

Prevalence of Reduced Drug Susceptibility in Treatment-Naive Patients in the UK

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BACKGROUND

Transmitted drug resistance is conventionally defined as presence of one or more drug-associated mutations (e.g. based on IAS list) in virus sampled from a treatment-naive individual. However this approach is problematic:

- what mutations to include?
- should it be subtype specific?
- should it be based on single mutations or patterns?
- should definitions vary by time depending on drugs that have been utilised prior to this?

These difficulties are obviated if one focusses instead on reduced drug susceptibility. This is also more relevant from a clinical perspective.

METHODS

Data

Resistance tests reported to UK HIV Drug Resistance Database, which was set up in 2001 as a central repository of resistance tests performed as part of routine clinical care in the UK.

The ART status of patients (naïve to treatment or experienced) at the time of each resistance test was determined from clinical data or the reason for the test specified on the request form. If a patient had more than one pre-therapy test, the first only was used in the analysis.

Genotypic Resistance

Resistance was defined as at least one major mutation according to IAS-USA (October, 2003) with the addition of (i) in RT, any 190 or 215 variant, or 69N (ii) for lopinavir, at least 7 relevant mutations.

Drug susceptibility

Based on Stanford HIVDB algorithm (version 2004.04). Resistance to each drug is determined by summing weights across relevant mutations and classifying as: "S" if score<15, "I" if score=15-29, "R" if score≥30

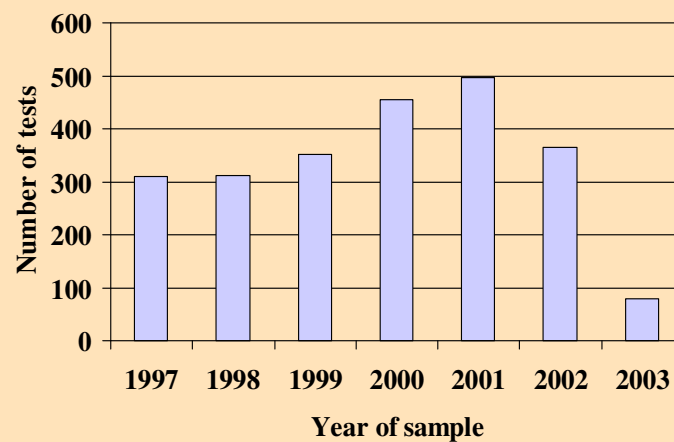
For resistance tests lacking nucleotide sequence, a sequence was synthesised from amino acid mutations by:

- choosing an arbitrary nucleotide triplet
- in mixtures the highest "scoring" aa was used
- insertions and deletions edited manually

RESULTS (1)

A total of 2,191 tests were available for analysis (Fig 1.). Data for 2003 are still very incomplete.

Fig 1. Number of tests by year of sample



8.9% of tests showed high level resistance ("R") to one or more antiretroviral drugs (Table 1). This figure increased to 11.9% if the "I" category was also considered as conferring resistance, still considerably lower than the proportion of tests with one or more major IAS mutations (18.0%).

The relative "over estimation" of the level of drug resistance using the list of IAS mutations was mainly due to mutations at codon 33 in PRO and the V118I mutation in RT.

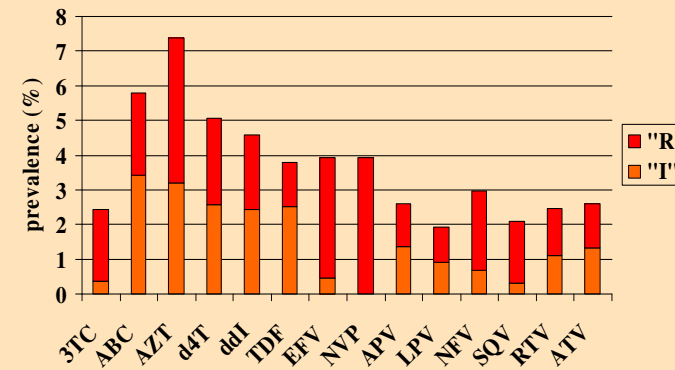
Table 1. Overall prevalence of drug resistance by IAS list and Stanford algorithm

Drug class	Prevalence of resistance (%)		
	IAS	Stanford: "I" or "R"	Stanford: "R"
NRTI	11.8	9.1	6.7
nNRTI	4.5	3.9	3.9
PI	6.7	3.0	2.3
Any class	18.0	11.9	8.9

RESULTS (2)

Among the NRTIs, the prevalence of reduced drug susceptibility ranged from 2.4% (lamivudine) to 8.4% (zidovudine) (Figure 2). Approximately half of these figures was due to intermediate resistance. The overall rate of drug resistance for each of the nNRTIs was 3.9%. The PI class showed the least resistance, the rate for individual drugs ranging from 1.9% to 2.9%.

Fig 2. Rate of resistance to individual drugs



Most resistance was limited to one class, with low levels of cross-class resistance (Table 2). 29 (1.3%) samples had reduced susceptibility to all three main drug classes.

Table 2. Patterns of cross-class resistance

Stanford: "I" or "R"			Number (%)
NRTI	nNRTI	PI	
			138 (6.3)
			35 (1.6)
			26 (1.2)
			22 (1.0)
			11 (0.5)
			29 (1.3)

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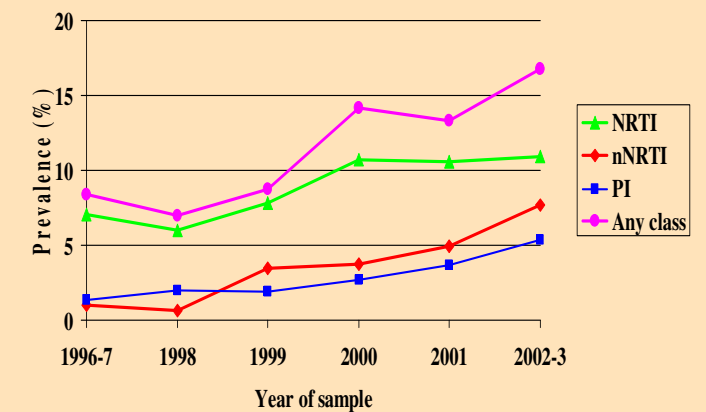
We gratefully acknowledge help from the Stanford HIV Drug Resistance Database.

This work was undertaken by the MRC Clinical Trials Unit who received funding from the Department of Health; the views expressed are those of the authors and not necessarily those of the Department of Health.

RESULTS (3)

Highly significant time trends were observed for each drug class (Figure 3), although the prevalence of reduced NRTI susceptibility appears to have stabilised in recent years. However, the rate of reduced susceptibility to nNRTIs and PIs continues to show approximately linear increases. In 2002-3, 16.7% of samples showed reduced susceptibility to at least one antiretroviral drug.

Fig 3. Trends in resistance by calendar time



COMMENTS

- Consistent with the results of Little et al. (NEJM, 2002, 347:385-94), mutations-based analyses were found to over-estimate the prevalence of clinically-significant drug resistance.
- The proportion of samples with resistance to one or more drugs doubled from 8.4% in 1996-7 to 16.7% in 2002-3.
- The analysis is based on any patient with a pre-therapy resistance test, not just patients who were recently infected. Thus, the true rate of current transmitted resistance may be considerably higher than 16.7% because of (a) infections may have occurred several years previously (b) the likelihood of back mutation.
- The level of transmitted drug resistance in the UK appears to be higher than that reported in most other countries.