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Papers

Treatment exhaustion of highly active antiretroviral therapy (HAART) among individuals infected with HIV in the United Kingdom: multicentre cohort study

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Abstract

Objectives To investigate whether there is evidence that an increasing proportion of HIV infected patients is starting to experience increases in viral load and decreases in CD4 cell count that are consistent with exhaustion of available treatment options.
Design Multicentre cohort study.
Setting Six large HIV treatment centres in southeast England.
Participants All individuals seen for care between 1 January 1996 and 31 December 2002.
Main outcome measures Exposure to individual antiretroviral drugs and drug classes, CD4 count, plasma HIV RNA burden.
Results Information is available on 16 593 individuals (13 378 (80.6%) male patients, 10 340 (62.3%) infected via homosexual or bisexual sex, 4426 (26.7%) infected via heterosexual sex, median age 34 years). Overall, 10 207 of the 16 593 patients (61.5%) have been exposed to any antiretroviral therapy. This proportion increased from 41.2% of patients under follow up at the end of 1996 to 71.3% of those under follow up in 2002. The median CD4 count and HIV RNA burden of patients under follow up in each year changed from 270 cells/mm^3 and 4.34 $\log_{10}$ copies/ml in 1996 to 408 cells/mm^3 and 1.89 $\log_{10}$ copies/ml, respectively, in 2002. By 2002, 3060 (38%) of patients who had ever been treated with antiretroviral therapy had experienced all three main classes. Of these, around one quarter had evidence of "viral load failure" with all these three classes. Patients with three class failure were more likely to have an HIV RNA burden >2.7 $\log_{10}$ copies/ml and a CD4 count <200 cells/mm^3.
Conclusions The proportion of individuals with HIV infection in the United Kingdom who have been treated has increased gradually over time. A substantial proportion of these patients seem to be in danger of exhausting their options for antiretroviral treatment. New drugs with low toxicity, which are not associated with cross resistance to existing drugs, are urgently needed for such patients.

Introduction

The widespread use of highly active antiretroviral therapy (HAART) has had a big impact on the prognosis of HIV infected individuals.[1 2] Although most people starting HAART will experience good virological responses to treatment, imperfect adherence, tolerability problems, inadequate drug concentrations, and pre-existing or newly developed antiretroviral resistance may mean that in some patients, virological responses on their first treatment combination will fail within the first few years.[3] Compared with the initial treatment regimen, subsequent regimens are progressively less likely to produce a durable virological response.[4] The possibility of cross resistance developing to other drugs in the same class (nucleoside reverse transcriptase inhibitors, protease inhibitors, or non-nucleoside reverse transcriptase inhibitors) means that individuals who experience virological failure while receiving drugs from one of these classes tend to be at a higher risk of virological failure if they are subsequently treated with other drugs from the same class. Although new drugs are continually being developed, concern has therefore arisen that patients will ultimately exhaust all currently available options for treatment.

We describe levels of exposure to antiretroviral treatment and assess, at a population level, the relations between exposure to antiretroviral drugs and immunological and virological status in a large multicentre cohort of HIV infected patients from the United Kingdom. We investigate whether there is evidence that an increasing proportion of HIV infected patients is starting to experience increases in viral load and decreases in CD4 count, consistent with exhaustion of available treatment options.

Methods

The UK Collaborative HIV Cohort (UK CHIC) is a collaboration of some of the largest HIV centres in the UK. The development and characteristics of the cohort have been described in detail elsewhere.[5]

Selection of patients

The criteria for inclusion of an individual in the UK CHIC study were that the patient was HIV positive, older than 16 years, and had attended one of the centres for care at any time after 1 January 1996. To date, data from existing clinical databases from six centres (Chelsea and Westminster NHS Trust, King's College Hospital, Mortimer Market Centre, St Mary's Hospital, Royal Free Hospital, and Brighton and Sussex University Hospitals, see bmj.com) have been merged. Data on demographics, AIDS events and deaths, antiretroviral treatment, and laboratory tests, were provided in a standardised format, including all

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Table 1 Exposure to different classes of antiretroviral drugs among individuals from the UK CHIC study

Year	No of patients under follow up	Nucleoside reverse transcriptase inhibitors		Protease inhibitors		Non-nucleoside reverse transcriptase inhibitors		Any antiretroviral drug	
		No (%) exposed	Median (range) No of drugs	No (%) exposed	Median (range) No of drugs	No (%) exposed	Median (range) No of drugs	No (%) exposed	Median (range) No of drugs
1996	7588	3086 (40.7)	0 (0-5)	1063 (14.0)	0 (0-3)	291 (3.8)	0 (0-2)	3130 (41.2)	0 (0-9)
1997	7918	4277 (54.0)	2 (0-6)	2656 (33.5)	0 (0-4)	910 (11.5)	0 (0-2)	4328 (54.7)	2 (0-11)
1998	8599	5231 (60.8)	2 (0-7)	3607 (42.0)	0 (0-4)	2040 (23.7)	0 (0-3)	5266 (61.2)	3 (0-14)
1999	9170	5992 (65.3)	2 (0-7)	3973 (43.3)	0 (0-5)	3363 (36.7)	0 (0-4)	6017 (65.6)	3 (0-14)
2000	9775	6643 (68.0)	2 (0-7)	4114 (42.1)	0 (0-6)	4461 (45.6)	0 (0-4)	6661 (68.1)	3 (0-16)
2001	10 549	7340 (69.6)	2 (0-7)	4312 (40.9)	0 (0-6)	5315 (50.4)	1 (0-4)	7356 (69.7)	3 (0-16)
2002	11 200	7973 (71.2)	2 (0-7)	4561 (40.7)	0 (0-6)	5986 (53.5)	1 (0-4)	7987 (71.3)	4 (0-16)

information from the time of diagnosis. The analyses presented here are based on data collected over the period 2003-4.

Clinics provided data in a pseudo-anonymised form, using Soundex codes derived from surnames. We identified patients who had transferred between the centres in the study by matching on the basis of Soundex code and date of birth, and their records were linked.

Statistical methods

Patients were included in the cohort from 1 January 1996, their first attendance at one of the centres, or their 16th birthday, whichever occurred latest. We classified patients as under follow up in each year if the dates when they were first and last seen at any of the centres indicated that they were under follow up at that centre in that year. We present data for 1996-2002.

We defined individuals as being exposed to an antiretroviral drug if their treatment history included any use of that drug. We reported use of the following antiretroviral drugs: nucleoside reverse transcriptase inhibitors (zidovudine, lamivudine, stavudine, didanosine, zalcitabine, lodenosine, and abacavir), protease inhibitors (ritonavir, saquinavir (soft gel or hard gel formulation), indinavir, nelfinavir, amprenavir, or lopinavir), non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine, delavirdine, and loviride), and a fusion inhibitor (enfuvirtide (T-20)). Use of two nucleotide reverse transcriptase inhibitors, adefovir and tenofovir, was limited over the study period; these drugs are included as nucleoside reverse transcriptase inhibitors in this analysis.

We used each patient's last available CD4 count and plasma HIV RNA burden in a year in the analysis of trends over time. We included patients only if they were under follow up and had a CD4 count or HIV RNA burden measured in that year. We did not consider patients who were lost to follow up as treatment failures.

We classified patients as having experienced virological failure to a regimen containing a protease inhibitor if two consecutive HIV RNA measurements had been above 500 copies/ml after at least six months' exposure to protease inhibitors. If patients had discontinued this class of drugs before the second HIV RNA measurement above 500 copies/ml we did not classify them as experiencing virological failure. We defined virological failure on a regimen that contained non-nucleoside reverse transcriptase inhibitors in a similar manner: we then classified patients as experiencing three class failure if they had experienced failure with regimens containing both protease inhibitors and non-nucleoside reverse transcriptase inhibitors (we assumed that failure had occurred with nucleoside reverse transcriptase inhibitors, as protease inhibitors or non-nucleoside reverse transcriptase inhibitors were rarely used without nucleoside reverse transcriptase inhibitors); we took the date of experiencing three class failure as the later of the dates of failure on a protease inhibitor and non-nucleoside reverse transcriptase inhibitors containing regimen. We considered CD4 count and HIV RNA trends separately in three groups: patients who had ever received antiretroviral therapy, patients who had been exposed to three or more classes of drugs, and patients who had experienced three class failure. We used the statistical package SAS, version 8, for all analyses.

Results

The database contains information on 16 593 individuals from six centres. Most (n = 13 378; 80.6%) were male, the predominant risk factor for HIV infection was homosexual or bisexual sex (10 340; 62.3%), with 4426 (26.7%) reporting a heterosexual risk. The median (interquartile range) age of the cohort at first study visit was 34 (29-39) years. Fifty six per cent (n = 9201) of the cohort were white, 2987 (18.0%) were of black African ethnicity, and 2101 (12.7%) were of other ethnicities (information on ethnicity is unknown for 13.9%). More than a quarter (4336; 26.1%) have developed AIDS, and 1255 (7.6%) have died.

The number of individuals under follow up in the cohort rose each year, from 7588 in 1996 to 11 200 in 2002. Changes in the number of individuals under follow up reflect the number of individuals attending one of the clinics for the first time in the year as well as the number of individuals who had previously been seen but were not seen at any of the cohort centres in that year. The proportions of cohort participants who were "new" to the cohort in 1997, 1998, 1999, 2000, 2001, and 2002 were 18.9%, 16.3%, 14.0%, 13.6%, 14.8%, and 14.0%, respectively, whereas the proportions who had been seen in the previous year but were not seen in these years were 15.4%, 9.2%, 8.5%, 8.1%, 8.2%, and 8.9%, respectively.

Overall, 10 207 of the 16 593 patients (61.5%) had been exposed to any antiretroviral therapy, 10 176 (61.3%) to nucleoside reverse transcriptase inhibitors, 5657 (34.1%) to protease inhibitors, and 6857 (41.3%) to non-nucleoside reverse transcriptase inhibitors. Only 450 (2.7%) patients had been exposed to enfuvirtide. As expected, patterns of exposure changed over time (table 1). By the end of 1996, 41.2% of patients under follow up in that year had been exposed to antiretroviral therapy (14.0% to protease inhibitors, 3.8% to non-nucleoside reverse transcriptase inhibitors). The maximum number of antiretroviral drugs to which each patient had been exposed was nine. By the end of 2002 the proportions of patients seen in that year who had been exposed to any antiretroviral therapy, protease inhibitors, and non-nucleoside reverse transcriptase inhibitors had risen to 71.3%, 40.7%, and 53.5%, respectively, and patients had been exposed to a median of four (range 0-16) different antiretroviral drugs.

Table 2 Overall trends in CD4 counts and HIV RNA levels over time among patients in the UK CHIC study

Year	No (%) of patients under follow up with more than one CD4 cell count in the year	Latest CD4 count (cells/mm^3) in year		No (%) of patients under follow up with more than HIV RNA measurement in the year	Latest HIV RNA (log_{10} copies/ml) in year	
		Median (interquartile range)	No (%) <200		Median (interquartile range)	No (%) >2.7
1996	5517 (72.7)	270 (120-447)	2094 (38.0)	2197 (29.0)	4.34 (3.51-4.97)	2022 (92.0)
1997	6188 (78.2)	310 (180-460)	1785 (28.9)	5830 (73.6)	3.55 (2.70-4.52)	4082 (70.0)
1998	6795 (79.0)	335 (206-490)	1594 (23.5)	6926 (80.5)	3.10 (2.54-4.27)	3907 (56.4)
1999	7588 (82.7)	369 (230-523)	1512 (19.9)	7680 (83.8)	2.65 (1.70-4.23)	3786 (49.3)
2000	8385 (85.8)	397 (260-570)	1340 (16.0)	8325 (85.2)	2.26 (1.70-4.19)	3761 (45.2)
2001	9545 (90.5)	404 (270-575)	1362 (14.3)	9506 (90.1)	1.90 (1.70-4.10)	4001 (42.1)
2002	10446 (93.3)	408 (275-583)	1393 (13.3)	10295 (91.9)	1.89 (1.70-4.11)	4180 (40.6)

The median CD4 count of patients under follow up in each year rose steadily from 270 cells/mm^3 in 1996 to 408 cells/mm^3 in 2002; the proportion with a CD4 count <200 cells/mm^3 fell from 38.0% to 13.3% over the same period (table 2). The median HIV RNA burden fell from 4.34 log_{10} copies/ml in 1996 to 1.89 log_{10} copies/ml in 2002, and the proportion of patients with a viral load >2.7 log_{10} copies/ml fell from 92.0% to 40.6%.

Among patients who had ever received antiretroviral treatment, the proportion with a CD4 count <200 cells/mm^3 fell from 57.1% in 1996 to 15.3% in 2002, whereas the proportion with an HIV RNA measurement >2.7 log_{10} copies/ml fell from 89.3% to 23.5% (table 3). The number of patients exposed to all three main classes of drugs increased from 1% of those under follow up in 1996 to 27.3% of those under follow up in 2002. The proportions of these patients who showed signs of therapeutic failure in each year were similar to those seen in the overall treated population. Among patients exposed to three drug classes, the proportion experiencing three class failure increased until 2000 but remained relatively stable thereafter. Among patients in this group, the proportions with a CD4 count <200 cells/mm^3 or an HIV RNA measurement >2.7 log_{10} copies/ml were high but seemed to be falling over time.

Discussion

Although patients infected with HIV in the United Kingdom are becoming increasingly exposed to different antiretroviral treatments over time, immunological and virological profiles of these patients continue to improve at a population level. However, a small number of these individuals seem to be in danger of exhaustion of future treatment options.

As expected, an increasing proportion of individuals with HIV infection in the United Kingdom have been treated with antiretroviral therapy over time and, in line with this, their virological and immunological status has improved. Currently little evidence exists to indicate that a large proportion of patients are starting to experience therapeutic failure; this proportion has remained relatively stable since 2000. Even among patients who had experienced therapeutic failure with regimens containing all three classes of drugs, immunological and virological status has improved. We believe that these findings reflect the increasing number of new drugs that become available each year and the growing emphasis that is now placed on achieving good adherence, even in patients who have previously experienced problems when taking these drugs. However, the immunological and virological status of patients who have experienced three class failure remains relatively poor, showing that for a small number, treatment options are in danger of becoming exhausted.

Several new drugs from existing and new classes have recently been licensed.[6–9] Other drugs in development may offer hopes of activity against existing resistant strains, or benefits in terms of reduced toxicity or a reduction in the number of pills that must be taken.[10] However, past experience shows that preliminary reports of new drugs being associated with minimal cross resistance to other drugs are often followed by less positive findings.[11] Whether the trends seen up to the end of 2002 in this current dataset have continued since will therefore be interesting to see.

Potential limitations

We have considered the impact of antiretroviral therapy on HIV infected individuals in the United Kingdom at a population level. Such trends should always be interpreted cautiously. In particular, increased CD4 counts over time may result from an increase in the number of newly diagnosed individuals with high CD4 counts attending the centres in the collaboration. However, results from the CD4 surveillance scheme in the United Kingdom[12] and from individual cohorts in the collaboration[13 14] indicate that this is not the case. A second concern is that as this is a dynamic cohort, patients may leave the cohort at any time as

Table 3 Trends in CD4 cell counts and HIV RNA levels over time among patients who had ever started antiretroviral therapy, patients with three class exposure, and patients who had previously experienced three class failure

Year	Ever started antiretroviral treatment			Exposure to three classes of drugs			Treatment failure with three classes of drugs		
	No (% of patients under follow up)	CD4 counts <200 cells/mm^3	HIV RNA measurements >2.7 log_{10} copies/ml	No (% of patients who ever received antiretroviral therapy)	CD4 counts <200 cells/mm^3	HIV RNA measurements >2.7 log_{10} copies/ml	No (% of patients exposed to three classes)	CD4 counts <200 cells/mm^3	HIV RNA measurements >2.7 log_{10} copies/ml
1996	3130 (41.2)	1589 (57.1)	1272 (89.3)	72 (2.3)	50 (70.4)	36 (80.0)	0	—	—
1997	4328 (54.7)	1517 (38.4)	2361 (60.5)	399 (9.2)	181 (47.6)	236 (61.9)	13 (3.3)	6 (46.2)	13 (100.0)
1998	5266 (61.2)	1382 (29.1)	2017 (41.7)	1159 (22.0)	423 (38.1)	466 (41.7)	117 (10.1)	68 (58.1)	101 (86.3)
1999	6017 (65.6)	1327 (23.9)	1913 (34.1)	1905 (31.7)	582 (31.6)	639 (34.5)	273 (14.3)	153 (56.9)	211 (77.9)
2000	6661 (68.1)	1172 (18.9)	1772 (28.8)	2413 (36.2)	508 (22.0)	638 (27.8)	371 (15.4)	164 (45.6)	224 (62.0)
2001	7356 (69.7)	1186 (16.8)	1730 (24.6)	2748 (37.4)	502 (18.7)	597 (22.3)	435 (15.8)	147 (34.4)	218 (50.9)
2002	7987 (71.3)	1182 (15.3)	1802 (23.5)	3060 (38.3)	502 (16.8)	693 (23.3)	467 (15.3)	150 (32.5)	210 (45.7)

they move to centres that are not part of the collaboration. CD4 counts and HIV RNA values cannot be included in our analyses once patients leave the cohort, which may be a source of bias, particularly if those who were starting to experience therapeutic failure were more likely to drop out of the cohort. Although it is certainly true that some patients will have dropped out with therapeutic failure, many will have dropped out for unrelated reasons. The median last available CD4 count and HIV RNA measurement for those who dropped out of the cohort was above 200 cells/mm^3 in 41% and <2.7 $\log_{10}$ copies/ml in 32%, respectively, implying that many of these patients did not have therapeutic failure at their last visit. These proportions have remained relatively stable over time; we therefore do not believe that this will affect the trends seen.

One of the benefits of using data from a large multicentre study is that it is more representative of the UK epidemic than cohorts from single centres. However, although the dataset currently includes data on a third of all HIV infected individuals seen for care in the United Kingdom[15] and patients in the cohort are broadly representative of HIV infected individuals in the UK,[5] the cohort includes disproportionately more homosexual men and individuals of white ethnicity than are seen in the United Kingdom as a whole. Furthermore, as all centres actively participate in research studies (including clinical trials of new drugs), it is possible that exposure to novel treatments in these clinics may occur sooner than in other centres. Finally, discrepancies may still occur in histories of antiretroviral treatment if patients attend other centres either before or during the periods of follow up and treatment information from previous centres is incomplete. In this situation, our estimates of exposure to antiretroviral therapy may be underestimated.

Meaning of the study

We have identified two groups thought to be at high risk of treatment exhaustion: patients exposed to three or more drug classes and those who had experienced virological failure on regimens including both protease inhibitors and non-nucleoside reverse transcriptase inhibitors. Not all treatment switches are made as a result of virological failure; individuals may also change treatments for convenience or to reduce toxicity. Thus, patients who have been exposed to three classes of drugs may not have experienced virological failure while receiving these drugs and may not necessarily show signs of treatment exhaustion. Patients who are known to have experienced virological failure while receiving these drugs, however, would be expected to have developed some resistance to their failing regimens, possibly leading to cross resistance to other drugs in the same class[16] and placing these individuals at high risk of therapeutic failure. Although this group had higher HIV RNA measurements and lower CD4 counts than other treated individuals, virological failure is an imperfect surrogate for the presence of resistance mutations, and some of these patients may not have developed resistance to both protease inhibitors and non-nucleoside reverse transcriptase inhibitors. Close links with the UK HIV Drug Resistance Database[17] will allow us to deal with this question directly once the use of resistance testing has become routine in this group. Further follow up of clinical events in these patients will allow us to assess whether our definition of three class failure is a good indicator of subsequent poorer clinical outcome.

Our findings show that new drugs with low toxicity, which are not associated with cross resistance to existing drugs, will be needed for such patients.

What is already known on this topic

Highly active antiretroviral therapy (HAART) has had a dramatic impact on the health of individuals infected with HIV

For several reasons, however, many patients may not be able to tolerate their initial treatment regimen or may experience virological failure while receiving HAART

It may therefore be necessary to switch treatments on one or more occasions, raising the concern that some patients may exhaust all currently available treatment options

What this study adds

The immunological and virological status of infected patients generally improved

A small but growing proportion of these patients, however, seem to be in danger of exhaustion of current treatment options

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Contributors: CAS contributed to the initial concept and design of the study, analysed and interpreted the data, and wrote the manuscript. She is guarantor. TH and RM provided the central coordination for the study, merged the datasets, and were involved with cleaning the datasets. FL provided input to the creation of datasets. ANP, RG, MAJ, MF, GS, PE, and BG contributed to the initial concept and design of the study, supervised the data collection, and provided input into the preparation of the manuscript. SB and MSY provided input into the preparation of the manuscript. All authors provided comments on the interpretation of the data and gave approval for the final version to be submitted for publication.

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