

Will Transmission of Drug Resistant HIV Be Driven By Individuals Infected with Drug Resistant Strains?

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Introduction

- Effective antiretroviral (ARV) therapy can
 - prolong AIDS-free survival and
 - reduce the probability of transmission of HIV by lowering viral loads in plasma and genital secretions
- BUT transmission of drug resistant virus can reduce the positive impact of therapy:
 - incidence of infection with drug resistant virus was found to be between 3% and 13% in North America and Europe^{1,2}.
 - Recently an increase in this incidence was described in a large multicenter study in North America³
 - a parallel increase was seen in the UK⁴.
- We have attempted to evaluate the current and probable future frequency of transmission of drug resistant HIV by analysis of retrospective clinic data.

Methods

Patients
Study participants (N = 123) were enrolled at clinics in San Diego and Los Angeles between 1996 and May 2000. They were predominantly men who reported a history of sex with men. None of the subjects had received more than 7 days of prior antiretroviral therapy prior to study entry and analysis of ARV susceptibility.

Frequency of resistance in patients with primary HIV infection
A consensus sequence was determined for the reverse transcriptase and protease coding regions from plasma samples by PCR amplification and ABI sequencing.

Prevalence of drug resistance
Retrospective analysis of quarterly clinic data for 1997 and 1999 was used to estimate the prevalence of virologic failure in the Owen Clinic, a UCSJ Hospital referral clinic serving the city of San Diego. A plasma viral load (pVL) > 1000 copies/ml was taken as evidence of failure of ARV therapy.

Uncertainty analysis
Each uncertain parameter was modeled using 100000 random numbers generated from a uniform distribution, to generate a range of estimates of the relative number of transmitters of resistant virus in 1997. We assumed that between 36 and 63% of infected individuals attend clinic⁵, and that 63% of clinic attendees had pVL greater than 1000 (see Results). We also assumed 86% of individuals attending clinic with pVL > 1000 have received some ARV therapy and that 70-80% of these harbored resistant virus. Among individuals not attending clinic, 80-90% were assumed to have pVL > 1000 and between 0 and 10% of these were assumed to harbor transmitted resistant virus.

Frequency of transmitted resistance

- From analysis of consensus genotypes:
- In 1996-1998: **6%** of subjects had mutations at sites associated with resistance (N = 65)
 - 1999-2000: **17%** had mutations at resistance-associated sites (N=58)
- The difference is significant (Exact p = 0.04)
- 1996/8:
 - 1 215Y, classical ZDV-associated mutation
 - 1 each 215S, 215D, 215E, (revertants of 215Y)
 - 1 PI-associated (V82T)
 - 1999/2000:
 - 3 ZDV - associated (41L, 2 with 215D)
 - 1 3TC - associated (184V)
 - 1 ddC - associated (T69D)
 - 1 MDR (69S mutation + 215F + K103N + Y181C + L90M)
 - 2 NNRTI - associated (K103N)
 - 2 PI - associated (V82A)

Who transmits drug resistant HIV?

- In 1997 54% of clinic patients who received ARV had pVL > 1000*
- if 75% of therapy failures fail because of resistance⁶, 54% x 0.75 = 40% of clinic patients are potential transmitters of drug resistant HIV.
 - Thus 40% x 0.5 = 20% of all HIV+ are potential transmitters of ARV-resistant HIV, or (20% + 74%) = 27% of all HIV transmitters.
- Re-estimating this value allowing for uncertainty in the contributing parameters (see Methods) we obtained an estimate of **30% ± 9%**
- But the incidence of primary resistance was just 6% in 1996-8 and only 17% by 1999.**

Why was drug resistant virus transmitted less often than expected?

- 1) *“Individuals with resistant virus are less infectious because they have lower viral loads than those who have not received ARV”* **NO**

We compared pVL for these two groups using data from this clinic (Figure 1) and found **NO DIFFERENCE** in mean pVL.

Mean pVL no ARV = 4.48 (N = 44); Mean pVL therapy failures = 4.50 (N = 126; p = 0.78)

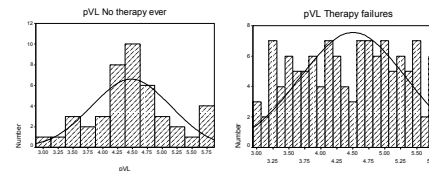


Figure 1. pVL for individuals never on ARV and for individuals failing ARV at the same clinic

This result confirms earlier observations made at a different clinic⁷.

Transmission of resistant virus (cont.)

- 2) *Resistant viruses are less likely to establish an infection because of lower “fitness”* **NO**
- Differences in fitness, for these mutations ~ 10%. But susceptible virus from patients with primary infection has a **4-fold** range in replicative capacity. A 10% difference in fitness is not significant against this level of background variation from other factors.
- 3) *Patients who acquire resistance on ARV retain a reservoir of susceptible virus.* **YES**
- viral reservoirs are established early in infection
 - interruption of ARV typically results in resurgence of wild-type virus within weeks⁸.
- 4) *Virus in genital secretions can differ in frequencies of drug resistant mutations from blood plasma* **YES**
- concentration of some ARVs in seminal fluid can be much lower than in blood plasma, reducing the selective advantage of resistant strains⁹⁻¹⁰.

BUT INDIVIDUALS INFECTED WITH A RESISTANT VIRUS WILL HAVE A HOMOGENEOUS VIRAL POPULATION AND RESISTANT VIRUS IN THEIR RESERVOIRS UNTIL A REVERTANT BECOMES PREDOMINANT. This requires between several months and years (Little et al CROI9, Abstract #95).

We have developed a model with both classes of potential transmitters of drug resistant HIV (Fig. 2)

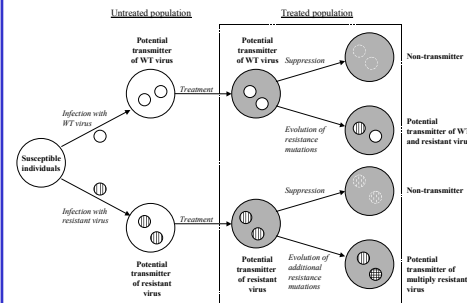


Figure 2. Model for transmission of ARV-resistant HIV

Projected transmission of ARV-resistant HIV

Analyzing a simplified model: $I_{PR}(t) = \frac{\beta \phi I_{AR}}{\beta' - \mu} (e^{(\beta' - \mu)t} - 1)$

β' is an infectivity constant (including probability of infection per contact and contact rate), μ is rate of loss due to death, reversion, suppression etc., t is time ϕ is the relative probability ϕ of a patient with acquired resistance transmitting resistant virus.

We project the importance of primary resistance (I_{PR}) versus acquired resistance (I_{AR}) in transmitting drug resistant strains.

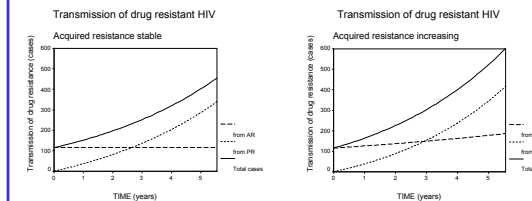


Figure 3. Projected transmissions of drug resistant HIV (Initial population of 1000 cases of acquired resistance. Parameter values from 1997)

Conclusions

- acquired drug resistance is transmitted about 30% as often as expected
- but from primary drug resistance, resistant strains will be transmitted for years
- primary resistance will become the major source of new transmissions of resistance
- substantial increases in the prevalence of primary drug resistance can be expected

References

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