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Time trends in primary resistance to HIV drugs in the United Kingdom: multicentre observational study

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Abstract

Objective To examine whether the level of primary resistance to HIV drugs is increasing in the United Kingdom.

Design Multicentre observational study.

Setting All virology laboratories in the United Kingdom carrying out tests for HIV resistance as part of routine clinical care.

Participants 2357 people infected with HIV who were tested for resistance before receiving antiretroviral therapy.

Main outcome measure Prevalence of drug resistance on basis of the Stanford genotypic interpretation system.

Results Over the study period (February 1996 to May 2003), 335 (14.2%, 95% confidence interval 12.8% to 15.7%) samples had mutations that conferred resistance to one or more antiretroviral drugs (9.3% high level resistance, 5.9% medium level resistance). The prevalence of primary resistance has increased markedly over time, although patterns are specific to drug class; the largest increase was for non-nucleoside reverse transcriptase inhibitors. In 2002-3, the prevalence of resistance to any antiretroviral drug, to nucleoside or nucleotide reverse transcriptase inhibitors, to non-nucleoside reverse transcriptase inhibitors, or to protease inhibitors was 19.2% (15.7% to 23.2%), 12.4% (9.5% to 15.9%), 8.1% (5.8% to 11.1%), and 6.6% (4.4% to 9.3%), respectively. The risk of primary resistance was only weakly related to most demographic and clinical factors, including ethnicity and viral subtype.

Conclusions The United Kingdom has one of the highest reported rates of primary resistance to HIV drugs worldwide. Prevalence seems still to be increasing and is high in all demographic subgroups.

Introduction

Combination antiretroviral therapy has improved the prognosis of patients infected with HIV. Concerns are mounting that a secondary epidemic of drug resistant virus would render treatment less effective.¹⁻³ We describe a national surveillance scheme for HIV drug resistance on the basis of routine clinical samples. Of about 13 000 samples tested between 1996 and 2003, over 2300 were from patients who had never received antiretroviral therapy. We used these data to analyse

the epidemiology of primary drug resistance in the United Kingdom, including temporal trends and associations with demographic and clinical factors.

Methods

The UK HIV drug resistance database is a repository of resistance tests carried out as part of routine care in the United Kingdom. The tests in our analysis were based on DNA sequencing of the *pol* gene. All sequences encompassed at least codons 4-99 of the protease gene and 34-234 of the reverse transcriptase gene. See bmj.com for data entered. Subtype was assigned using the STAR algorithm.⁴

We classified the patients' treatment status from several sources (see bmj.com). We defined a test as relating to recent infection if the patient was enrolled in the UK register of HIV seroconverters,⁵ and the sample was taken within 18 months of a negative HIV antibody test result or other laboratory test result indicating acute infection.

We verified the information on therapy status for a sample of patients with one or two major mutations⁶ and all patients with three or more major mutations. Information on antiretroviral therapy was incorrect in 26 (18%) of the 142 cases checked; we excluded these patients from the analysis.

The analysis includes all resistance tests on patients aged over 16 years who were naive to antiretroviral therapy. We used the Stanford HIVdb algorithm to assess the level of resistance to drugs⁷: a matrix of scores for each drug-mutation combination are summed across all mutations in the sample, and drug susceptibility is classified as "sensitive" (total score < 15), "intermediate" (15-29), or "resistant" (≥ 30). We refer to the last two categories as medium level and high level resistance.

Statistical analysis

We derived confidence intervals for proportions using the "exact" method. Logistic regression analysis was used to examine the association between demographic and clinical factors and the prevalence of resistance,



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adjusting for calendar year (fitted as a categorical variable) and centre. For CD4 count, we used the closest measurement within six months of the date of the resistance sample provided it preceded any use of antiretroviral therapy.

Results

A total of 2357 resistance tests on samples from antiretroviral therapy naive patients between February 1996 and May 2003 were available for analysis. One hundred and seventy two (7%) samples were from patients recently infected at the time of testing. Overall, 116 (4.9%, 95% confidence interval 4.1% to 5.9%) samples showed medium level resistance and 219 (9.3%, 8.1% to 10.5%) showed high level resistance to one or more drugs. When these categories were combined, reduced drug susceptibility was identified in 335 (14.2%, 12.8% to 15.7%) samples. All further analyses are based on this inclusive definition of resistance unless stated otherwise.

Patterns of resistance

In total, 233 (9.9%, 8.7% to 11.2%), 106 (4.5%, 3.7% to 5.4%), and 108 (4.6%, 3.8% to 5.5%) samples harboured mutations that cause resistance to nucleoside or nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors, respectively. Most samples (n = 257; 10.9%, 9.7% to 12.2%) were resistant to one drug class only.

See table 1 on bmj.com for most commonly observed mutations among the 335 resistant samples. Mutations at codon 215 in the reverse transcriptase gene, including the reversion mutations T215C/D/E/S, were most commonly observed; these were often associated with M41L. We did not observe K65R, I74V, or Y115F, associated with abacavir, didanosine, and tenofovir resistance. No mutations were detected associated with resistance to multinucleoside or nucleotide reverse transcriptase inhibitors, such as Q151M or insertions at codon 69. The most common non-nucleoside reverse transcriptase inhibitor mutation was K103N.

Among individual nucleoside or nucleotide reverse transcriptase inhibitors drugs the prevalence of reduced drug susceptibility ranged from 2.5% (lamivudine) to 7.6% (zidovudine) (see bmj.com). Due to strong cross resistance, we observed virtually identical figures for the non-nucleoside reverse transcriptase inhibitors delavirdine (4.1%), efavirenz (4.2%), and nevirapine (4.3%). Resistance was generally least common among individual protease inhibitors, ranging from 2.1% (lopinavir) to 4.3% (nelfinavir).

The table shows the most commonly prescribed first line antiretroviral therapy regimens in the six participating centres in the UK collaborative HIV cohort study over the study period (February 1996 to May 2003). Around 9% of first line regimens may have had reduced efficacy due to primary resistance. Estimates depended on regimen.

Temporal trends

The prevalence of primary drug resistance has increased noticeably, although patterns are drug class specific and partly depend on whether medium level resistance is included (figure). The proportionate

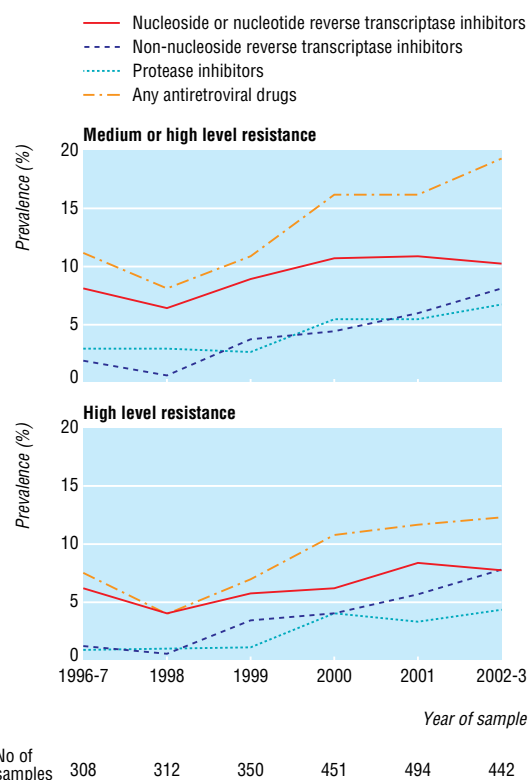
Prevalence of primary resistance to drugs for HIV comprising most common first line regimens used in UK collaborative HIV cohort study

| Regimen | Percentage of all first line regimens (n=6326)* | Prevalence (%) of resistance to one or more drugs in regimen† | |
|--|---|---|-----------------------|
| | | Medium level or high level resistance | High level resistance |
| Zidovudine+lamivudine+efavirenz | 16.7 | 11.8 | 8.2 |
| Zidovudine+lamivudine+nevirapine | 14.0 | 10.7 | 7.2 |
| Didanosine+stavudine+nevirapine | 5.6 | 5.9 | 3.4 |
| Stavudine+lamivudine+nevirapine | 5.3 | 6.4 | 3.4 |
| Zidovudine+lamivudine+indinavir | 4.8 | 7.9 | 5.2 |
| Zidovudine+lamivudine+abacavir | 3.8 | 9.2 | 5.7 |
| Stavudine+lamivudine+efavirenz | 3.6 | 8.1 | 5.7 |
| Zidovudine+lamivudine+nevirapine | 3.6 | 9.2 | 5.6 |
| Stavudine+lamivudine+nevirapine | 3.4 | 7.5 | 5.1 |
| Stavudine+lamivudine+indinavir | 3.4 | 6.2 | 2.3 |
| Didanosine+stavudine+efavirenz | 2.3 | 7.1 | 4.5 |
| Zidovudine+didanosine+nevirapine | 2.2 | 8.8 | 5.7 |
| Zidovudine+lamivudine+abacavir+efavirenz | 2.1 | 12.5 | 9.1 |
| Zidovudine+lamivudine+lopinavir | 2.0 | 10.3 | 6.3 |

*Regimens with frequency of at least 2%.

†Based on patterns observed in resistance database, assuming these were representative of all patients in study. Estimates are adjusted for variation in prevalence of resistance and use of different regimens (within annual time periods).

increase in resistance to nucleoside or nucleotide reverse transcriptase inhibitors was much smaller than for the non-nucleoside reverse transcriptase inhibitors or protease inhibitors, with some evidence of a levelling off in prevalence. In contrast, the rate of increase of resistance to non-nucleoside reverse transcriptase inhibitors has been approximately linear and has become as common as resistance to nucleoside or nucleotide reverse transcriptase inhibitors.



Prevalence of medium or high level drug resistance and high level drug resistance by calendar time. Values are number of samples tested at each time point

The pattern with protease inhibitors was less clear. During 2002-3 the prevalence of resistance to any antiretroviral drug, nucleoside or nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors was 19.2% (95% confidence interval 15.7% to 23.2%), 12.4% (9.5% to 15.9%), 8.1% (5.8% to 11.1%), and 6.6% (4.4% to 9.3%), respectively.

Demographic and clinical factors

See bmj.com for prevalence of drug resistance according to selected demographic factors. Some of the crude comparisons are misleading because of confounding by calendar year and centre. More reliable inference is through the odds ratios adjusted for these two factors. Mode of infection was not a strong risk factor apart from an apparently lower risk among injecting drug users. Associations with ethnicity and subtype of HIV, which are closely inter-related, were marginally significant. The rate of resistance was higher, although not substantially, in white patients and in those infected with subtype B virus. Patients younger than 30 had the highest level of resistance, although no clear trend was observed across older age groups. The strongest determinant of primary resistance was acute infection: 22% of patients in this category had mutations conferring resistance compared with 14% of patients with an unknown duration of infection. We found no apparent effect of CD4 count, a marker of the duration of infection, both overall and in a subanalysis excluding recently infected patients (data not shown).

Discussion

The prevalence of primary resistance to antiretroviral therapy in people infected with HIV in the United Kingdom is high in all demographic subgroups and seems still to be increasing. As current potent regimens completely suppress viraemia in most patients, prevalence might have been expected to decrease. The fact that the opposite trend was observed implies there are important levels of transmission from patients who know that they are infected, pointing to the need for educational messages aimed at this group.

The definition of transmitted HIV drug resistance is problematic.³ A central issue is how to distinguish natural polymorphisms from mutations that have arisen as a consequence of selective drug pressure in the individual who infected the index patient. This distinction is important from a public health perspective but less relevant for a prescribing clinician. We therefore used a genotypic interpretation system—the Stanford HIVdb algorithm—rather than the conventional definition of primary resistance.⁶ Further, the clinical significance of medium level resistance (included in our definition) is debatable.

Temporal trends

The overall prevalence of primary drug resistance in our study was 14%, but this masks a strong underlying time trend with an estimated rate of 19% for the most recent period (2002-3). Resistance to non-nucleoside reverse transcriptase inhibitors showed the sharpest increase, consistent with high levels of prescribing of this drug class in the United Kingdom,⁸ a high likelihood of developing resistance to this class,⁹ and trends in the prevalence of resistance observed in

What is already known on this topic

Primary HIV drug resistance limits therapeutic options

Its spread could negate the large reductions in morbidity and mortality since combination antiretroviral therapy was introduced

Knowledge on the level and patterns of primary drug resistance in the United Kingdom is limited

What this study adds

The United Kingdom has one of the highest reported rates of primary resistance to HIV drugs

treated patients.¹⁰ The cost effectiveness of testing for drug resistance before therapy is highly sensitive to the prevalence of primary resistance. We estimated that 13% of first line regimens started in 2002-3 may have been suboptimal due to resistance to one or more drugs in the regimen.

Demographic factors

The higher level of primary resistance in younger patients warrants further investigation. A lower prevalence was observed in Asian and Caribbean patients and those infected through injecting drug use, although this should be interpreted cautiously because of the small number of samples tested. African patients, who comprise around 45% of new diagnoses of HIV-1 infection in the United Kingdom,¹¹ had a similar prevalence to white patients. This was unexpected as most of the infections are likely to have been acquired in Africa, where access to antiretroviral therapy has been limited.

Methodological considerations

Comparisons with other studies are complicated by the use of different definitions of resistance. With this caveat, our rate of primary resistance (14%) is considerably higher than estimates in chronically infected patients reported from other countries.¹² We considered the possibility of bias in our estimates. Resistance testing was ad hoc over the study period and patients may have been selectively tested if there was a suspicion they had been infected by someone who had received antiretroviral therapy. The potential for such a bias is strong: the ratio of the number of resistance tests in patients naive to antiretroviral therapy (2357) to the number of new diagnoses in the United Kingdom over the same period (about 29 000) was only 1:12. Furthermore, an estimated one third of HIV infections are thought to be undiagnosed.

Another potential bias arises from the misclassification of treatment experienced patients as treatment naive. Firstly, treatment status was largely inferred from information from local databases, which are prone to inaccuracy. Secondly, many patients received care at two or more sites. Thirdly, some treatment experienced patients may have denied receiving therapy.¹³

Conclusion

Collating the results of routine HIV drug resistance tests can provide valuable insights into the population spread of drug resistant HIV at marginal additional

cost. By limiting the therapeutic options for a significant number of patients, the secondary epidemic of drug resistant HIV represents a major clinical and public health problem.

The UK Group on Transmitted HIV Drug Resistance is a collaboration between the UK Collaborative Group on HIV Drug Resistance, the UK Collaborative HIV Cohort Study, and the UK Register of HIV Seroconverters. Members of the writing group are Patricia Cane, Ian Chrystie, David Dunn, Barry Evans, Anna Maria Geretti, Hannah Green, Andrew Phillips, Deenan Pillay, Kholoud Porter, Anton Pozniak, Caroline Sabin, Erasmus Smit, Jonathan Weber, and Mark Zuckerman; affiliations are on bmj.com. We thank Tommy Lui (Stanford) and Patrick Woodburn for help with various aspects of the analysis, and the clinicians, virologists, data managers, and research nurses in participating centres who assisted with the provision of data.

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Competing interests: None declared.

Ethical approval: This study was approved by the UK multi-centre research ethics committee and relevant local research ethic committees.

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Cannabis intoxication and fatal road crashes in France: population based case-control study

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Abstract

Objectives To evaluate the relative risk of being responsible for a fatal crash while driving under the influence of cannabis, the prevalence of such drivers within the driving population, and the corresponding share of fatal crashes.

Design Population based case-control study.

Participants 10 748 drivers, with known drug and alcohol concentrations, who were involved in fatal crashes in France from October 2001 to September 2003.

Main outcome measures The cases were the 6766 drivers considered at fault in their crash; the controls were 3006 drivers selected from the 3982 other drivers. Positive detection of cannabis was defined as a blood concentration of Δ^9 tetrahydrocannabinol of over 1 ng/ml. The prevalence of positive drivers in the driving population was estimated by standardising controls on drivers not at fault who were involved in crashes resulting in slight injuries.

Results 681 drivers were positive for cannabis (cases 8.8%, controls 2.8%), including 285 with an illegal blood alcohol concentration (≥ 0.5 g/l). Positive cannabis detection was associated with increased risk of responsibility (odds ratio 3.32, 95% confidence interval 2.63 to 4.18). A significant dose effect was

identified; the odds ratio increased from 2.18 (1.22 to 3.89) if $0 < \Delta^9$ tetrahydrocannabinol < 1 ng/ml to 4.72 (3.04 to 7.33) if Δ^9 tetrahydrocannabinol ≥ 5 ng/ml. The effect of cannabis remains significant after adjustment for different cofactors, including alcohol, with which no statistical interaction was observed. The prevalence of cannabis (2.9%) estimated for the driving population is similar to that for alcohol (2.7%). At least 2.5% (1.5% to 3.5%) of fatal crashes were estimated as being attributable to cannabis, compared with 28.6% for alcohol (26.8% to 30.5%).

Conclusions Driving under the influence of cannabis increases the risk of involvement in a crash. However, in France its share in fatal crashes is significantly lower than that associated with positive blood alcohol concentration.

Introduction

Consumption of cannabis diminishes the faculties needed for vehicle driving,^{1 2} but it is unclear if it increases the risk of car crashes. The low number of

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