Drug resistance surveillance

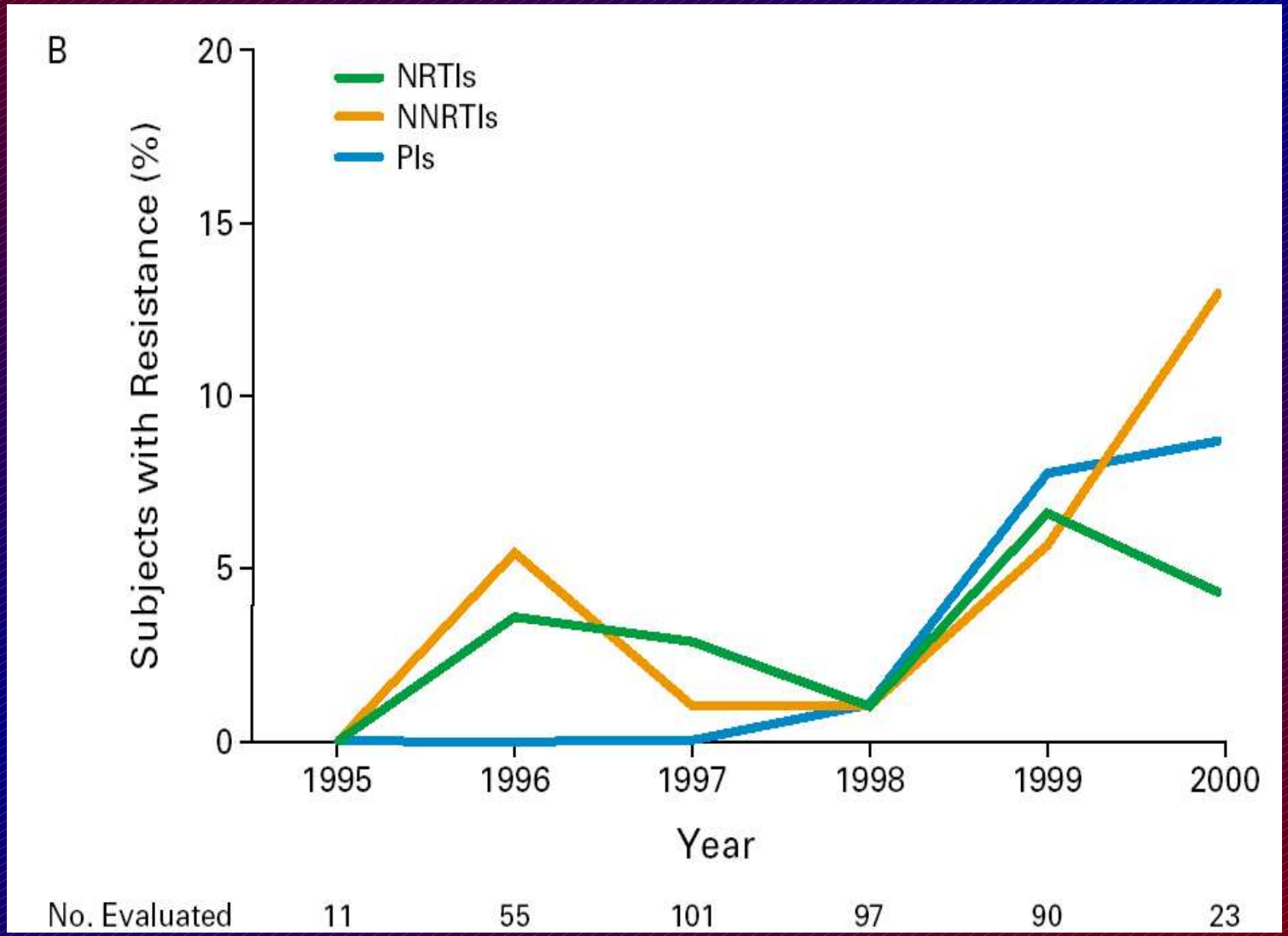
Simon D.W. Frost, D.Phil.

Department of Pathology,
Antiviral Research Center,
AIEDRP Statistical and Coordinating Center
University of California, San Diego

How do we estimate the prevalence/incidence of HIV DR?

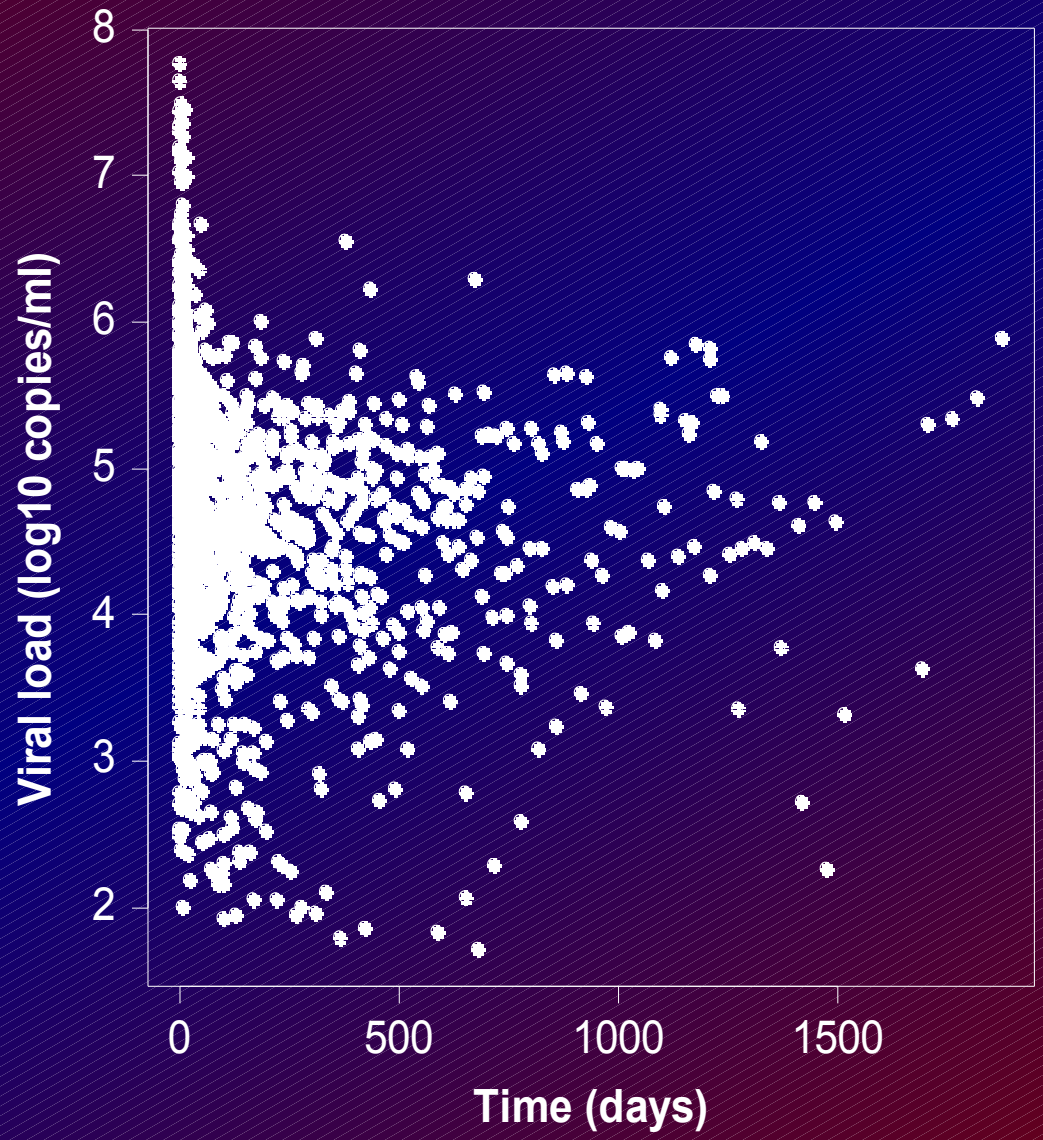
- HIV drug resistance reverts to wild type during the infection period
- This may occur at different rates for different classes of drug resistance
- Correcting for this effect is complicated by the correlation between viral load and drug resistance

Transmission of NNRTI resistant virus is high, and increasing

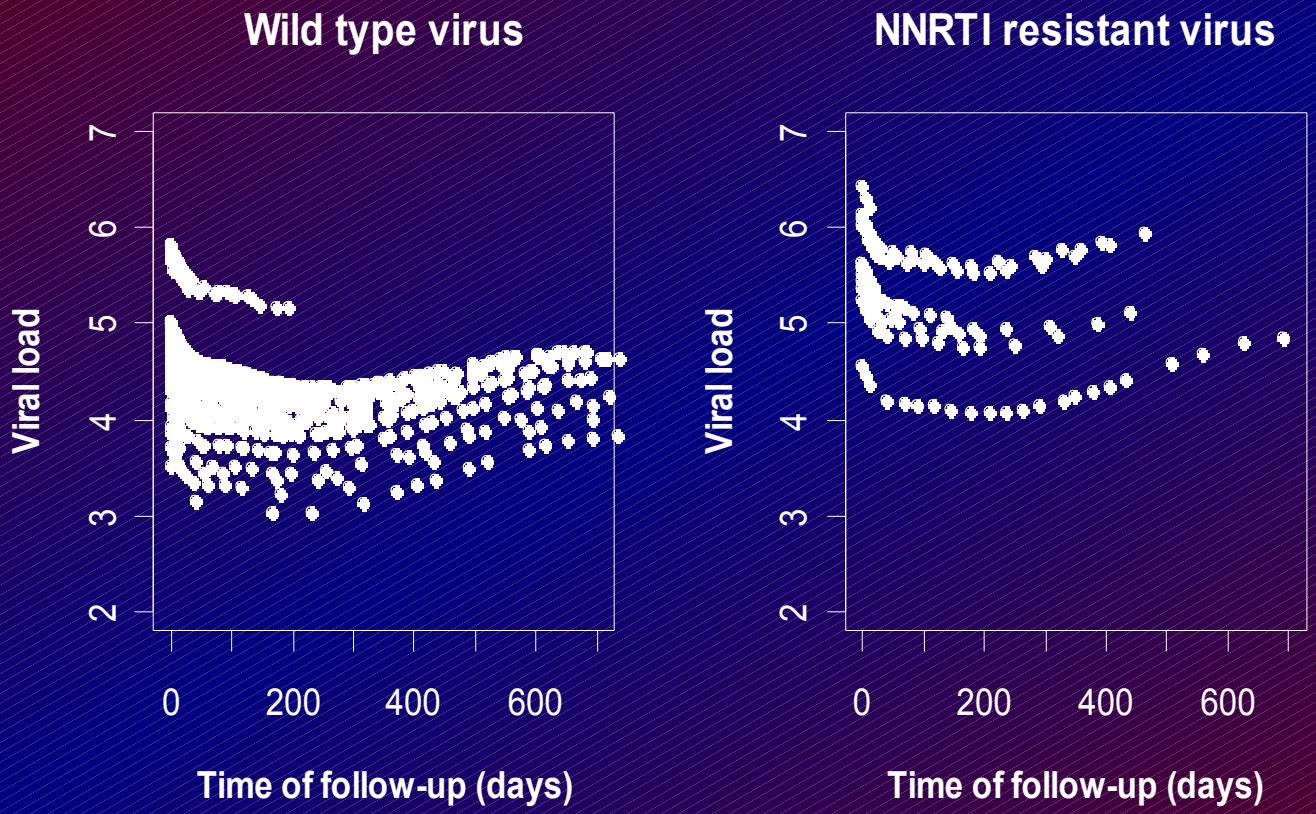


Little et al.
NEJM 2002

Raw viral load data



Fixed effects plot of NNRTI resistant vs. wild type virus



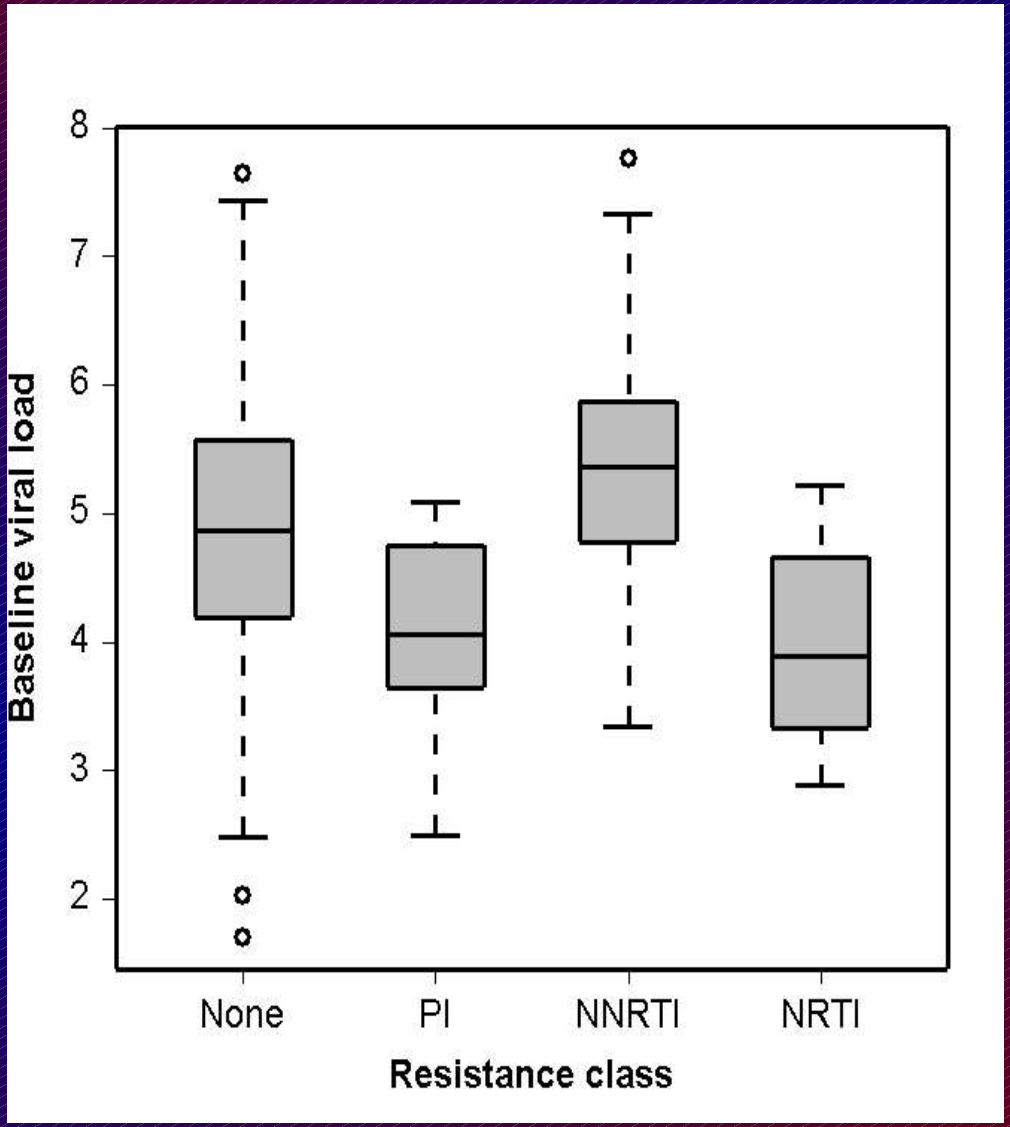
Parameter estimates

- Viral dynamics are nonlinear
  - LRT=214, 24 d.f, $P < 0.0001$
- Very early HIV infection (HIV RNA, no antibodies) is associated with higher viral loads
  - 0.8 log10 copies/ml
- Longer followup is associated with lower viral loads
  - 0.3 log10 copies/ml/year lower
- NNRTI resistance is associated with higher viral loads
  - 0.6 log10 copies/ml

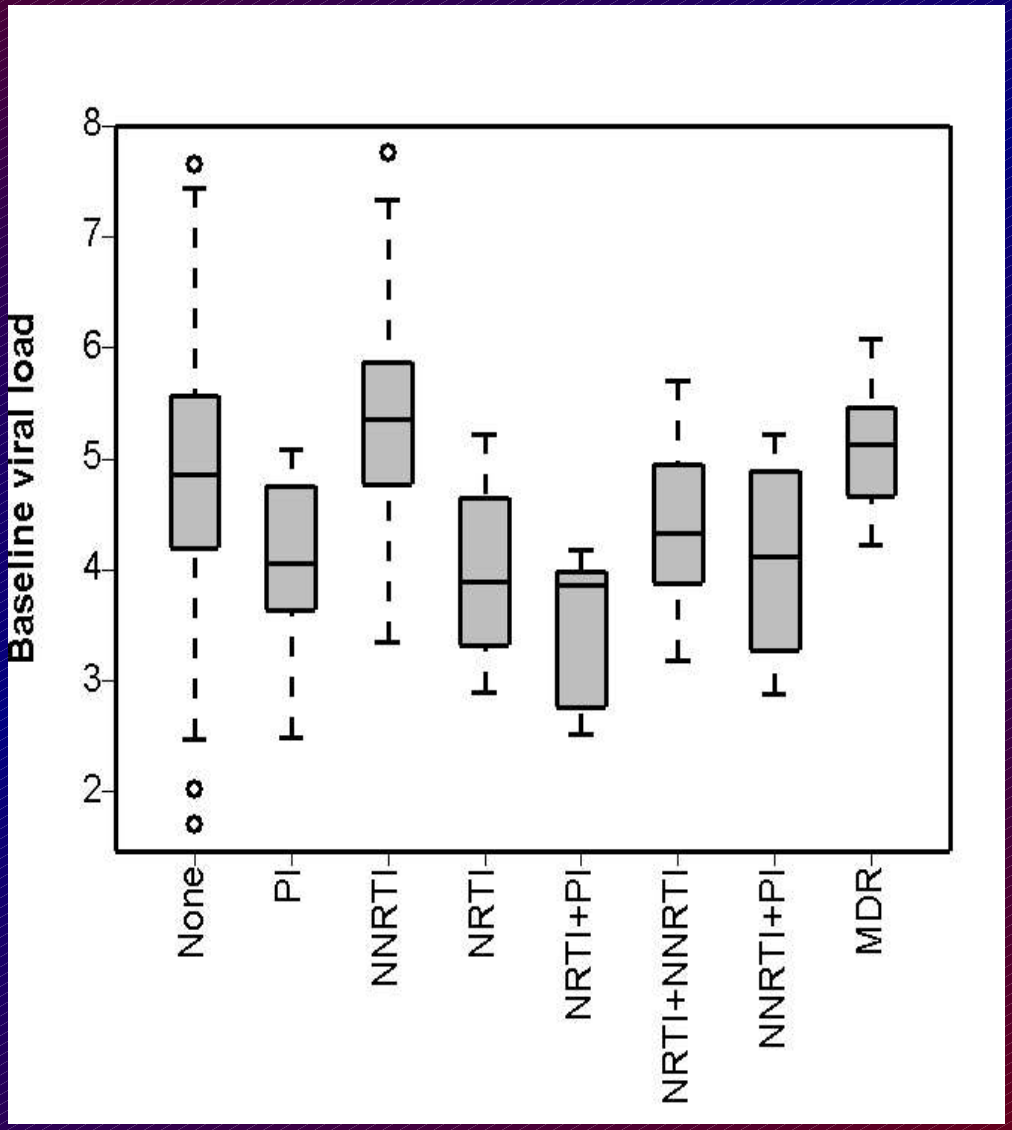
Are other types of drug resistance correlated with higher viral loads?

- Expanded analysis to look at resistance to NRTIs and PIs, alone and in combination
- Preliminary results available using baseline viral loads from national AIEDRP database
    - San Diego
    - Los Angeles
    - San Francisco
    - Seattle
    - Vancouver
    - Montreal
    - New York
    - Birmingham
    - Denver

PI and NRTI resistance are associated with lower baseline VL



Impact of transmission of multiple drug resistance



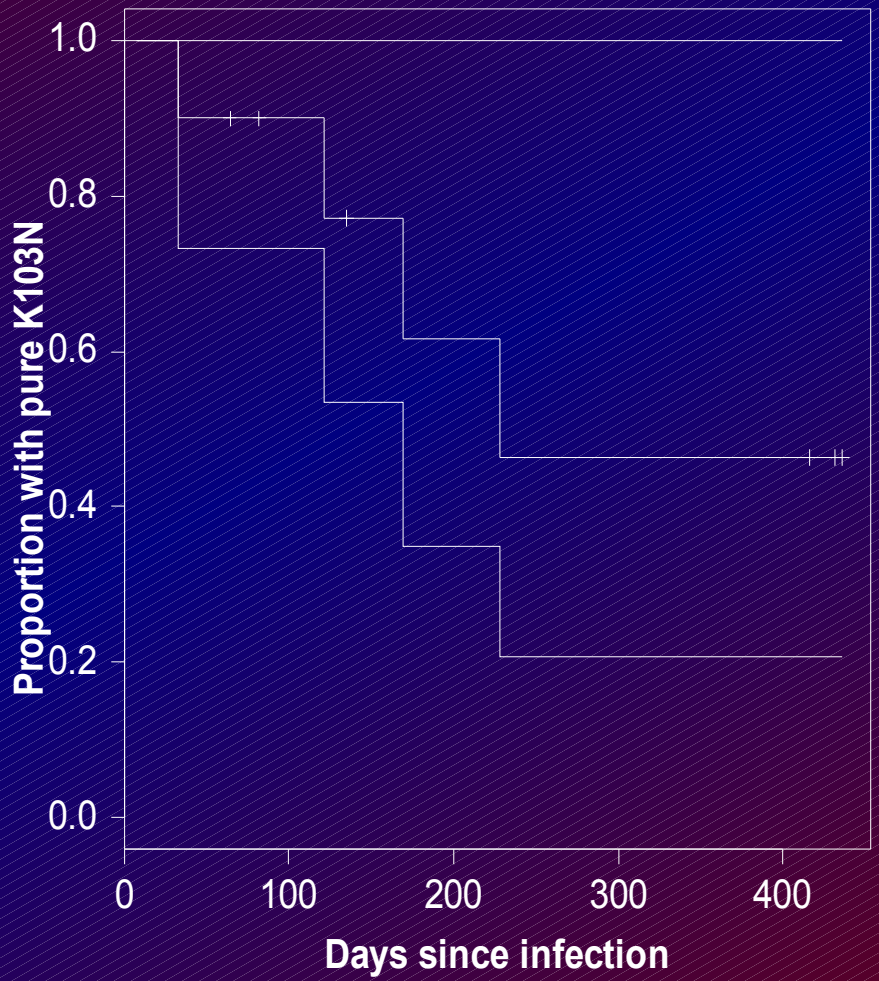
Conclusions

- Transmission of NNRTI resistant virus is associated with higher viral loads, both alone and in the presence of NRTI- and PI-resistance associated mutations
- This may account for the high frequency of transmitted NNRTI resistance
- Is this a direct or indirect effect?

Evolution of transmitted NNRTI resistance

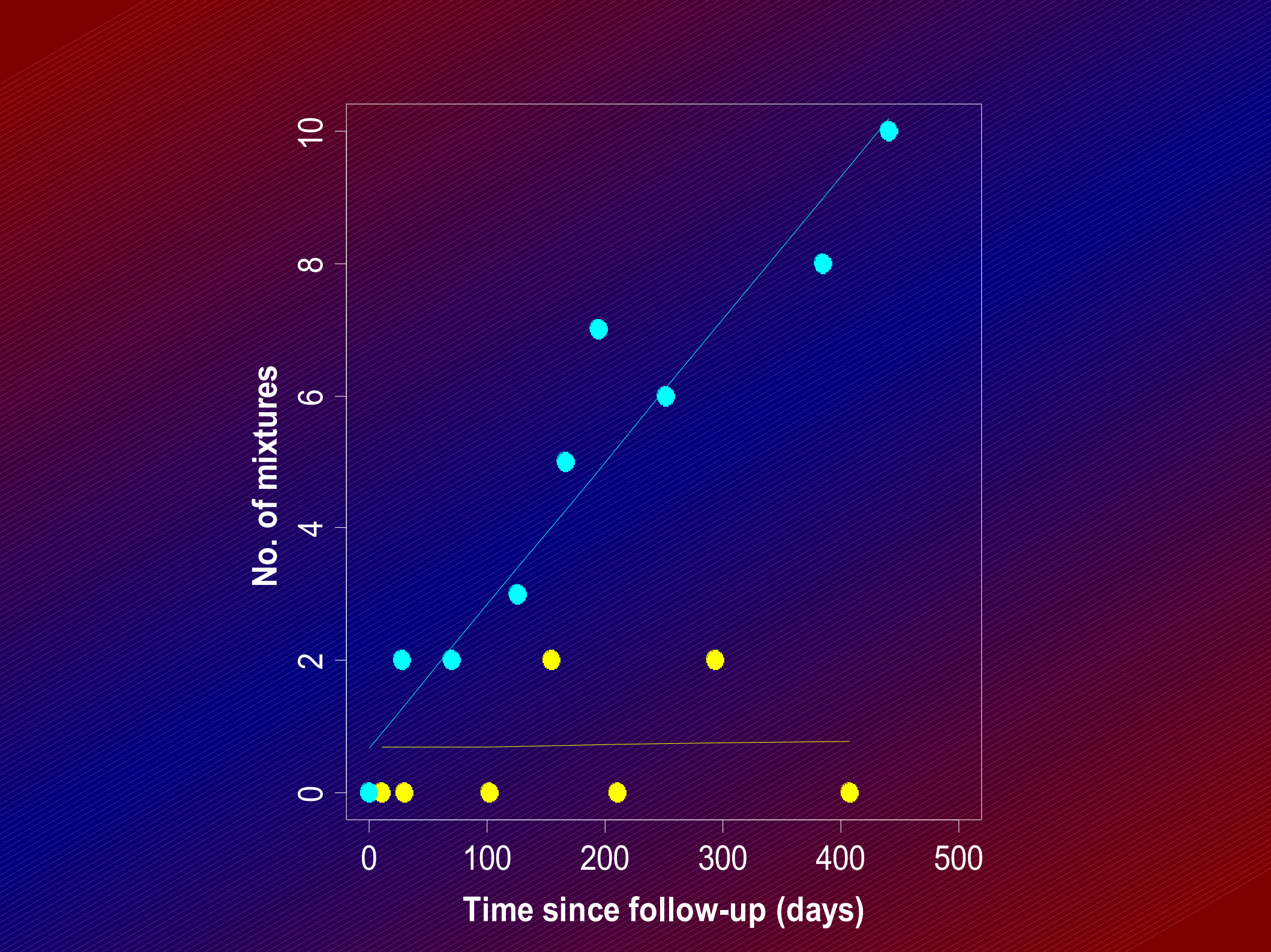
- In the absence of drug selection pressure, we would expect virus to revert to drug-sensitive virus
- Resistant virus reverts to wild type within 3 months in individuals with primary drug resistance
  - Stresses the need for drug resistance testing at diagnosis
- How long does reversion take in individuals with transmitted drug resistance?

Time to reversion of resistance to a mixed resistant/wild type population



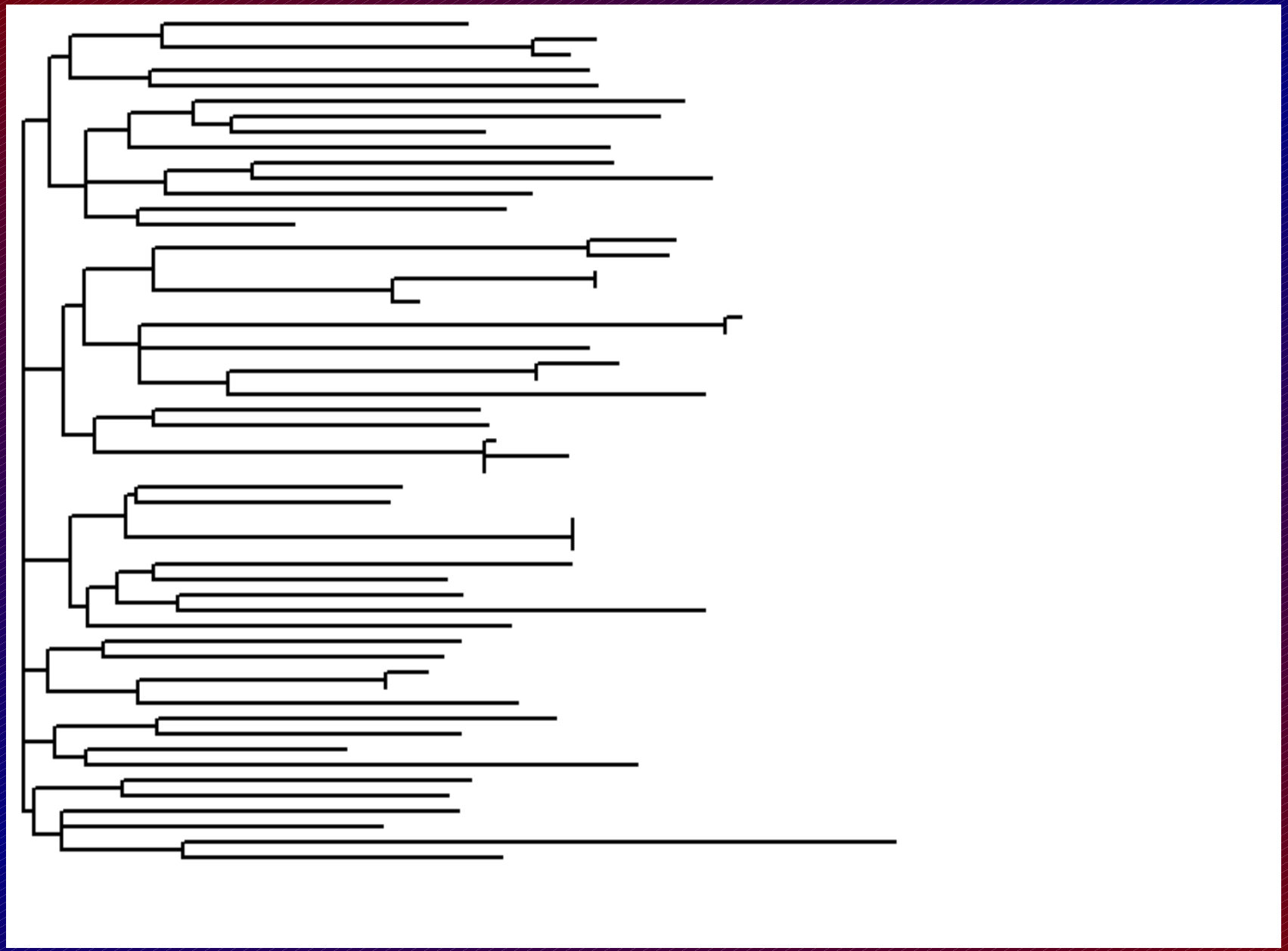
Accumulation of mutations over time

- We counted the number of amino acid mixtures at all sites in protease and reverse transcriptase over time
- Most individuals showed a progressive increase in the number of mixtures over time,
- Viral loads (and hence replication) are also high in these patients
- Reversion to K103N is not due to lack of mutational input


No. of mixtures
0
2
4
6
8
10
0
100
200
300
400
500
Time since follow-up (days)

Sequence vs. point mutation assays

- Point mutation assays may be more sensitive for detection of polymorphisms
  - Which mutations to look for?
- Sequences can be used for phylogenetic analysis
  - Look for clustering by risk group, area, demographics, etc.



Which genes?

- Most 'genotyping' assays sequence only a partial pol gene
- What about new drugs?
  - Integrase inhibitors
  - Fusion and coreceptor inhibitors (env)

Which compartment?

- Blood is the most frequently sampled
- Drug resistance may persist in genital secretions, latently infected cells, the central nervous system