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HIV-1 Subtypes and Virological Response to HAART in Europe

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BACKGROUND

Antiretroviral (AR) regimens may vary in ability to suppress viral load (VL) in people infected with different HIV subtypes, e.g. due to differences in resistance development. AR drugs have predominantly been developed in Western Europe and the US on the basis of HIV-1 subtype B, as B is the most prevalent strain. Resistance mutations have also been defined according to consensus sequences from subtype B. However, non-B subtypes, which are widespread in Africa, Asia and much of Eastern Europe are increasingly spreading worldwide through travel and migration.

OBJECTIVE

To compare virological response to highly active antiretroviral therapy (HAART) in patients infected with different HIV-1 subtypes in Europe.

METHODS

Analysis was carried out on HIV-1 infected patients in the EuroSIDA study who met the following inclusion requirements:

- Started HAART defined as at least three antiretroviral drugs including at least one protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI), abacavir (ABC) or tenofovir (TFV), with no prior PI/NNRTI/ABC/TFV experience.
- Subtype determined before starting HAART.
- Unsuppressed viral load defined as $\geq$ 500 copies/mL, measured within six months before starting HAART.

Virological response to HAART (whether or not first viral load measured 6-12 months from start of HAART was suppressed, i.e. $\leq$ 500 copies/mL) was analysed via logistic regression to compare HIV-1 B and non-B infected patients. Stratification of non-B subtypes into A, C and 'Other' was also investigated. Patients with no available viral load between months 6-12 were dealt with in two ways; by defining them as virological failures or excluding them from analyses.

RESULTS (1)

- 684 (6%) of the 11229 patients in EuroSIDA met the inclusion criteria, of which 79 (12%) were infected with subtype A, 547 (80%) with B, 24 (4%) with C and 34 (5%) with any other subtype.
- 488 (71%) of the subtypes were determined by phylogenetic analysis; 83% of B patients, 24% of non-B. The remaining subtypes were determined from EuroSIDA follow-up forms, sample analysis and virology paper forms.
- Median dates of starting HAART were July 1998 and May 1997 for B and non-B respectively, p<.001 (Table 1).
- Baseline viral loads were similar between B and non-B infected patients (4.7 and 4.6 $\log_{10}$copies/mL, p=0.289), as were baseline CD_4 counts (244 and 240 cells/mm^3, p=0.545).
- 56% of B and 22% of non-B patients had RT (reverse transcriptase) genetic sequences available with which to study the pattern of resistance mutations, within one year before starting HAART. Levels of NRTI resistance, defined as at least one IAS USA (Oct 2004) NRTI mutation, were similar between groups, p=0.519.
- The prevalence of different subtypes was found to differ significantly between regions, p<0.001 (Figure 1). However there may be some bias in patient selection for subtype testing and so results cannot be assumed to faithfully reflect the underlying prevalence in the regions.
- HAART regimens also did not differ significantly between groups, p=0.087 (Figure 2). Over 50% started regimens containing one PI, and 53% of B and 44% of non-B were AR-naïve at baseline, p=0.05.

Table 1

Characteristics at start of HAART regimen, B vs Non-B

	B		Non-B		p*
All (n, %)	547	80.0	137	20.0	-
Male	444	81.2	88	64.0	<.001
Homo-/bi-sexual exposure	301	55.0	45	32.8	<.001
Previous AIDS diagnosis	100	18.3	25	18.2	0.993
Antiretroviral-naive	292	53.4	60	43.8	0.045
Resistance results available?	308	56.3	30	21.9	<.001
NRTI resistance?	89	28.9	7	23.3	0.519
(Median, IQR)					
Date started HAART	Jul 98	(Jun 97-May 00)	May 97	(Nov 96-Apr 98)	<.001
Date of subtype test	Jul 97	(Jan 97-Mar 99)	Aug 96	(Feb 95-Jul 97)	<.001
CD_4 count (cells/mm^3)					
Baseline	244	(137-340)	240	(119-330)	0.545
Nadir	185	(100-272)	190	(102-295)	0.899
Viral load ($\log_{10}$cps/mL)					
Baseline	4.7	(4.1-5.2)	4.6	(3.8-5.2)	0.289
Max ever	5.0	(4.5-5.5)	5.0	(4.5-5.6)	0.824

*p values obtained from Chi-square and Kruskal-Wallis tests

Figure 1

Subtypes in EuroSIDA regions

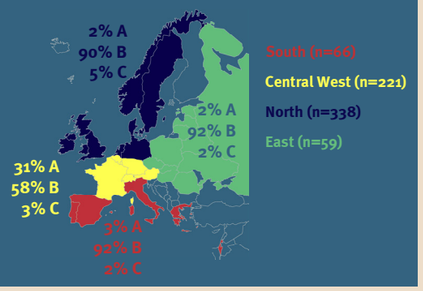
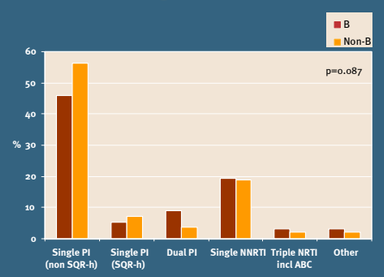


Figure 2

HAART regimens - B vs Non-B



RESULTS (2)

- Before adjustment for other variables, virological response rates did not differ significantly between patients infected with A (57%), B (64%), C (71%) or 'Other' (74%) when treating missing values of viral load as virological failures, n=684, p=0.192 (Figure 3).
- There was a borderline significant difference when missing values were excluded, n=613, p=0.056, showing a slightly lower virological success rate in those with subtype B compared to C and 'Other'. However, results using the missing value = virological failure approach are reported as the two methods gave similar results in the adjusted analysis.
- After adjustment for date starting HAART, baseline CD_4 nadir, vl, age, prior AIDS diagnosis, origin, AR-naïve or not, no. of new drugs and regimen type, no significant difference was found in virological response between subtype B (reference) and non-B, odds ratio (OR): 1.31, 95% CI (0.81-2.11), p=0.27 (Figure 4). Likewise in A, C and 'Other' subtypes compared to B, no significant differences were found, adjusted ORs: 1.09, (0.63-1.89), p=0.76; 1.56, (0.53-4.58), p=0.41; 2.20, (0.86-5.62), p=0.10 respectively.
- Sensitivity analyses gave results consistent with the main analysis. There was no significant difference between B and non-B infected patients when restricting to:
  - Patients with subtypes determined by phylogenetic analysis only (the most reliable source), n=488, p=0.137.
  - AR-naïve patients, n=352, p=0.204.
  - Patients with subtypes determined by phylogenetic analysis or post-1999 (due to problems with assays before then), n=544, p=0.140.

Figure 3

% achieving viral suppression

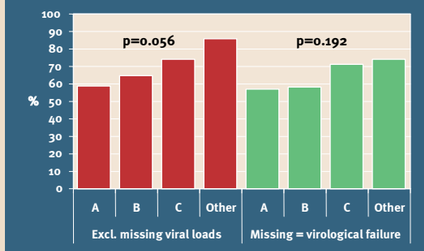
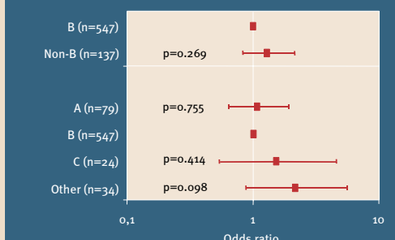


Figure 4

Adjusted odds ratios of achieving viral suppression



CONCLUSIONS

There was no evidence of a significant difference between B and non-B infected patients in terms of achieving a successful virological response to HAART. Further stratification by A and C subtypes also supported a conclusion of no significant differences compared with B. The continued expansion of the EuroSIDA resistance database and the exclusive use of phylogenetic analysis to determine subtypes will allow more sensitive analyses in the future with increased power to detect any true differences.

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