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Long term probability of detecting HIV drug resistance in drug-naïve patients starting currently recommended first-line combination antiretroviral therapy

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BACKGROUND

There are relatively limited data available on the probability of detecting HIV resistance after the first few years of combination antiretroviral therapy (cART) in patients starting currently recommended first-line regimens (i.e. containing either an NNRTI or ritonavir boosted PI with 2 nucleosides) as part of routine care.

OBJECTIVES

i) To identify the predictors of having a resistance test at time of virological failure of first cART
ii) To estimate a lower limit for the long term probability of detecting HIV resistance after start of cART
iii) To compare rates of accumulation of resistance according to the initial regimen started

PATIENTS AND METHODS

We considered HIV-infected patients included in a large UK patient cohort (the UK CHIC Study) who started their first cART with 2 nucleosides plus either a NNRTI or a PI/r after 1997 and when drug-naive. All results of the genotypic tests performed on these patients are recorded in a linkable resistance database; the results of the tests recorded after the date of first cART were used in this analysis.

Statistical analysis

Time of virological failure was defined as the time from the date of cART initiation to the first of 2 consecutive viral loads >400 copies/mL. Virological rebounds that occurred while patients were off-ART were not included for the calculation of the incidence of failure.

Conditioning on having experienced virological failure according to this definition, factors associated with the probability of having a resistance test in a time window ranging between 6 months before and 12 months after the estimated date of failure were identified using logistic regression.

Time to resistance was defined as the time to detection of ≥1 major mutation among those listed by IAS (September 2007). Time to drug-class resistance was defined as the time to detection of ≥1 major mutation for the class. We did not insist on the fact that there had to be evidence of virological failure for this analysis. Standard survival analysis was employed by means of Kaplan Meier estimates and Cox proportional hazards model stratified by calendar year of starting cART.
The logistic regression model included the same set of potential confounders used in the Cox regression models with the addition of calendar year of cART (fitted as continuous) as shown in Table 2 and bottom of Table 4.

RESULTS

Table 1 shows the main characteristics of our study population. These were typical of the HIV epidemic in the UK with a small percentage patients who acquired HIV via injecting drug use and with a low CD4 count at the time of ART initiation. The majority of patients started a regimen containing 2 nucleosides and a NNRTI (85%). The percentage of patients who started lamivudine were 82% in the NNRTI group and 80% in the PI/r group. The corresponding proportion of people starting zidovudine were 62% and 48%.

Overall, 1,016 patients (17%) showed evidence of virological failure (VF) on treatment according to our definition. Of these, 478 (47%) were tested for drug resistance in the time window ranging between -6 months before the estimated date of VF and +12 months after this date. The median absolute time between the date of VF and the date of test was 2 months (range:0-12). Interestingly, patients with low CD4 count and those who had been diagnosed with AIDS before starting cART were more likely to be tested for drug resistance at time of virological failure than those with less advanced HIV disease at baseline.

Table 1

Characteristics of n=6,009 patients at the date of starting 2 nucleosides and a NNRTI or PI/r

Gender, n(%)	
Female	1,596 (27%)
Mode of HIV exposure, n(%)	
IDU	192 (3%)
Homosexual contacts	3203 (53%)
Heterosexual contacts	2389 (40%)
Age, median (range)	
Years	36 (18-84)
CD4 count, median (range)	
Cells/µl	200 (1-748)
Viral load, median (range)	
Log_{10} copies/mL	4.99 (2.70-7.64)
Previous AIDS, n(%)	1,232 (21%)
Calendar year, median (range)	2002 (1998-2005)
Type of first regimen, n(%)	
NNRTI	5,080 (85%)
PI/r	929 (15%)

Table 2

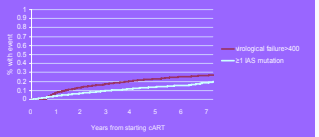
Predictors of having a resistance test around the time of virological failure from fitting a logistic regression (n=1,016, 47% with test)

	Crude OR (95% CI) p-value	Adjusted OR (95% CI) p-value
HIV Exposure		
Homosexuals	1.00	1.00
IDU	0.56 (0.31-1.02) p=0.06	0.49 (0.26-0.92) p=0.03
Heterosexuals	0.81 (0.63-1.05) p=0.11	0.71 (0.50-0.99) p=0.05
CD4		
>350	1.00	1.00
201-350	1.77 (1.15-2.71) p=0.009	1.76 (1.14-2.72) p=0.01
0-200	2.11 (1.41-3.15) p=0.0003	2.03 (1.33-3.10) p=0.001
Previous AIDS		
No	1.00	1.00
Yes	1.64 (1.22-2.19) p=0.0009	1.59 (1.17-2.17) p=0.003

Adjusted for: year of enrolment, age, gender and viral load at cART

Figure 1

Proportion of patients with virological failure >400 copies/mL and with drug-resistance mutation detected yearly after cART initiation



Also patients who acquired HIV via injecting drug use or heterosexual contacts were less likely to be tested than homosexual men (Table 2).

Figure 1 shows the Kaplan Meier estimates of the percentage of patients with virological failure and the percentage for whom ≥1 IAS mutation had been detected yearly after starting cART. By 7 years from starting cART 27% of patients (95% CI: 25-29) had experienced virological failure. This might be considered to represent the upper limit of the percentage of people who have newly developed resistant virus populations that lead to viral rebound by that point in time; the Kaplan-Meier estimate of the probability that resistance was actually detected by that point was somewhat lower at 20% (95% CI: 18-22). The absolute number of patients with detected IAS-resistance over the whole follow-up was 603 (10%).

Interestingly, in the Kaplan-Meier analysis while there was no evidence that the proportion of patients with nucleoside resistance was different in patients who started 2 nucleosides + NNRTI compared to those who started 2 nucleosides + PI/r (log-rank test p=0.22, Figure 2), there was a significant difference in the incidence of class-specific drug resistance. In particular, patients who started a regimen including a PI/r as the third drug were at significantly lower risk of having a PI mutation detected over time than those who started a NNRTI to accumulate NNRTI-resistance (log rank test p=0.0001, Figure 2. Of note, in the group of patients who started 2 nucleosides + NNRTI the rate of accumulation of NNRTI resistance seemed to be similar to that of nucleoside resistance (Figure 2, Table 3).

Table 3 shows the same Kaplan-Meier estimates reported in Figure 2 but extended to specific subgroups of nucleoside mutations (e.g. 184V and TAMs) and to an overall measure of accumulation of drug resistance (≥1 IAS mutation) at specific time points (3, 5 and 7 years). Overall, as expected, the incidence of 184V (11.5% by 7 years) was around 2-fold higher than that of ≥1 TAMs (6%). When we compared the incidence of 184V and TAMs between the NNRTI and PI/r group again we found no difference between the groups.

Finally, Table 4 shows the adjusted relative hazards of detection of drug resistance according to type of mutations and regimen started. After controlling for a number of potential confounders (listed at the bottom of the Table), again, the only significant difference in rate of resistance detection between the two groups was in the rate of class-specific mutations (i.e. NNRTI mutations in those starting 2 nucleosides + NNRTI and PI mutations in those starting 2 nucleosides and a PI/r). Specifically, we estimated a 60% reduction in the risk of detecting class-specific resistance in patients starting PI/r-containing regimens as compared to NNRTI-based regimens (Table 4).

Other factors independently associated with a lower risk of detecting ≥ 1 IAS mutations were older age (RH=0.68 per 10 years older, 95% CI: 0.61-0.76, p=0.0001) and female gender (vs. male RH=0.75, 95% CI:0.59-0.95, p=0.02). In contrast, a diagnosis of AIDS before baseline (vs. AIDS-free, RH=1.22, 95% CI:1.00-1.47, p=0.05) and patients with a baseline CD4 count of 201-350 (RH=1.30, 95% CI:0.95-1.78, p=0.09) and those with a count of 0-200 (RH=1.58, 95% CI:1.21-2.06, p=0.0007) were at higher risk of resistance detection than those with a CD4 count >350 cells/µl.

CONCLUSIONS

Patients who have an advanced clinical disease when they start cART, once they have shown evidence of virological failure, seem more likely to be tested for drug resistance than patients who have less advanced HIV disease.
In patients starting currently recommended first-line regimens in routine clinical practice, the rates of virological failure and of resistance detection are lower than is sometimes assumed, but nevertheless appreciable (27% and 20%, respectively, by 7 years); resistance to PI in patients who started PI/r was particularly low, although still detectable (5% by 7 years); as only 56% of patients with virological failure were tested, our percentages with resistance detected are lower limit estimates.
The choice of drugs in the initial regimen did not seem to be associated with different long-term risk of detecting nucleoside mutations; in contrast, the risk of accumulation of PI mutations in patients who were initiated on PI/r regimens was markedly lower than that of detecting NNRTI mutations in those who started a NNRTI. These results should be interpreted with caution as the comparison is not randomised and residual confounding cannot be ruled out.
The fact that we found no statistical evidence for a difference in rate of TAMs and 184V when comparing PI/r- and NNRTI- based regimens is not consistent with the results of clinical trials.

Figure 2

Proportion of patients with ≥1 NRTI mutations (solid lines), ≥1 NNRTI or ≥1 PI mutations (dotted lines) detected yearly after cART initiation and by class of third drug employed

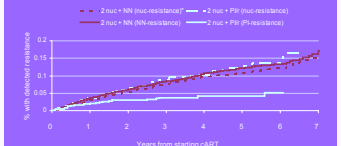


Table 3

Proportion of patients with drug resistance detected by time from cART initiation and according to mutations and regimen started

Mutations	Regimen started	3 years	5 years	7 years
TAMs	NNRTI	3%	5%	5%
	PI/r	4%	7%	7%
184V	NNRTI	5%	8%	11%
	PI/r	6%	10%	12%
≥1 IAS Nucleoside	NNRTI	8%	11%	15%
	PI/r	9%	13%	16%
≥1 Major PI	PI/r	4%	4%	5%
≥1 NNRTI	NNRTI	8%	12%	17%
≥1 Major IAS	NNRTI	10%	14%	20%
	PI/r	11%	17%	20%

Table 4

Relative hazards of detection of drug resistance according to mutations and regimen started

Mutations	Regimen started	Relative Hazard Crude (95% CI)	Adjusted (95% CI)
TAMs	NNRTI	1.00	1.00
	PI/r	1.45 (1.00-2.09)	1.31 (0.90-1.91)
184V	NNRTI	1.00	1.00
	PI/r	1.26 (0.94-1.70)	1.20 (0.88-1.62)
≥1 IAS Nucleoside	NNRTI	1.00	1.00
	PI/r	1.20 (0.93-1.55)	1.12 (0.86-1.45)
≥1 Major PI (if PI/r)	NNRTI	1.00	1.00
≥1 NNRTI (if NNRTI)	PI/r	0.44 (0.29-0.62)	0.39 (0.27-0.57)
≥1 Major IAS	NNRTI	1.00	1.00
	PI/r	1.19 (0.95-1.49)	1.11 (0.88-1.39)

Adjusted for: age, HIV exposure, gender, viral load and CD4 count at cART and diagnosis of AIDS before cART initiation. Stratified by calendar year of cART

MRC Medical Research Council

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