Exposure to antiretroviral (ARV) therapy in a large UK-based cohort of HIV-infected individuals: relationship to immunological and virological status

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INTRODUCTION

- The majority of ARV-naïve patients starting HAART will experience good virological and immunological responses to treatment. However, inadequate drug levels, the development of resistance, less than perfect adherence and tolerability problems mean that a minority will experience virological failure on their first treatment regimen, necessitating a switch in treatments (1).
- It is thought that an individual's initial treatment combination offers the greatest chance of sustained virological response, and those starting second- or third-line regimens generally have worse outcomes than those starting first-line regimens (2,3).
- This has raised the concern that some patients may ultimately exhaust all currently available treatment options

AIMS

- To describe levels of exposure to ARV treatment in a large multicentre cohort of HIV-infected patients from the UK
- To assess, at the population level, the relationships between ARV exposure and immunological and virological status

METHODS

- The UK Collaborative HIV Cohort (CHIC) is a collaboration of 7 HIV centres in the UK (Chelsea & Westminster, King's College, Mortimer Market, St. Mary's, Royal Free, Brighton General, St. Thomas').
- Individuals included in the cohort were HIV-positive, 16 years or older, and had attended one of the centres for care after 1st January 1996. To date, the database contains information on 13,833 individuals followed at 6 of the 7 centres.

- Information is provided on patient demographics, clinical events and deaths, ARV treatment and laboratory tests. Data are provided in a standardised format, agreed by all centres at the outset of the study.
- Patients transferring between centres are identified and their records linked. Patients are defined as under follow-up in any year if first and last seen dates at any of the centres suggested that they were under follow-up at that centre during the year
- A patient was defined as ‘exposed ‘ to an ARV drug if his/her treatment history recorded any use of the drug.
- Treatment failure was defined if (a) HIV RNA levels did not fall below 500 copies/ml in first 6 months on that regimen, or (b) HIV RNA levels fell <500 copies/ml but then rebounded above 1000 copies/ml at least once whilst on the same regimen. Patients were defined as experiencing 3-class failure if they had experienced treatment failure on a regimen including a PI and on one including a NNRTI

RESULTS

- The number of patients under follow-up in the cohort rose from 7294 in 1996 to 9231 in 2001. Patients in the cohort are broadly representative of HIV+ve individuals in the UK (82% male, 63% homosexual, 24% heterosexual, median age 34 years at first visit).
- By the end of 1996, only 41% of patients had been exposed to ARV therapy (Table 1), the maximum number of drugs exposed to was 9 and only 1% of patients had been exposed to three drug classes. By the end of 2001, 70% of patients seen in that year had been exposed to ARV therapy, patients had been exposed to a maximum of 15 ARV drugs and 26% had been exposed to three drug classes.
- Of those under follow-up in 2001 who had ever received ARV therapy, 37% had been exposed to all three classes, and the median (range) number of drugs exposed to was 8 (3-15).

Table 1: Exposure to ARV drugs among individuals in the UK CHIC study

Year	No. under Follow-up	NRTIs		PIs		NNRTIs		Any drug		% exposed to 3 classes
		% exposed	No. drugs	% exposed	No. drugs	% exposed	No. drugs	% exposed	No. drugs	
1996	7294	40.1	0 (0-5)	12.9	0 (0-3)	3.8	0 (0-2)	40.7	0 (0-9)	0.9
1997	7708	52.6	1 (0-6)	30.9	0 (0-4)	10.9	0 (0-2)	53.3	1 (0-11)	4.8
1998	8350	61.1	2 (0-6)	41.9	0 (0-4)	23.5	0 (0-3)	61.6	3 (0-13)	12.5
1999	8899	66.0	2 (0-6)	43.6	0 (0-5)	37.0	0 (0-3)	66.3	3 (0-13)	20.1
2000	9375	68.9	2 (0-7)	42.8	0 (0-6)	46.2	0 (0-4)	69.1	3 (0-15)	24.4
2001	9231	69.7	2 (0-7)	42.1	0 (0-6)	49.9	0 (0-4)	70.0	3 (0-15)	25.9

- The median CD4 count of patients under follow-up in each year rose from 207 cells/mm^3 in 1996 to 400 cells/mm^3 in 2001 (Figure 1); the percent with a CD4 count<200 cells/mm^3 declined from 38% to 15%.
- The median HIV RNA level decreased from 4.35 $\log_{10}$ copies/ml in 1996 to 2.93 $\log_{10}$ copies/ml in 2001, with the percentage with a viral load < 500 copies/ml increasing from 7% to 47% over the same period
- Median CD4 counts of those who started therapy in 1998/99 or 2000/01 declined until the year of starting therapy, whereafter they increased, and median HIV RNA levels following initiation of therapy decreased (Figure 2). CD4 and HIV RNA trends in those starting prior to 1996 and in 1996/97 were similar, with sustained increases in median CD4 counts and decreases in median HIV RNA levels. There was some suggestion of a 'flattening off' of CD4 and viral loads in these two groups in the last year of follow-up, but little evidence of failure.

Figure 1 : CD4 and HIV trends over time in the UK CHIC study

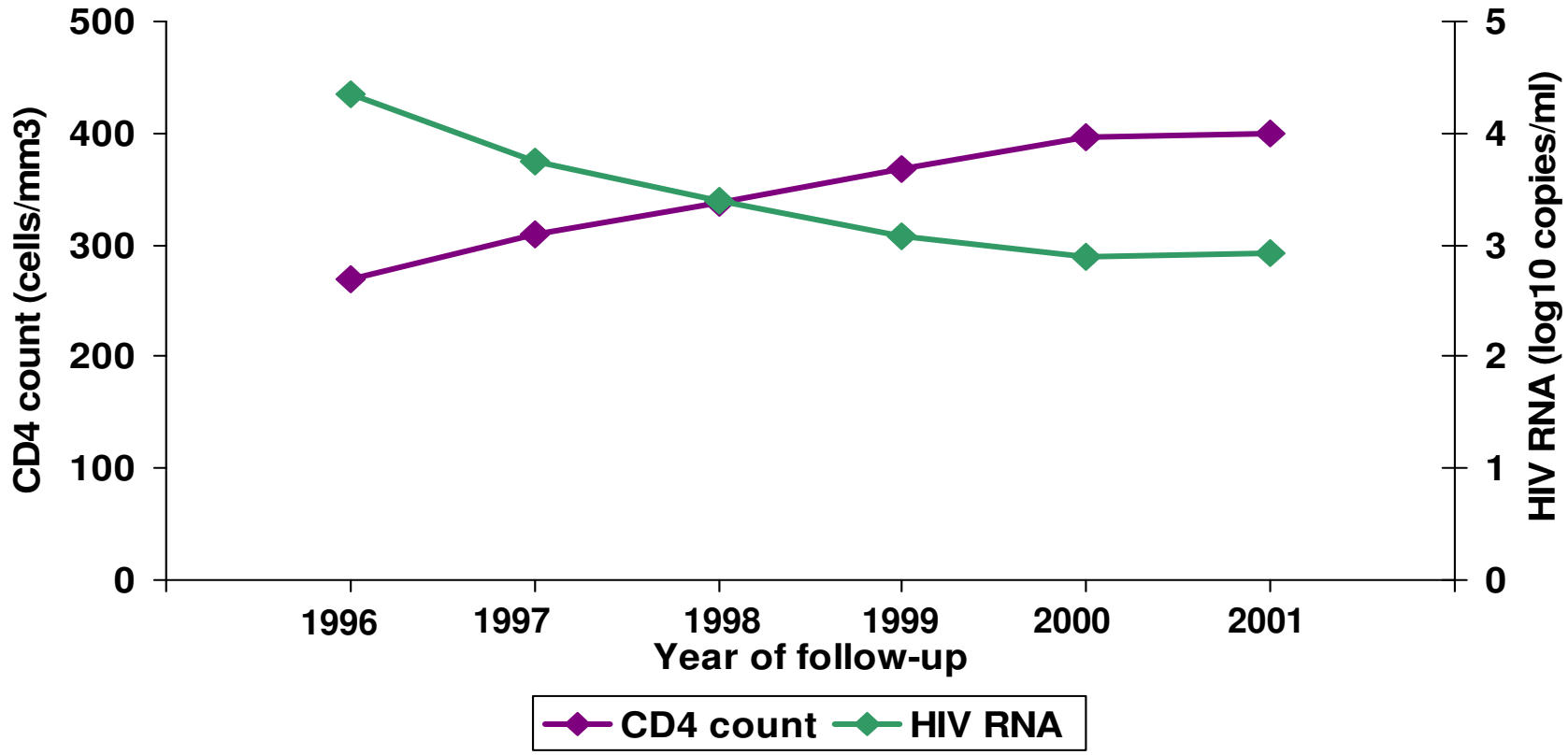
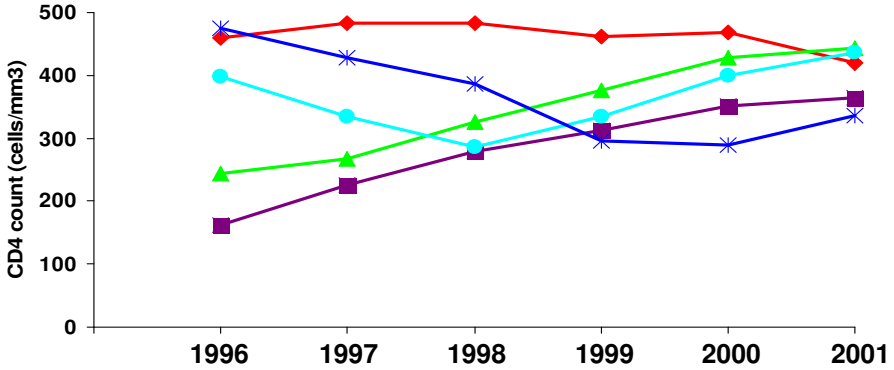
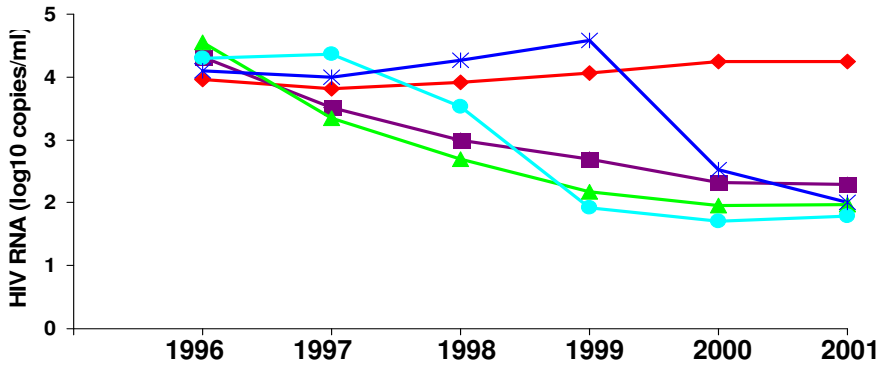


Figure 2 : CD4 and HIV RNA trends over time, stratified by year of starting ARV therapy



(i) CD4 trends



(ii) HIV RNA trends

Year of starting therapy: None <1996 1996-1997 1998-1999 2000-2001

- The proportion of patients under follow-up in each year who had an HIV RNA level >500 copies/ml at the end of each year was highest in those who started treatment prior to 1996 (Table 2) but continued to decrease over time
- Although the number of patients exposed to all three classes of drugs increased over time, (Table 3) median CD4 counts increased and HIV RNA levels decreased in these individuals
- The proportion who had experienced virological failure on combinations including PIs and NNRTIs reached around 21% by 1999 but has remained at that level since. Although individuals who had experienced 3 class failure generally had poorer CD4 counts and HIV RNA levels than those who hadn't experienced three-class failure, median CD4 counts still increased and HIV RNA levels decreased in this group.

Table 2 : Proportion of patients who have an HIV RNA level >500 copies/ml at the end of each year, stratified by year of starting ARV treatment

	Year of initiation of ARV therapy				
Year	Prior to 1996	1996/97	1998/99	2000/01	Not started
1996	91.6	93.6	96.4	98.0	93.4
1997	73.2	68.5	89.3	94.7	85.6
1998	57.4	47.1	61.1	96.5	89.2
1999	49.6	40.4	33.4	94.7	90.4
2000	44.4	37.0	28.3	46.7	91.4
2001	40.4	35.2	32.8	30.7	89.8

Table 3 : Trends in CD4 counts and HIV RNA levels over time in those exposed to three classes of drugs

Year	No. patients exposed to 3 drug classes	Latest CD4 in year	Latest HIV RNA in year	% experiencing failure on all 3 classes
		Median (IQR)	Median (IQR)	
1996	63	139 (96-202)	4.6 (3.5-5.2)	1.6
1997	368	213 (120-308)	3.7 (2.7-4.8)	6.5
1998	1042	240 (130-379)	2.9 (1.8-4.3)	15.7
1999	1787	300 (163-460)	2.3 (1.7-4.0)	21.3
2000	2286	351 (216-518)	2.0 (1.7-3.6)	21.7
2001	2394	380 (237-556)	2.0 (1.7-3.3)	20.8

SUMMARY

- As expected, individuals with HIV infection in the UK have gradually become more treatment experienced over time; by the end of 2001, more than 1 in 3 of those who had received ARV therapy had been exposed to all three existing classes of drugs
- The virological and immunological status of patients has improved over time, in line with the increased use of antiretroviral therapy.
- At this time, however, our results do not suggest that those exposed to three classes of drugs have a dramatically worse immunological or virological profile than other treated patients. However, the high levels of cross-resistance between drugs from the same class means that there are now concerns about the possible lack of effective therapy for some of these individuals in the future. These individuals should be monitored closely for signs of possible treatment failure.

CONCLUSIONS AND LIMITATIONS

- Treatment patterns in individual clinics may be dependent on centre protocols or clinician preferences. Thus, a major benefit of using a large multi-centre cohort to describe ARV exposure, is that the results from the study may more accurately reflect treatment use in the UK.
- However, the validity of our treatment data does rely on accurate transfer of treatment information when a patient attends a clinic outside of the 6 centres that form this cohort. Thus, our estimates of ARV exposure may, in some cases, be slightly underestimated.
- Interpretation of trends at a population level should also be made cautiously. Increased CD4 counts over time may also result from an increase in the number of newly diagnosed individuals with high CD4 counts attending one of the centres. Results from centres within the collaboration, however, would suggest that this has not been the case with CD4 counts at diagnosis remaining low (3,4).

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