Original article

Population trends in the prevalence and patterns of protease resistance related to exposure to unboosted and boosted protease inhibitors

The UK Collaborative Group on HIV Drug Resistance and the UK Collaborative HIV Cohort Study†

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Background: In recent years, several new drugs from the protease inhibitor (PI) class designed to treat HIV infection have become available and the use of ritonavir-boosting has increased in popularity. These changes might be expected to affect the prevalence and patterns of protease resistance in the population of patients who experience treatment failure.

Methods: The UK HIV Drug Resistance Database aims to capture the results of all genotypic resistance tests conducted nationally. Tests on antiretroviral therapy-experienced patients were identified through linkage with the UK Collaborative HIV Cohort Study, from which detailed clinical information on these patients, including a full antiretroviral therapy history, was obtained.

Results: Analyses were on the basis of 8,553 genotypic resistance tests carried out between 1998 and 2005, during which time the overall prevalence of protease resistance halved from 35% to 16%. Substantial declines were observed regardless of whether the patient had been exposed to unboosted PIs and/or boosted PIs. The frequency of protease resistance among patients who had received boosted PIs fell sharply until 2002 with a weaker trend thereafter, falling to 12% in 2005. Individual mutations L33F, M46I/L, V82A/F/T/S/L and I84V became relatively more frequent over the period of study.

Conclusions: The decline in protease resistance was partly due to increasing use of ritonavir-boosting. Nonetheless, the prevalence of resistance was higher than suggested by clinical trials, indicating that prolonged exposure to a boosted PI could ultimately select for major protease mutations.

Introduction

Knowledge of the resistance profiles of antiretroviral drugs and the rate of drug resistance acquisition during antiretroviral therapy has been largely gained from clinical trials. However, strict eligibility criteria might result in a highly selected population who undergo frequent monitoring and rapid assessment of emerging drug resistance [1]. Furthermore, many studies are limited to patients with no prior antiretroviral exposure and follow-up rarely extends beyond 2 years [2,3]. This gives an incomplete picture of prevalence and patterns of drug resistance in the general clinical population, where many patients have experienced multiple and complex regimens over many years. Although drug regulatory agencies recommend post-marketing (Phase IV) surveillance of resistance, this is difficult to achieve in practice [4,5].

Clinical guidelines recommend that resistance testing should be performed at each occurrence of virological failure to inform the selection of a new antiretroviral regimen [6,7]. The large number of routine clinical resistance tests being generated forms a valuable resource for epidemiological studies and can provide important insights regarding the extent of resistance within and across drug classes, trends over calendar time and estimates of the number of individuals with multi-class resistance [8]. Such analyses are often reported by single-reference laboratories and single-centre cohorts [9,10]. However, in the UK virtually all genotypic resistance test results performed by the National Health Service and affiliated laboratories have been centralized, allowing conclusions to be drawn at the national rather than regional level [11]. Furthermore, the majority of tests have been linked to detailed clinical information, including antiretroviral treatment (ART) history.

The period for which resistance test data were available for this analysis (1998–2005) coincides with important changes in ART-prescribing patterns,
particularly for protease inhibitors (PIs). Four new drugs from this class were licensed and the use of low-dose ritonavir-boosting to enhance the pharmacokinetic profile of other PIs gradually became more established. In this paper, we report changes in the prevalence of PI resistance, both overall and in terms of specific mutations, among ART-experienced patients. Stratified analyses were performed to assess the effect of the declining use of unboosted PIs in favour of boosted PIs.

Methods

The UK HIV Drug Resistance Database was established in 2001 as a central repository of genotypic resistance tests carried out as part of routine clinical care in the UK [11]. As drug resistance testing first became available between 1997 and 1998, tests conducted prior to 2001 were collected retrospectively. Currently, 14 virology laboratories provide test results in the form of pol gene sequences generated from plasma samples. Amino acid sequences and mutations (relative to the consensus B sequence) were derived via the Stanford Algorithm web service (Sierra, Stanford, CA, USA) algorithm [12]. This report includes resistance tests completed up to the end of 2005 (with the calendar year defined according to the date of plasma sampling rather than the date of testing), which could be linked to participants in the UK Collaborative HIV Cohort (UK CHIC) Study, a collaboration of 10 major centres providing clinical care for HIV-infected patients. UK CHIC includes approximately 25,000 patients and is broadly nationally representative [13,14]. Data on patient demographics, clinical events, ART histories (excluding drug dosage) and laboratory monitoring are pooled annually.

As the focus of this paper is acquired (secondary) resistance, analyses are on the basis of patients with known prior ART exposure at the time of the resistance test. All tests on patients over the age of 16 years, including multiple tests on the same patient within the same year, have been included. Analyses are effectively cross-sectional and estimate the prevalence of resistance (class- and mutation-specific) among all tests performed within each calendar year. Sensitivity analyses including multiple tests on the same patient within the same year, have been included. Analyses are on the basis of patients with ART exposure at the time of the resistance test. As ritonavir dose was not available in the dataset, a boosted PI was defined as the use of any PI coprescribed with ritonavir. Following convention, drug resistance was defined as one or more major mutations listed on the 2006 International AIDS Society guidelines [15]; the PI mutations that were regarded as major were D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50V/L, I54M/L, L76V, V82A/F/T/S/L, I84V, N88S and L90M. Changes in the frequencies of individual mutations, among samples with one or more mutations, were assessed using the $\chi^2$ test for trend (statistical significance defined as $P<0.05$).

Results

A total of 8,553 genotypic resistance tests were performed between 1998 and 2005 on ART-experienced patients. The number of tests per patient were one test (2,226, 53.5%), two tests (902, 21.7%), three tests (450, 10.8%), four tests (244, 5.9%) and five or more tests (342, 8.2%). From 1999 onwards the number of tests per year remained fairly stable, both in absolute number (range 929–1,375) and as a ratio relative to the number of patients who experienced virological failure (range 0.55–0.71; Figure 1). The prevalence of protease resistance declined in an approximately linear manner over the period of study, halving between 1998 (35%, 95% confidence interval [CI] 32–39) and 2005 (16%, 95% CI 14–18). A similar trend was observed in the sensitivity analyses carried out on the basis of the first or last test.
Population trends in protease resistance per patient (Figure 1). As expected, the lowest level was observed in the analysis of first tests, when cumulative PI exposure is lowest. All the above trends were highly statistically significant ($P < 0.001$, $\chi^2$ test for trend).

Among samples with at least one major protease mutation ($n=2,192$), the majority harboured just one (41%) or two mutations (28%). However, complex patterns involving multiple mutations became increasingly frequent over time and the proportion of samples with five or more protease resistance mutations increased from 4.2% (95% CI 2.6–6.6) in 2000 to 7.8% (5.1–11.4) in 2002 and 15.0% (9.9–21.5) in 2005. This was accompanied by a shift in the relative frequency of individual mutations, expressed as a percentage among samples with one or more major mutations (Figure 2). L90M remained the most common mutation, at a stable frequency of 48–56%. Highly significant increasing trends were observed for the L33F, M46I/L, V82A/F/T/S/L and the I84V mutations, most strikingly in the case of L33F, which increased in prevalence from 6.4% (95% CI 4.2–9.2) in 2000 to 25.6% (19.1–33.1) in 2005 (Figure 2A). The frequency of D30N (uniquely selected by nelfinavir) increased until 2000 before declining after 2002. For the less common mutations (V32I, I47A/V, I50V/L, I54M/L, L76V and N88S) underlying trends were less easily discerned, although statistically significant increases in prevalence were observed for I47A/V, I50V/L, I54M/L and L76V (Figure 2B).

A natural question is the extent to which the changes in the prevalence of protease resistance can be attributed to changes in prescribing practices, in particular the shift to non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line therapy in the UK [16] and the growth in the use of ritonavir-boosting of PIs. Table 1 and Figure 3 describe the characteristics of cumulative PI exposure before the resistance test, including the individual PIs to which patients had been exposed. The percentage of tests with no associated PI exposure (that is, prior exposure only to nucleoside reverse transcriptase inhibitors and/or NNRTIs) varied between 26–37% The low, constant level of protease resistance in these patients (range 2.9–5.6%) might reflect either transmitted drug resistance, undisclosed use of PIs or natural polymorphisms at some resistance positions (Figure 4A).

Further insights are gained by distinguishing between unboosted and boosted PIs. First, the proportion of tests carried out on patients who had been exposed to unboosted PIs only showed a marked fall from 47% in 1998 to 13% in 2005 (Figure 3). This group exhibited declining levels of protease resistance with a noticeable drop between 2002 and 2003 (Figure 4A). The reasons for this trend are unclear, but might reflect an increasingly selective group of patients who have successfully achieved prolonged viral suppression using what is now considered a suboptimal regimen. Second, tests among patients exposed to both unboosted and boosted PIs comprised approximately 30% of the total number of tests from 2000 onwards. Despite reducing levels of protease resistance, this group showed the highest prevalence of resistance across all calendar years, consistent

![Figure 2. Change in relative frequency of major protease inhibitor mutations](Dunn.indd 773)

Change in relative frequency of individual major protease mutations among samples with at least one mutation. (A) Mutations with prevalence >10% at any time point. (B) Mutations with prevalence <10% at all time points. Trend significant for L33F ($P < 0.001$), M46I/L ($P < 0.001$), I47A/V ($P < 0.001$), I50V/L ($P < 0.001$), I54M/L ($P < 0.001$), L76V ($P < 0.005$) and I84V ($P = 0.008$). Trend for V82A/F/T/S/L significant from 2001 onwards ($P = 0.002$). n, number of tests.

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Fos(amprenavir), atazanavir and tipranavir were almost always coprescribed with ritonavir. IQR, interquartile range; PI, protease inhibitor; VL, viral load.

### Table 1. Characteristics of PI exposure prior to the resistance test

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
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<tbody>
<tr>
<td>Number of tests</td>
<td>618</td>
<td>1,093</td>
<td>1,375</td>
<td>1,167</td>
<td>1,249</td>
<td>1,106</td>
<td>929</td>
<td>1,016</td>
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<td>PI exposure</td>
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<td></td>
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</tr>
<tr>
<td>None, n (%)</td>
<td>184 (30)</td>
<td>285 (26)</td>
<td>417 (30)</td>
<td>412 (35)</td>
<td>409 (34)</td>
<td>411 (37)</td>
<td>310 (33)</td>
<td>307 (30)</td>
</tr>
<tr>
<td>Boosted PI only, n (%)</td>
<td>19 (3)</td>
<td>46 (4)</td>
<td>68 (5)</td>
<td>93 (8)</td>
<td>154 (12)</td>
<td>172 (16)</td>
<td>203 (22)</td>
<td>288 (28)</td>
</tr>
<tr>
<td>Unboosted PI only, n (%)</td>
<td>290 (47)</td>
<td>570 (46)</td>
<td>487 (35)</td>
<td>332 (28)</td>
<td>335 (27)</td>
<td>210 (19)</td>
<td>133 (14)</td>
<td>132 (13)</td>
</tr>
<tr>
<td>Boosted+unboosted PIs, n (%)</td>
<td>125 (20)</td>
<td>255 (23)</td>
<td>403 (29)</td>
<td>330 (28)</td>
<td>351 (28)</td>
<td>313 (28)</td>
<td>283 (30)</td>
<td>289 (28)</td>
</tr>
<tr>
<td>Number of previous PIs</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0, n (%)</td>
<td>184 (30)</td>
<td>285 (26)</td>
<td>417 (30)</td>
<td>412 (35)</td>
<td>409 (34)</td>
<td>411 (37)</td>
<td>310 (33)</td>
<td>307 (30)</td>
</tr>
<tr>
<td>1, n (%)</td>
<td>190 (31)</td>
<td>380 (35)</td>
<td>409 (30)</td>
<td>312 (27)</td>
<td>384 (31)</td>
<td>284 (26)</td>
<td>250 (27)</td>
<td>297 (29)</td>
</tr>
<tr>
<td>2, n (%)</td>
<td>153 (25)</td>
<td>249 (23)</td>
<td>303 (22)</td>
<td>206 (18)</td>
<td>218 (17)</td>
<td>181 (16)</td>
<td>161 (17)</td>
<td>170 (17)</td>
</tr>
<tr>
<td>3, n (%)</td>
<td>71 (11)</td>
<td>136 (12)</td>
<td>152 (11)</td>
<td>119 (10)</td>
<td>118 (9)</td>
<td>130 (12)</td>
<td>93 (10)</td>
<td>115 (11)</td>
</tr>
<tr>
<td>≥4, n (%)</td>
<td>20 (3)</td>
<td>43 (4)</td>
<td>94 (7)</td>
<td>118 (10)</td>
<td>120 (10)</td>
<td>99 (10)</td>
<td>115 (12)</td>
<td>127 (12)</td>
</tr>
<tr>
<td>Median cumulative exposure to PIs with VL &gt;1,000 copies/ml, months (IQR)</td>
<td>6.3</td>
<td>6.8</td>
<td>8.8</td>
<td>9.5</td>
<td>6.6</td>
<td>6.0</td>
<td>5.7</td>
<td>5.9</td>
</tr>
<tr>
<td>PIs with VL&gt;1,000 copies/ml,</td>
<td></td>
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</tr>
<tr>
<td>none, n (%)</td>
<td>1.3–14.5</td>
<td>1.7–16.6</td>
<td>1.8–18.7</td>
<td>2.0–23.1</td>
<td>0.4–21.3</td>
<td>0.6–23.4</td>
<td>0.2–20.5</td>
<td></td>
</tr>
<tr>
<td>PIs received</td>
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<td></td>
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<tr>
<td>Indinavir (boosted), n (%)</td>
<td>239 (39)</td>
<td>408 (37)</td>
<td>396 (29)</td>
<td>290 (25)</td>
<td>286 (23)</td>
<td>236 (21)</td>
<td>163 (18)</td>
<td>147 (14)</td>
</tr>
<tr>
<td>Indinavir (unboosted), n (%)</td>
<td>18 (3)</td>
<td>80 (7)</td>
<td>193 (14)</td>
<td>202 (17)</td>
<td>188 (15)</td>
<td>147 (13)</td>
<td>114 (12)</td>
<td>99 (10)</td>
</tr>
<tr>
<td>Ritonavir, n (%)</td>
<td>76 (12)</td>
<td>104 (9)</td>
<td>141 (10)</td>
<td>102 (8)</td>
<td>103 (8)</td>
<td>84 (8)</td>
<td>81 (9)</td>
<td>69 (7)</td>
</tr>
<tr>
<td>Saquinavir (boosted), n (%)</td>
<td>189 (31)</td>
<td>319 (29)</td>
<td>348 (25)</td>
<td>257 (22)</td>
<td>226 (18)</td>
<td>172 (16)</td>
<td>136 (15)</td>
<td>120 (12)</td>
</tr>
<tr>
<td>Saquinavir (unboosted), n (%)</td>
<td>138 (22)</td>
<td>235 (21)</td>
<td>315 (23)</td>
<td>236 (20)</td>
<td>243 (19)</td>
<td>229 (21)</td>
<td>187 (20)</td>
<td>201 (20)</td>
</tr>
<tr>
<td>Nelfinavir, n (%)</td>
<td>145 (23)</td>
<td>390 (36)</td>
<td>540 (40)</td>
<td>429 (37)</td>
<td>408 (33)</td>
<td>311 (28)</td>
<td>235 (25)</td>
<td>247 (24)</td>
</tr>
<tr>
<td>Fos(amprenavir), n (%)</td>
<td>0 (0)</td>
<td>22 (2)</td>
<td>49 (4)</td>
<td>69 (6)</td>
<td>78 (6)</td>
<td>74 (6)</td>
<td>77 (8)</td>
<td>103 (10)</td>
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<tr>
<td>Lopinavir, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>45 (3)</td>
<td>163 (14)</td>
<td>285 (23)</td>
<td>327 (30)</td>
<td>367 (39)</td>
<td>415 (41)</td>
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<tr>
<td>Atazanavir, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>7 (0.7)</td>
<td>86 (10)</td>
<td>229 (23)</td>
</tr>
<tr>
<td>Tipranavir, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>22 (3)</td>
<td>25 (2)</td>
</tr>
</tbody>
</table>

Fos(amprenavir), atazanavir and tipranavir were almost always coprescribed with ritonavir. IQR, interquartile range; PI, protease inhibitor; VL, viral load.

with such patients having had the longest and most varied exposure to drugs within the PI class. Finally, the proportion of tests among patients who had received boosted PIs only increased steadily, reaching 28% in 2005 (Figure 3). The frequency of protease resistance in this group fell sharply up to 2002, with a weaker trend thereafter, falling to 12% (95% CI 8–16) in 2005.

As the above analyses are on the basis of cumulative drug exposure, levels of resistance could have been underestimated due to the ‘loss’ (below detectable levels in plasma) of protease mutations after the removal of selective PI pressure. However, the limited available evidence suggests that major protease mutations are generally maintained for at least 1 year [17,18]. The analysis of Figure 4A was therefore repeated with the exclusion of patients who had had no PI exposure within 1 year prior to the resistance test (Figure 4B). This modification made only a marginal difference to estimates with the exception of patients who had only received unboosted PIs, where estimates were increased and similar to those exposed to both unboosted and boosted PIs. This differential effect is likely due to the disproportionately high number of exclusions (that is, patients with historical exposure) in the unboosted PI only group (43%) compared with the other two groups (21%).

Regarding individual PIs received prior to the resistance test, the largest observed changes were a decrease in the frequency of unboosted indinavir and unboosted saquinavir and a rapid increase in lopinavir and atazanavir from 2001 and 2004 onwards, respectively (Table 1). We conjectured that the fall in the prevalence of protease resistance over time might be due to a reduction in drug selection pressure, that is, less time spent on average on a virologically-failing regimen. However, this was not supported by an analysis of the median duration that patients had been on a PI-containing regimen, as evidenced by the interquartile range.

Finally, we examined the sequences of 9,150 PI-naive patients in the UK HIV Drug Resistance Database to exclude the possibility that findings in ART-experienced patients were influenced by pre-existing (transmitted) protease resistance. Only 163 (2.5%) of samples harboured one or more major PI mutations, with a frequency of <0.20% for all individual amino acid changes apart from those described in Table 1.
from L33F (0.28%), M46I (0.27%), M46L (0.24%), V82A (0.42%) and L90M (0.89%). These values are insignificant relative to the levels of acquired resistance that were observed.

Discussion

By exploiting the results of routine genotypic resistance tests, we have demonstrated a large decline in the prevalence of acquired protease resistance among participants in the UK. A similar approximate twofold reduction between 1999 and 2005 was described among samples submitted to a reference laboratory in Madrid, Spain [10]. However, in this study the levels of protease resistance were high throughout and remained at 30% in 2005 compared with our estimate of 16%. Another study from Marseille, France, reported a much more gradual reduction in protease resistance, from 51% in 1999 to 42% in 2002 [9]. However, the results from these studies are difficult to interpret without information on changes in prescribing patterns. A unique strength of our study was the ability to link the resistance test result to a full ART history of individual patients. An analysis stratified by drug class exposure (Figure 4A) showed that a decrease in protease resistance occurred within all subgroups classified by prior exposure to unboosted PIs and/or boosted PIs, that is, the overall trend was not entirely due to the previously documented shift to NNRTI-based first-line therapy [16].

Several limitations in our study should be noted. First, the sample is not representative of all patients receiving ART; to be included a patient, by definition, had to have a viral load above the laboratory’s threshold level for performing a resistance test and the clinician must have decided that a resistance test was warranted. However, we found no evidence to suggest that the propensity to perform a resistance test varied over time. Second, our analysis provides no information on the likelihood of developing resistance for a
given regimen. Obtaining such estimates requires a longitudinal analysis of a clearly defined population [19]; our analysis, by contrast, is essentially retrospective. Third, we presented results on lifetime antiretroviral exposure, including patients not currently on a PI at the time of the resistance result, which could have resulted in misleadingly low estimates of protease resistance. However, a sensitivity analysis excluding patients who had not received PIs in the year prior to the resistance test indicated that any such bias is likely to have been minor.

A key finding in clinical trials of patients on boosted PI-based regimens has been the virtual absence of major protease mutations detected at virological failure [20–23]. The mechanism underlying this has not been elucidated, but is thought to be due to high C_{trough} plasma levels and non-linear pharmacokinetics [20]. However, with the exception of the TITAN study [24], most of these trials were limited to PI-naive patients and were of relatively short duration. Our analysis helps to fill the knowledge gap about the development of resistance under prolonged and possibly sequential exposure to different boosted PI regimens in the routine clinical setting. We found appreciable levels of protease resistance under these circumstances. Rates were particularly high before 2002, a period when the vast majority of boosted regimens included either saquinavir or indinavir. It might also be relevant that saquinavir was likely to have been combined with ritonavir 400/400 mg twice daily rather than with small boosting doses in this period. In addition to the relative genetic barrier of different PIs, earlier regimens had lower potency and inferior tolerability, likely to be associated with poorer adherence. Furthermore, the high dose of ritonavir in earlier regimens might have contributed to the selection of resistance. Although we did not observe a specific decline of primary ritonavir-resistant patients and were of relatively short duration. Our analysis helps to fill the knowledge gap about the development of resistance under prolonged and possibly sequential exposure to different boosted PI regimens in the routine clinical setting. We found appreciable levels of protease resistance under these circumstances. Rates were particularly high before 2002, a period when the vast majority of boosted regimens included either saquinavir or indinavir. It might also be relevant that saquinavir and indinavir were likely to have been combined with therapeutic ritonavir doses (for example, saquinavir/ritonavir 400/400 mg twice daily) rather than with small boosting doses in this period. In addition to the relative genetic barrier of different PIs, earlier regimens had lower potency and inferior tolerability, likely to be associated with poorer adherence. Furthermore, the high dose of ritonavir in earlier regimens might have contributed to the selection of resistance. Although we did not observe a specific decline of primary ritonavir-associated mutations, this could be due to common pathways of resistance shared by other PIs, including saquinavir and indinavir [25,26]. Further analyses are planned to assess the durability of individual PIs against the development of resistance and to test the hypothesis that most of the resistance we observed was due to less effective potent first-generation PIs.

Within the context of an overall decline in protease resistance, we observed a shift in the relative importance of major mutations. As expected, the D30N mutation became less frequent, in accordance with falling use of nelfinavir. In contrast, L33F, M46I/L, V82A/F/T/S/L and I84V became increasingly prevalent, reflecting the introduction of lopinavir, atazanavir and fosamprenavir into clinical practice. We also observed an increase in the prevalence of the I47A/V and L76V mutations, consistent with selection pressure from lopinavir [27]. These trends are important in light of the role of these mutations in conferring reduced susceptibility to newer PIs such as tipranavir and darunavir.

Writing Group

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Disclosure statement

The contributors declare no competing interests.

Additional file

An additional file ‘Steering committees 30 July 2008’ can be accessed via the Volume 13 Issue 6 contents page for Antiviral Therapy, which can be found at www.intmedpress.com (by clicking on ‘Antiviral Therapy’ then ‘Journal PDFs’).

References


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