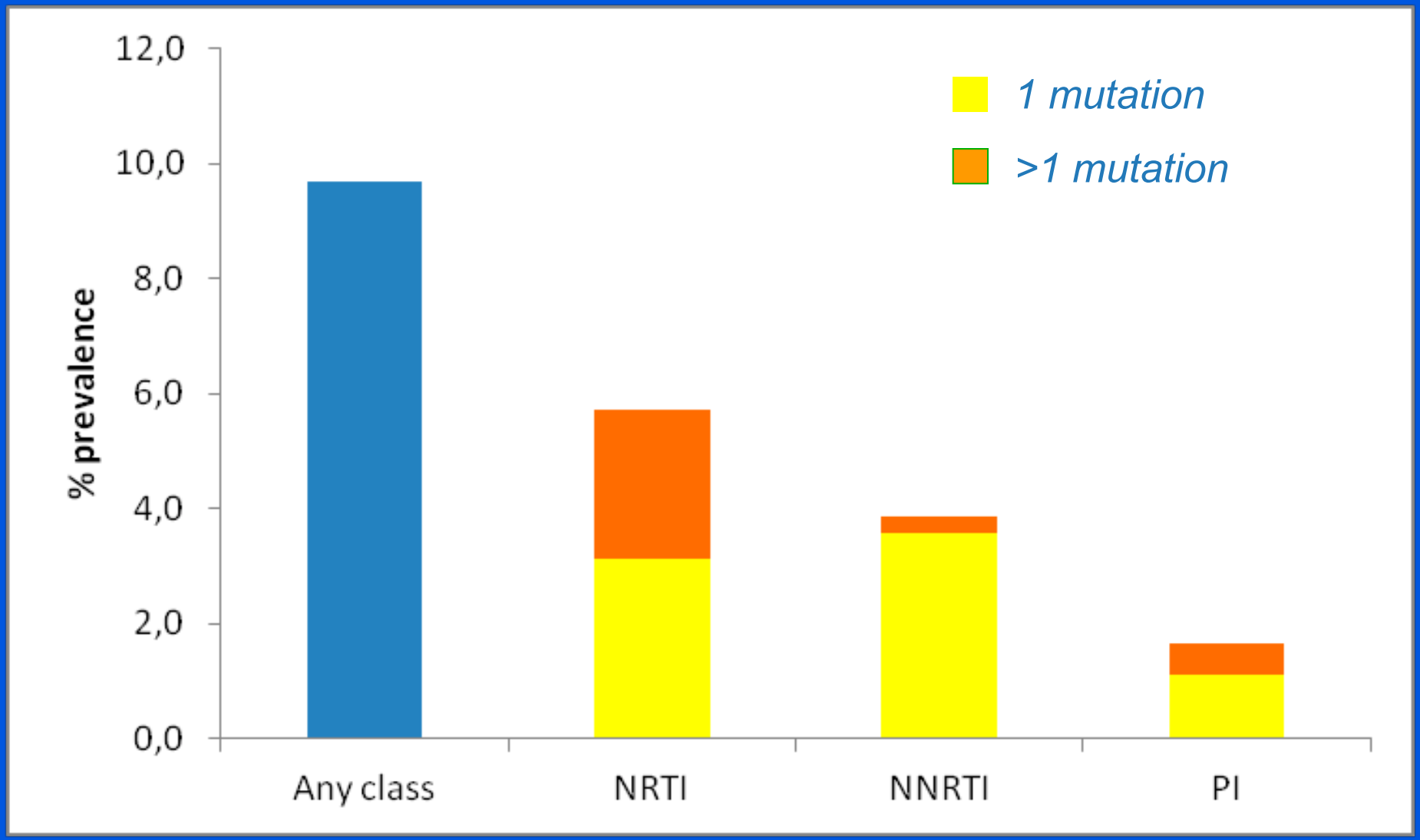
Transmission of HIV-1 resistance in Europe.

Transmitted drug resistance in Europe

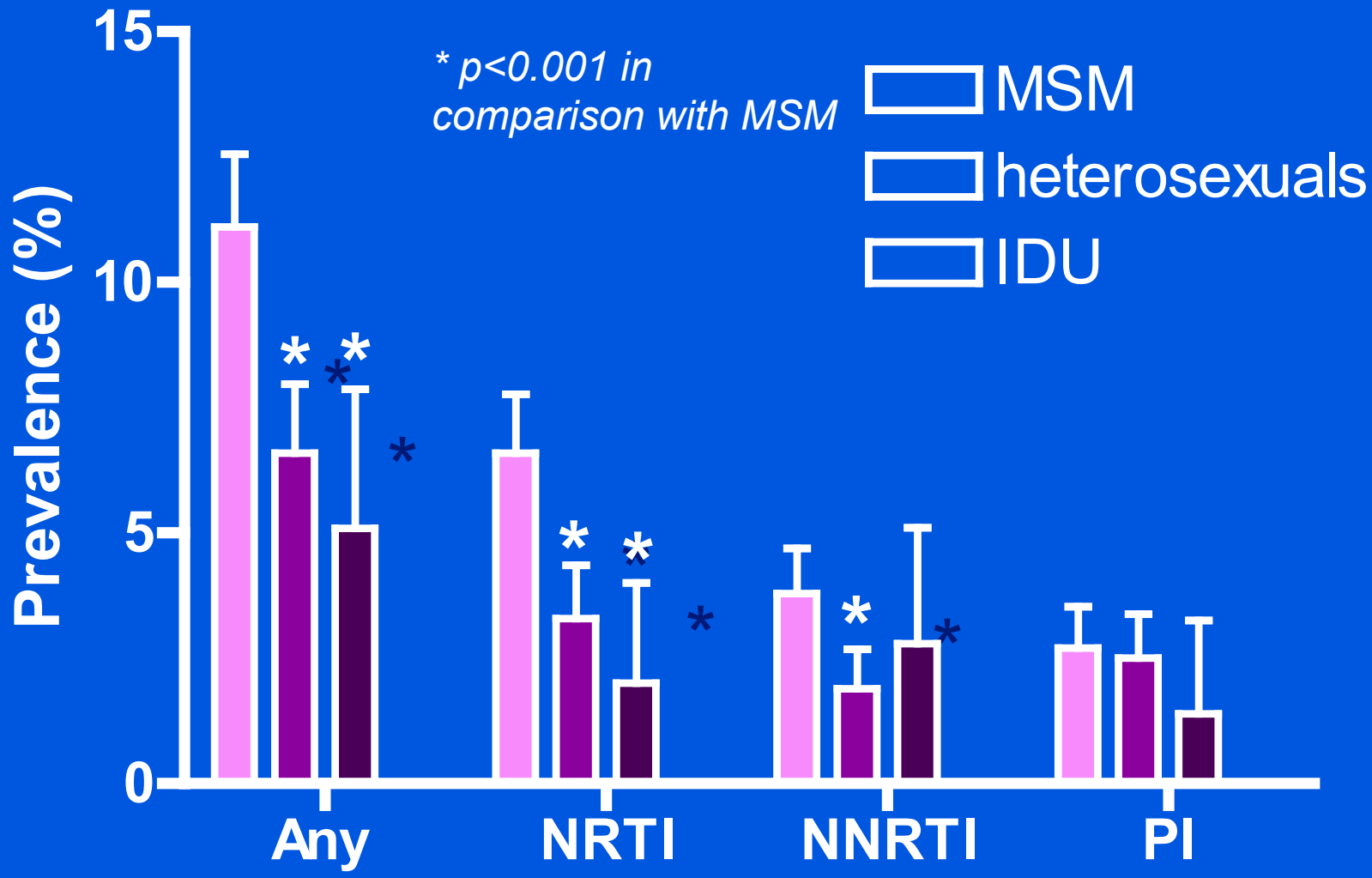


D. Frentz on behalf of SPREAD

Transmitted drug resistance: limited profiles

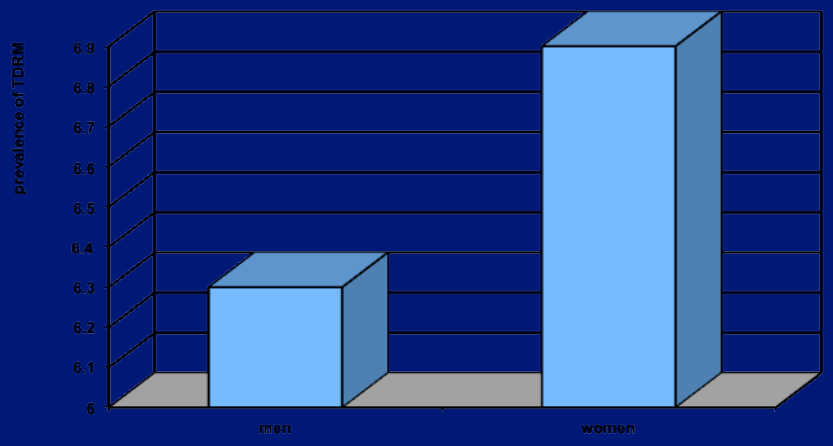


Risks groups and classes



TDRM men/women

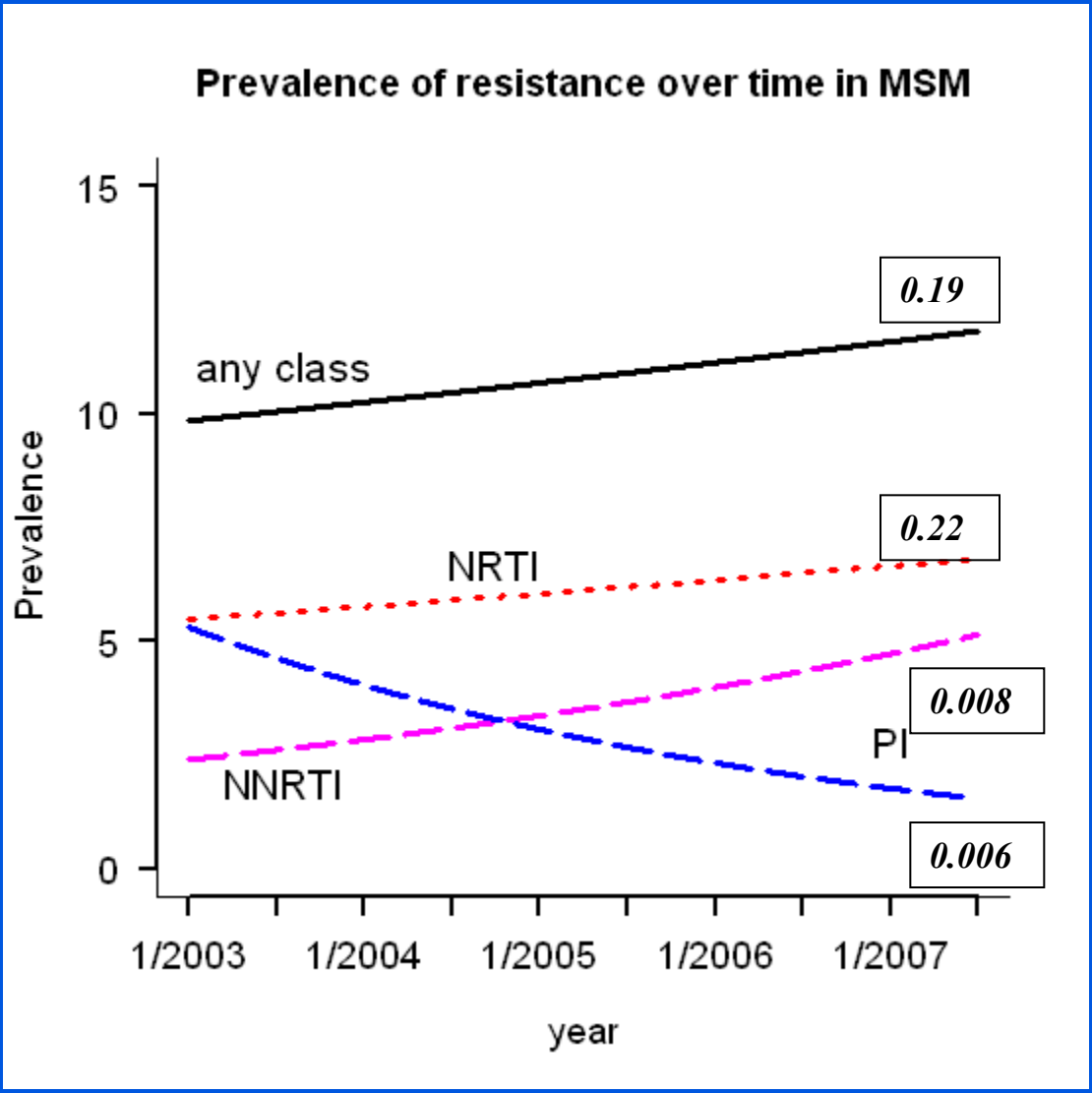
- In heterosexual men: 6.3%
- In heterosexual women: 6.9%



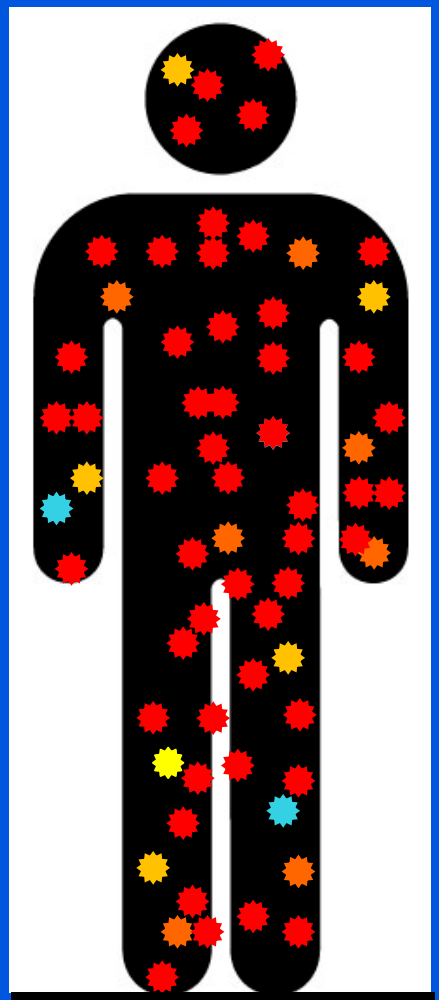
Mutational patterns

	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)

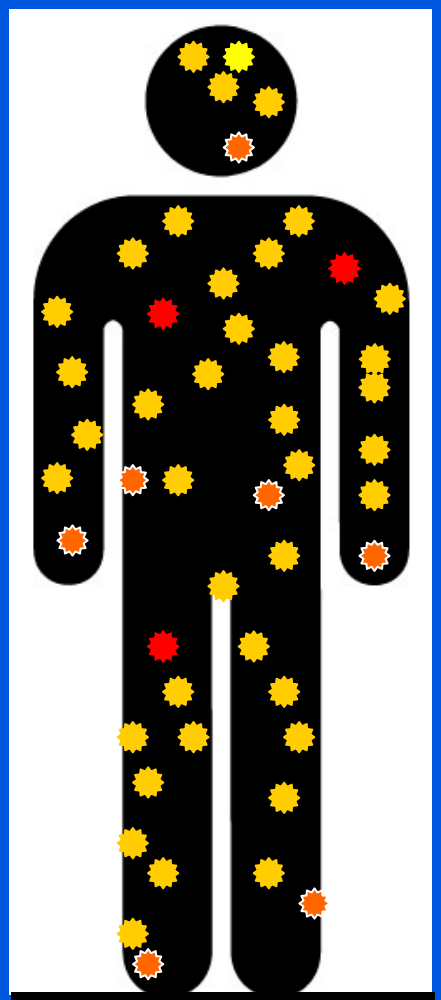
MSM


Prevalence of resistance over time in MSM
15
10
5
0
Prevalence
any class
0.19
NRTI
0.22
PI
0.008
NNRTI
0.006
1/2003
1/2004
1/2005
1/2006
1/2007
year

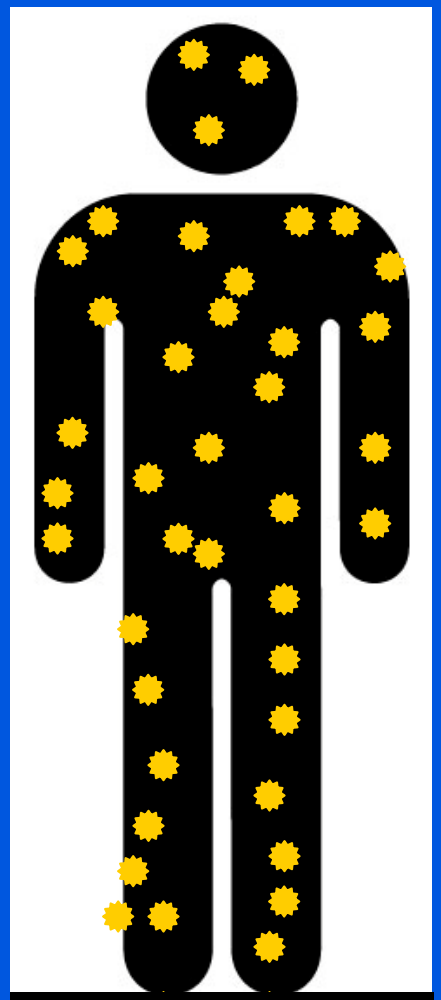
Continuous circulation of resistant strains



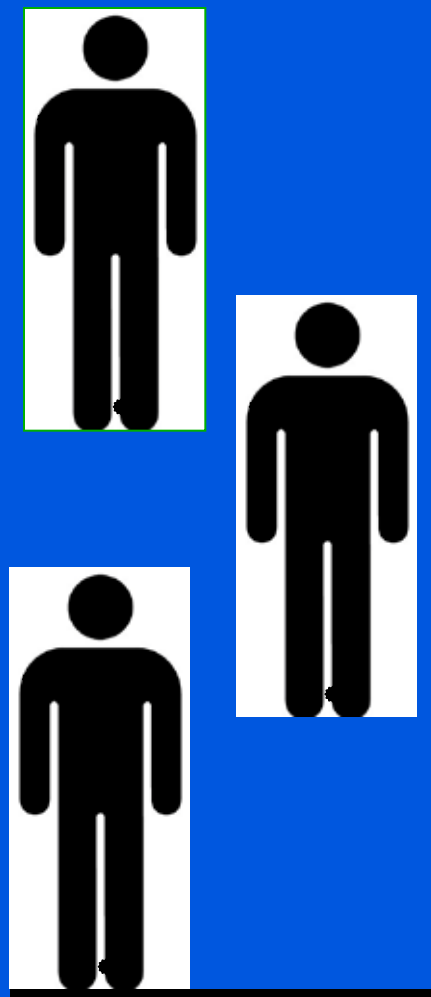
Treated patient
Extensive profile



Infected patient
(partial) reversion

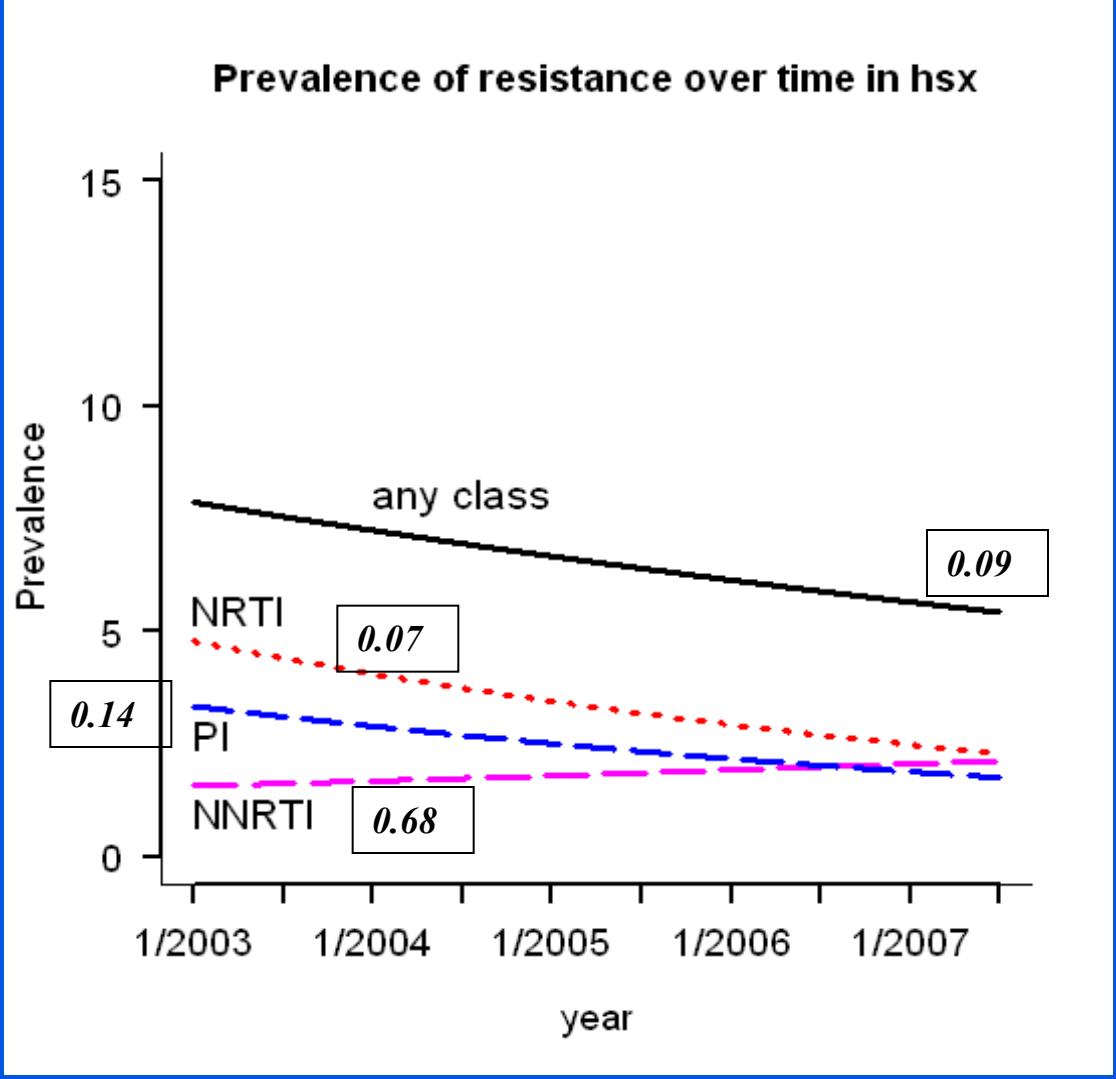


Infected patient 2



Circulation

Heterosexual



Transmitted mutations Europe

- Continuous circulation of (single) NRTI mutations mostly in MSM

- Increase in the transmission of single NNRTI mutations (4%) predominantly in MSM

- Decrease in transmission of PI mutations overall

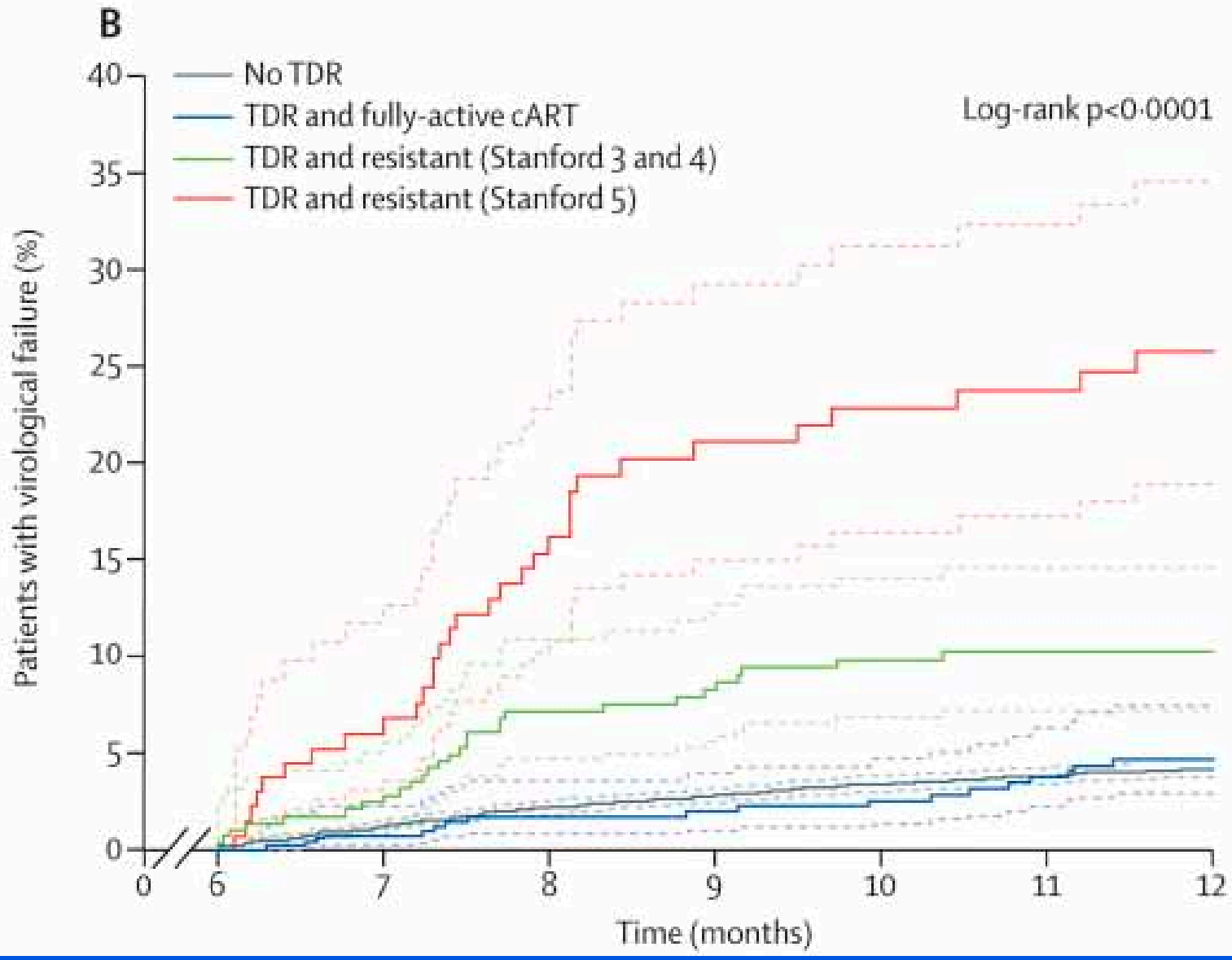
Increase in Transmitted NNRI resitance

- Frequent use of NNRTI in first line
- Patients who fail early develop NNRTI mutations
.
- NNRTI mutations can persist in absence of drugs after transmission.

Treatment impact of TDRM

Transmitted single PI mutations will have very limited impact on boosted PI regimens.

Novel NRTI based regimens (tenofovir) are not affected by the circulation of single NRTI mutations



(Wittkop, Lancet 2011)

Treatment impact of TDRM

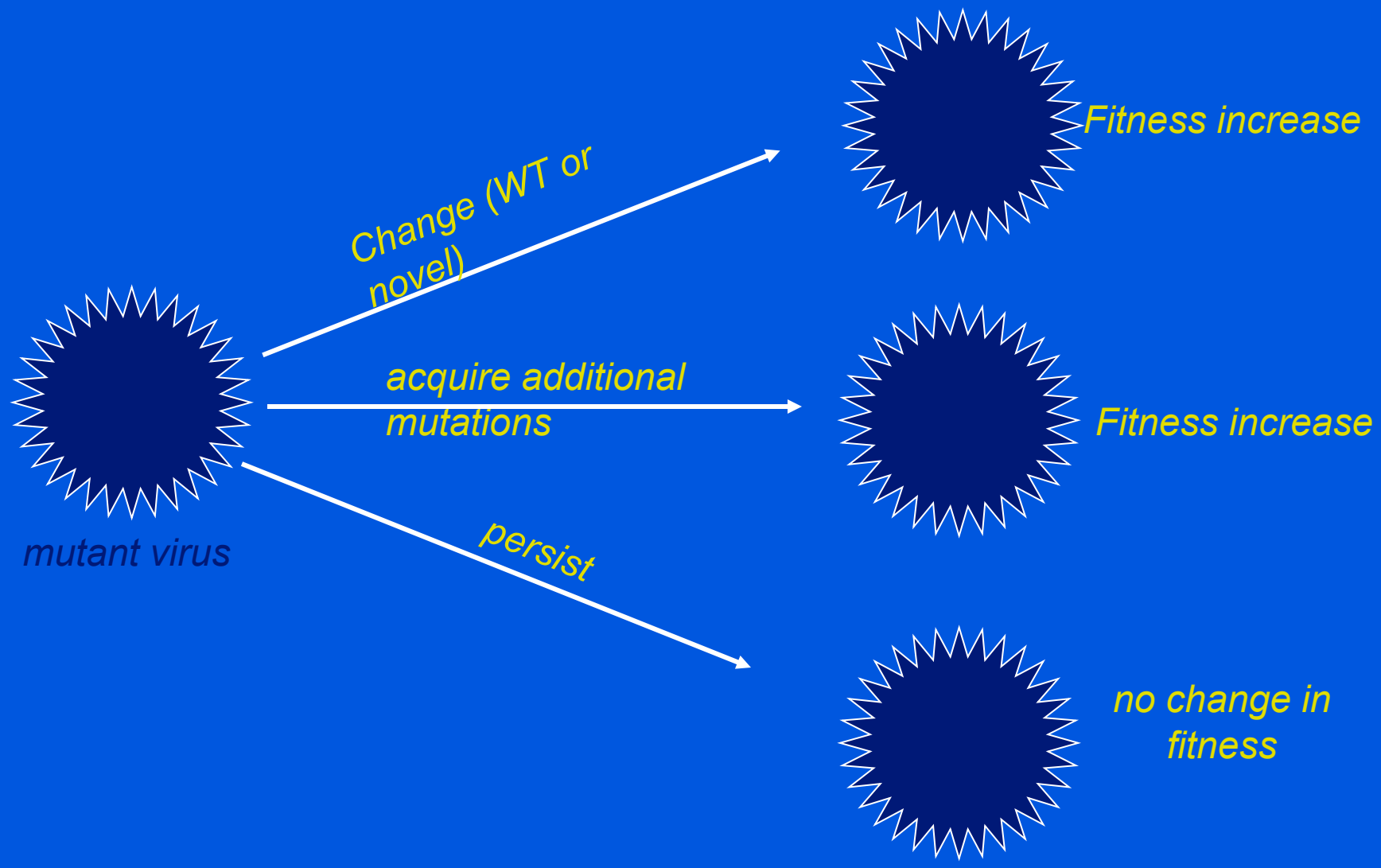
NNRTI mutations will decrease efficacy:

- 25% with first line NNRTI (EFV/NVP)

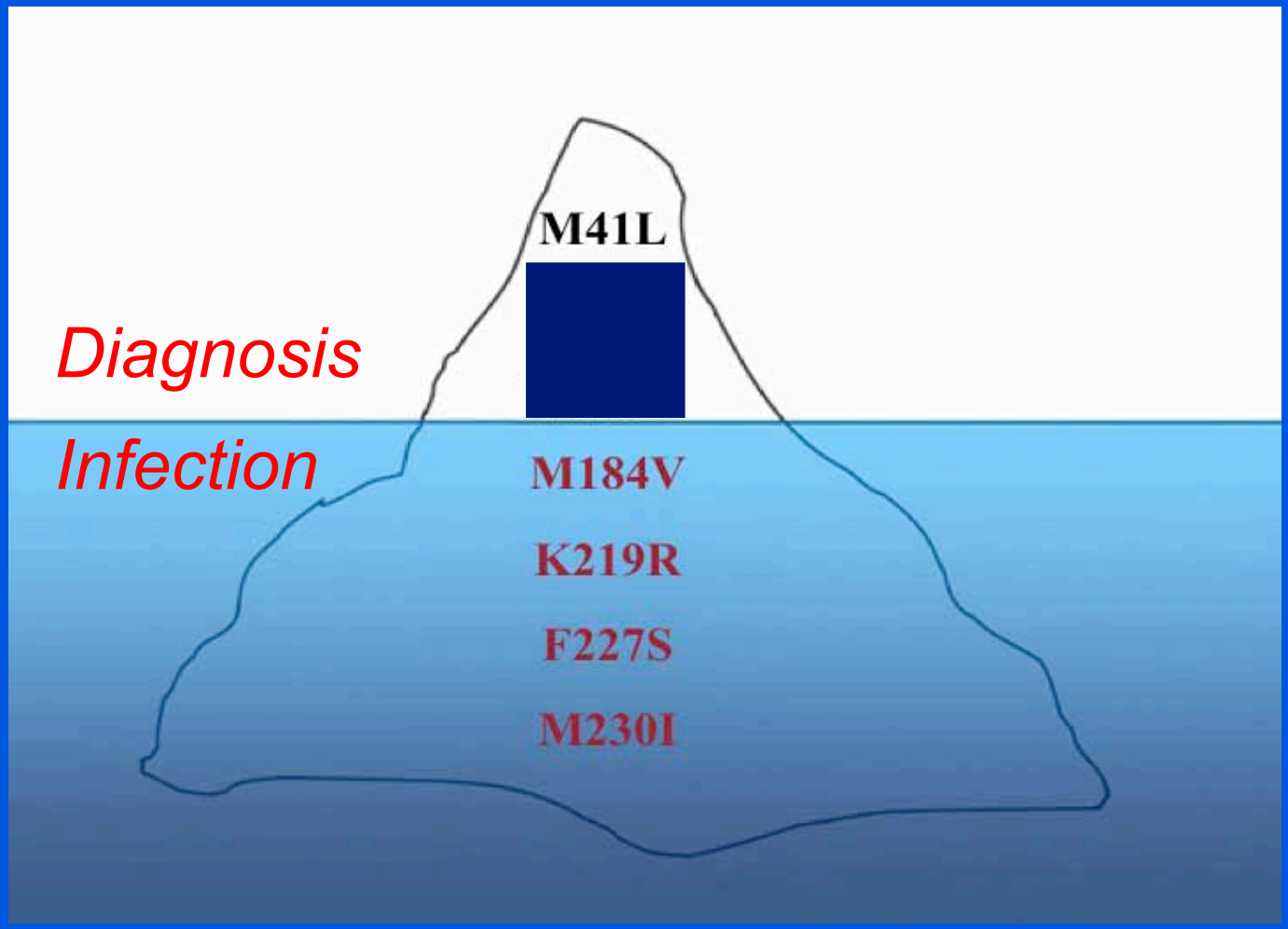
- even if present as minority (not detected by population sequencing)

Multiple mutations will impact second line NNRTI (etravirine/rilpivirine)

Evolutionary pathways in the absence of drugs



Single mutations can be the tip of the iceberg !



Approach

- To investigate whether a limited resistance profile is an indicator of transmission of a more extensive resistance profile
-
- 10 patients identified in 2003-2008 with HIV harbouring a single TDRM detected by population sequencing before therapy!

Sequencing results: population vs UDP

ID	Population sequencing	HIV RNA
A	M41L	$>10x10^5$
B	T69N	$>10x10^5$
C	M184V	$>10x10^5$
D	T215E	$>10x10^5$
E	T215E	$>10x10^5$
F	T215L	$>10x10^5$
G	T215S	$>10x10^5$
H	T215S	$>10x10^5$
I	T215S	$>10x10^5$
J	K219Q	$>10x10^5$

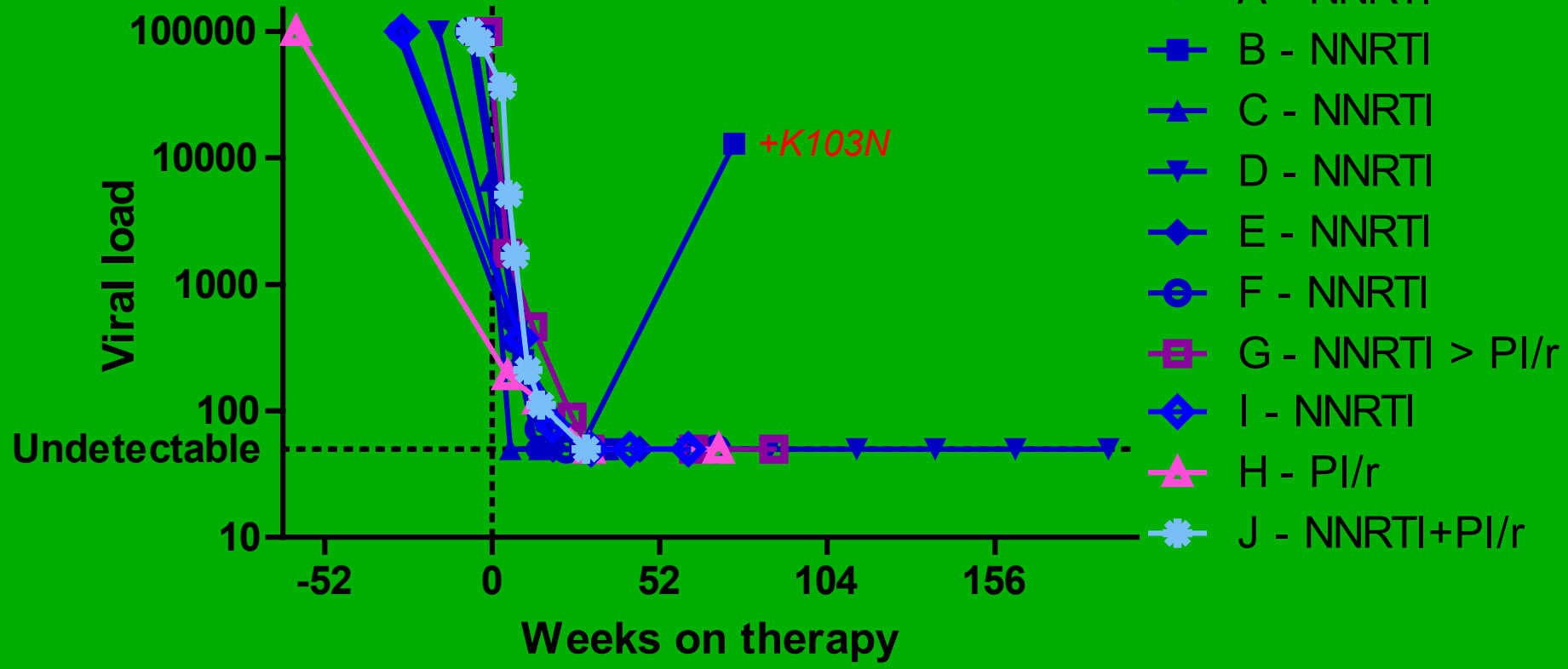
M. Pingen et al, HIV medicine 2012.

population vs ultradeep sequencing

ID	Population sequencing	UDPS	reads
A	M41L		2623
B	T69N		2516
C	M184V		3277
D	T215E		2582
E	T215E		2115
F	T215L		2513
G	T215S		2246
H	T215S		2685
I	T215S		2680
J	K219Q		2562

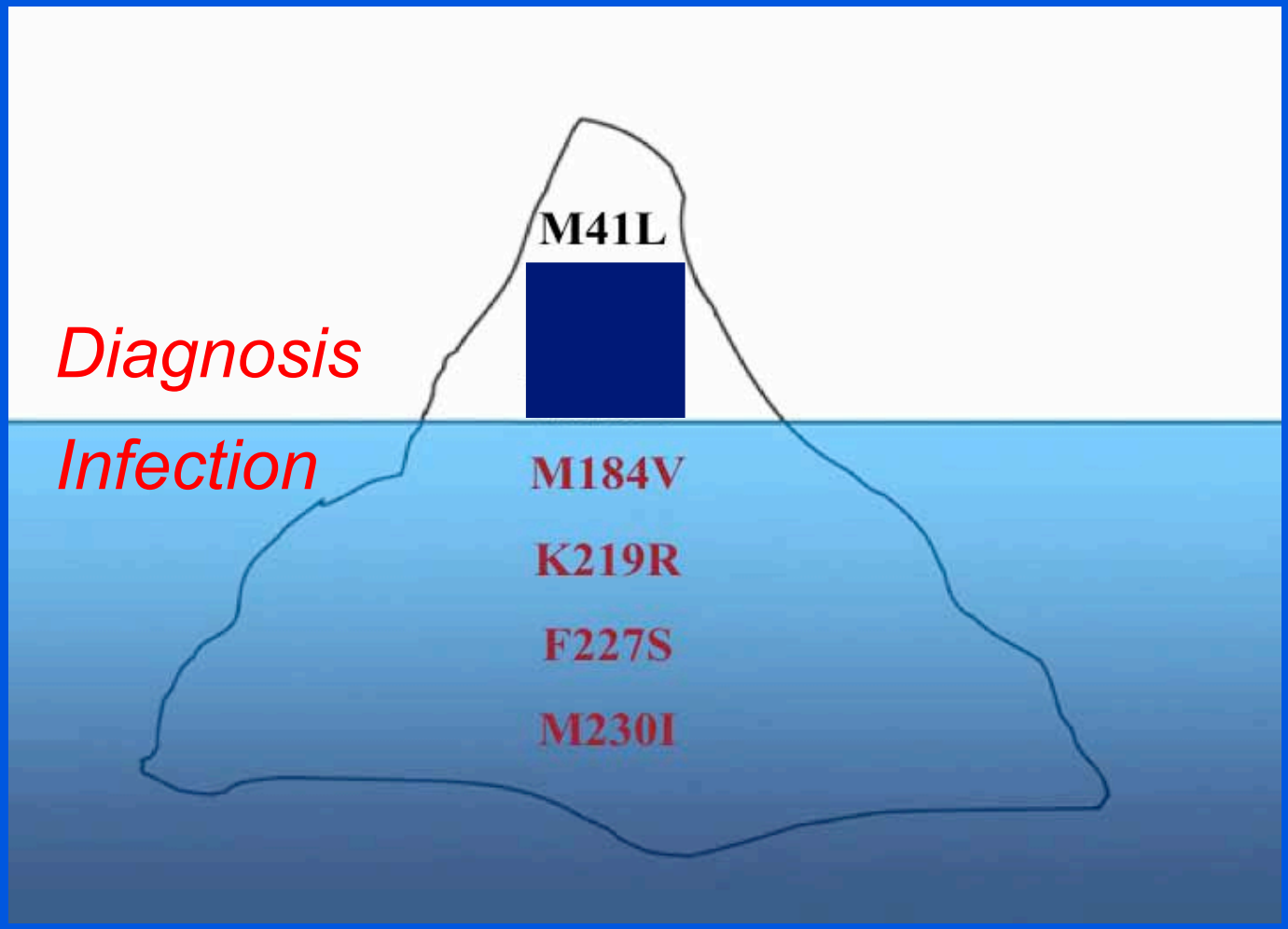
M. Pingen et al, HIV medicine 2012.

Therapy outcome



M. Pingen et al, HIV medicine 2012.

Single mutations are not anymore the tip of the iceberg !



Conclusions

- Recently diagnosed patients infected with single transmitted drug resistance mutations may represent onward transmission (circulation).

- Further clinical studies are warranted to determine the implication of single transmitted mutations at baseline for the choice of initial therapy

Prevention

Limit the number of failing individuals

Patients with potential compliance problems should be monitored carefully,

Patients with potential compliance problems may be better of on boosted PI therapy.

Treatment

In patients with transmitted drug resistance high genetic barrier regimens (boosted PI) should be considered

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EU grant LSHPCT-2006-518211

Aids Fonds

Grant 2007034