Resistance to the most recent protease and non-nucleoside reverse transcriptase inhibitors across HIV-1 non-B subtypes

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Objectives: Limited data are available on resistance to etravirine, rilpivirine, darunavir and tipranavir in patients infected with HIV-1 non-B subtypes, in which natural polymorphisms at certain positions could influence the barrier and/or pathways to drug resistance.

Methods: FASTA format sequences from the reverse transcriptase and protease genes recorded within the Spanish Drug Resistance database (ResRIS) were examined.

Results: From 8272 genotypes derived from 5930 different HIV-1 patients included in ResRIS, 5276 genotypes had complete treatment information. Overall, 85% were from antiretroviral-experienced subjects and 7.5% belonged to HIV-1 non-B subtypes: CRF02_AG, C, F and G being the most prevalent variants. For etravirine, only G190A was more prevalent in B than non-B subtypes, whereas V90I and V179E were more frequent in non-B than B subtypes. For rilpivirine, V108I and Y188I were more frequent in B than non-B subtypes, whereas V90I was more prevalent in non-B subtypes. Despite these differences, the overall prevalence of resistance did not differ significantly when comparing etravirine or rilpivirine in B versus non-B subtypes (11.3% versus 7.4%, \( P = 0.13 \), and 10.5% versus 7.4%, \( P = 0.23 \), respectively). Despite more frequent natural polymorphisms in non-B than B subtypes at tipranavir resistance positions, the prevalence of tipranavir resistance was greater in B than non-B subtypes (11% versus 4.3%, \( P = 0.004 \)), reflecting a greater antiretroviral exposure in the former. Darunavir resistance did not differ significantly when comparing B and non-B subtypes (5.8% versus 5.5%, \( P = 0.998 \)).

Conclusions: The rate of resistance to the most recently approved protease and non-nucleoside reverse transcriptase inhibitors is low in antiretroviral-experienced patients, regardless of the HIV-1 subtype.

Keywords: HIV-1 diversity, drug resistance, etravirine, rilpivirine, tipranavir, darunavir

Introduction

HIV-1 is characterized by a high genetic diversity. The variability within a given HIV-1 subtype can be up to 15%–20%, whereas variation between distinct subtypes rises to 25%–35%.1 Approximately one-half of reverse transcriptase (RT) codons from non-B subtypes and circulating recombinant forms (CRFs) are polymorphic in antiretroviral-naïve patients.2 This rate is even higher for the protease gene. Naturally occurring changes may appear at positions associated with drug resistance. Although the impact of these changes on a reduced susceptibility to treatment and/or a reduced treatment response seems to be limited,

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HIV-1 drug resistance in non-B subtypes

Recent reports have highlighted their importance for specific antiretroviral agents. In this regard, a different rate of polymorphisms in distinct HIV-1 variants might influence the barrier and/or pathway to resistance for some antiretroviral agents.

The proportion of circulating HIV-1 non-B variants is steadily increasing in Western Europe, where clade B viruses have predominated since the beginning of the epidemic. This trend has been confirmed in Spain, where HIV-1 non-B subtypes have increasingly been seen during the last few years. This larger circulation of non-B variants, along with a wider use of antiretroviral drugs, may have modified the rate and/or patterns of drug resistance mutations among the current HIV-1 population. In order to ensure and maximize the success of antiretroviral therapy it is important periodically to assess this information, especially with respect to the most recently approved antiretroviral agents.

The aim of our study was to examine the prevalence of HIV-1 non-B subtypes, as well as of drug resistance mutations and patterns to the most recently approved non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) in a large population of HIV-infected individuals who had failed antiretroviral therapy in Spain.

Patients and methods

Study population

Genotypes and clinical information from HIV-1-infected individuals who attended 22 clinics belonging to the Spanish AIDS Research Network between 1996 and December 2011 were merged into a single national HIV drug resistance database (ResRIS). Briefly, this database records information about resistance-associated mutations (RAMs), antiretroviral therapy at the time of genotyping, HIV clade, viral load and CD4 counts. Clinicians with access to the database may at any time check real-time virtual interpretations of drug resistance mutations.

HIV-1 subtyping

Bulk sequencing of the pol gene was carried out in plasma samples, and HIV-1 subtypes were further characterized using phylogenetic analyses. Reference sequences used to build trees were obtained from the NIH/NIAID-funded HIV database, which includes the major HIV-1 subtypes and CRFs.

Phylogenetic and molecular evolutionary analyses were conducted using MEGA 4, DNA sequences were aligned using the ClustalX 2.0 program and the tree topology was obtained using the neighbour-joining method.

Drug resistance interpretation

Drug resistance mutations were examined taking into account the updated mutation list of the IAS-USA panel (December 2011) as well as changes considered in the Spanish resistance interpretation algorithm, which additionally provides a weighting impact for each mutation.

For etravirine, the following mutations of the RT gene were considered: V90I, A98G, L100I/V, K101E/V/P, V106A/I/M, E138A/G/K/Q, V179D/E/F/I/L/M/T, Y181C/I/S/V, Y188C/H/L, G190A/C/E/Q/S/T/V, P225H, F227C/L, M230L and K238N/T.

For rilpivirine, resistance mutations considered were: V90I, L100I, K101E/P/T, V106A/V, V108I, E138A/G/K/Q/R, V179I/F/I/L, Y181C/I/V, Y188I, G190E, H221Y, F227C/L and M230I/L. These changes have been collected mainly from information derived from the IAS-USA panel list, the Spanish resistance algorithm, the ECHO and THRIVE trials, and in vitro studies.

For tipranavir, changes in the protease gene considered as resistance mutations were: L10V, V32I, L36F, M36I/L, K43T, M46L, I47AV, Q58E, T74R, V82C/I/L/M, N83D, I84A/C/V and L89I/M/V. Moreover, changes L24I, I50L, I54L, and K54E were considered as hypersensitivity mutations, following the Spanish resistance interpretation algorithm.

For darunavir, the following changes were considered to be associated with resistance: V11I, V32I, L36F, I47A/V, L50I/V, M46L, I47AV, Q58E, T74R, V82C/I, L89I/M/V. By contrast, changes L50I and N88S were considered as leading to hypersensitivity.

The definition of drug resistance for any of these drugs was based on the most recently updated Spanish criteria for genotypic HIV-1 drug resistance interpretation (www.retic-ris.net).

Statistical analyses

All results were expressed as absolute numbers and percentages. The prevalence of resistance mutations in HIV-1 subtype B viruses was compared with that seen in non-B subtypes using the \( \chi^2 \) test. Significant differences were considered only for \( P \) values <0.05. All statistical analyses were performed using SPSS v15.0 (SPSS Inc., North Chicago, IL, USA).

Results

Up to December 2011 a total of 8272 genotypes from 5930 different HIV-1-infected patients had entered the ResRIS database. The median number of genotypes per patient was 1 (IQR 1–2). The median age of the ResRIS population was 44 years; 77.4% were male and 65% had acquired HIV-1 infection through sexual contact, being either men who had sex with men (41%) or heterosexuals (24%). Overall, 32.1% of patients admitted prior injection drug use. The median (IQR) CD4 T cell count at the time of genotypic testing was 263 (48–460) cells/mm\(^3\) and the median (IQR) plasma HIV-RNA was 11,000 (1571–53,897) copies/mL. Complete information about antiretroviral drug experience was available for 5276 genotypes, most of which (85%) were from antiretroviral-experienced patients failing their current therapy. The final examination of resistance mutations was conducted on 4052 genotypes in which the subtype information was also available.

Distribution of HIV-1 non-B subtypes

A total of 75.6% of patients were native Spanish. Of the remainder, 14% came from South America, 5.6% were African and 4.8% came from other regions. Overall, HIV-1 non-B subtypes were found in 7.5% of the whole study population in ResRIS. Table 1 depicts the distribution of non-B subtypes in this population. By order of frequency it was as follows: CRF02_AG (29.6%), C (12%), F (10.4%), G (10.1%), D (5.4%), A (4.7%), CRF01_AE (4%), CRF12_BF (3.3%) and others (8.2%). Forty-five unique recombinant forms (URFs) were found, which represented 12.3% of patients infected with non-B viruses.

The prevalence of non-B subtypes in the ResRIS database increased from 4.5% in the period 1996–2006 to 11% in the period 2007–2011 (P<0.0001). It should be highlighted that within the subset of patients infected with HIV-1 non-B subtypes 26.5% were native Spaniards, and that CRF02_AG (19.6%) was the predominant variant in this group.
**Drug resistance mutations**

Comparing B versus non-B subtypes in antiretroviral-experienced patients, which included 4052 genotypes, the prevalence of thymidine analogue mutations (TAMs) was higher in the former than in the latter (42.8% versus 22.7%, \( P < 0.0001 \)) (Figure 1). The TAM-1 pathway, which includes mutations M41L, L210W and T215Y, was more prevalent in subtype B than non-B (27.2% versus 10.4%, 19.8% versus 4.3% and 25.3% versus 9.8%, respectively, \( P < 0.0001 \) for every mutation). By contrast, the TAM-2 pathway (changes D67N, K70R, K219E/Q and T215F) was present at similar rates in B and non-B clades, except for change D67N, which was more frequent in subtype B than non-B viruses (22.5% versus 13.5%, \( P = 0.007 \)).

The presence of \( \geq 5 \) TAMs, which results in cross-resistance to all nucleoside reverse transcriptase inhibitors (NRTIs), was at a low rate, without significant differences between B and non-B subtypes (3.8% versus 4.3%, respectively). The NRTI resistance mutations L74V and M184V were also more frequently found in B than non-B variants (7.2% versus 2.5%, \( P = 0.01 \), and 31% versus 23.9%, \( P < 0.04 \), respectively). There were no significant differences when comparing B with non-B subtypes for K65R (2.6% versus 4.3%), 69INS (1.6% versus 2.2%) and Q151M (1.6% versus 0%). However, mutation K65R was more prevalent in subtype G compared with CRF02_AG, C and F (15% versus 0%, 9.1% and 0%, respectively, \( P = 0.02 \)). This difference was similarly found when comparing subtypes G and B (15% versus 2.6%, \( P = 0.01 \)) (Table 2).

For NNRTIs, K103N was recognized in 20.6% of subtype B and 20.3% of non-B subtypes (\( P = 0.9 \)). These figures were, respectively, 12% and 8.6% for Y181C (\( P = 0.2 \)). The V106M mutation was more prevalent in non-B than B variants, but the difference did not reach statistical significance (1.2% versus 0.3%, \( P = 0.08 \)). This change was more frequently observed in subtype C compared with CRF02_AG, F and G (18.2% versus 0%, 0% and 0%, respectively, \( P < 0.001 \)), and this difference was also statistically significant when compared with B variants (18.2% versus 0.3%, \( P < 0.0001 \)) (Table 2).

Figure 2 summarizes the rate of etravirine and rilpivirine RAMs. Only three etravirine changes showed a different prevalence when comparing B and non-B viruses. G190A was more frequent in B than non-B subtypes (10.2% versus 1.8%, \( P < 0.001 \)) whereas V90I and V179E were more prevalent in non-B than B viruses (8.6% versus 4.8%, \( P = 0.041 \), and 3.1% versus 0.9%, \( P = 0.02 \), respectively). As shown in Table 2, there were no significant differences in the prevalence of V179E when comparing distinct HIV-1 non-B variants, but this mutation was more frequent in

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**Table 1.** Distribution of non-B subtypes in the ResRIS population and treatment information at the time of virological failure

<table>
<thead>
<tr>
<th>Non-B subtypes</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRF02_AG</td>
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<td>29.6</td>
</tr>
<tr>
<td>C</td>
<td>42</td>
<td>12</td>
</tr>
<tr>
<td>F</td>
<td>35</td>
<td>10.4</td>
</tr>
<tr>
<td>G</td>
<td>37</td>
<td>10.1</td>
</tr>
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<td>4</td>
</tr>
<tr>
<td>CRF12_BF</td>
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<td>3.3</td>
</tr>
<tr>
<td>other CRFs</td>
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<td>8.2</td>
</tr>
<tr>
<td>URFs</td>
<td>45</td>
<td>12.3</td>
</tr>
</tbody>
</table>

Antiretroviral agents at the time of failure

<table>
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<th>boosted PIs</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
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<td>lopinavir/ritonavir</td>
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<td>35.5</td>
</tr>
<tr>
<td>saquinavir/ritonavir</td>
<td>1431</td>
<td>27.5</td>
</tr>
<tr>
<td>darunavir/ritonavir</td>
<td>167</td>
<td>3.2</td>
</tr>
<tr>
<td>tipranavir/ritonavir</td>
<td>218</td>
<td>4.2</td>
</tr>
</tbody>
</table>

NNRTIs

| nevirapine            | 2028   | 38.9       |
| efavirenz             | 2184   | 41.9       |
| etravirine            | 54     | 1          |
| three nucleoside analogues<sup>a</sup> | 3134 | 60.2 |

<sup>a</sup>Mainly Trizivir® (zidovudine, lamivudine and abacavir).

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**Figure 1.** Prevalence of NRTI RAMs in antiretroviral-experienced patients infected with HIV-1 B and non-B subtypes.
to NNRTIs

\[
\begin{array}{cccccc}
\text{Mutations} & \text{CRF02_AG, n (%)} & \text{C, n (%)} & \text{F, n (%)} & \text{G, n (%)} & \text{P value a} \\
\hline
\text{To NRTIs} & K65R & 0 (0) & 1 (9.1) & 0 (0) & 3 (15) & 0.02 \\
& L74V & 0 (0) & 1 (9.1) & 0 (0) & 0 (0) & 0.05 \\
& M184V & 9 (17.6) & 4 (36.4) & 4 (33.3) & 5 (25) & 0.4 \\
\hline
\text{To NNRTIs} & V90I & 10 (19.6) & 1 (9.1) & 0 (0) & 1 (5) & 0.1 \\
& V106M & 0 (0) & 2 (18.2) & 0 (0) & 0 (0) & 0.001 \\
& V179E & 3 (5.9) & 0 (0) & 0 (0) & 2 (10) & 0.5 \\
& Y181C & 10 (19.6) & 0 (0) & 0 (0) & 0 (0) & 0.02 \\
& G190A & 0 (0) & 2 (18.2) & 0 (0) & 1 (5) & 0.01 \\
\hline
\text{To PIs} & L10V & 5 (9.8) & 0 (0) & 5 (41.7) & 1 (5) & 0.005 \\
& M36I & 50 (98) & 11 (100) & 10 (83.3) & 18 (90) & 0.1 \\
& I50V & 0 (0) & 0 (0) & 2 (16.7) & 0 (0) & 0.003 \\
& I54V & 0 (0) & 3 (27.3) & 0 (0) & 1 (5) & 0.001 \\
\end{array}
\]

\( a \) Differences in the prevalence of each mutation between the most prevalent non-B subtypes in ResRIS: CRF02_AG, C, F and G. Significant P values (\( P < 0.05 \)) are shown in bold.

\( b \) Differences in the prevalence of each mutation between the B subtype and each non-B subtype (CRF02_AG, C, F and G). Significant P values (\( P < 0.05 \)) are shown in bold.

Table 2. Prevalence of drug resistance mutations across distinct HIV-1 subtypes

Discussion

This study reports the prevalence of mutations conferring drug resistance to the most recently approved PIs and NNRTIs in a large clinical database in Spain, in which drug resistance genotypes from nearly 6000 HIV-1 patients are recorded along with relevant clinical information. Of note, none of these patients was enrolled in clinical trials at the time of testing. Thus, our results accurately reflect routine clinical practice. Although clade B continues to be the major circulating HIV-1 variant in Spain, non-B subtypes are on the rise. Our findings are in agreement with other reports that have noticed a steady yearly increase in Spain in the proportion of non-B variants in both newly diagnosed HIV-1 individuals and antiretroviral-experienced patients. Similar findings have been reported in other neighboring European countries, and mainly result from the large migration flows from highly endemic regions in sub-Saharan Africa, South-East Asia and Central and South America during the last two decades.

The distribution of non-B variants differs among European countries, mainly depending on the major source of the immigrant population and some founder effects. Thus, while in Italy the spread of subtype F1 and B/F recombinants predominates, supporting a strong link with South America, CRF02_AG is the most frequent non-B variant circulating in Spain, France and Portugal, most likely reflecting the huge immigration coming from Central and West Africa in recent years.

The overall prevalence of RAMs was higher in clade B than non-B subtypes in our study. Our results are in agreement with prior reports and most likely reflect a more extensive exposure to antiretroviral agents in patients infected with clade B than non-B viruses. Natives of Western countries have been more often infected by B viruses and have had earlier and easier access to medications whereas immigrants are generally
infected with non-B subtypes and have more difficult access to therapy. Mutations producing multidrug resistance, such as 69INS or Q151M, were rarely found in our study population, regardless of HIV-1 subtype. This observation most likely reflects that the most ancient genotypes accumulated in our database were obtained at the beginning of the triple combination treatment era.
The suboptimal older regimens of mono or dual NRTI therapy have not been used since then. TAMs may be selected in patients failing any NRTI-based regimen, although they are mainly seen in those failing on zidovudine- or stavudine-containing antiretroviral combinations. It is noteworthy that the TAM-1 pathway was more prevalent in subtype B than non-B variants, whereas the rate of the TAM-2 pathway was not influenced by HIV-1 subtype. By

Figure 3. Prevalence of tipranavir (a) and darunavir (b) RAMs in antiretroviral-experienced patients infected with HIV-1 B and non-B subtypes.

therapy era. The suboptimal older regimens of mono or dual NRTI therapy have not been used since then.25 TAMs may be selected in patients failing any NRTI-based regimen, although they are mainly seen in those failing on zidovudine- or stavudine-containing antiretroviral combinations. It is noteworthy that the TAM-1 pathway was more prevalent in subtype B than non-B variants, whereas the rate of the TAM-2 pathway was not influenced by HIV-1 subtype. By
contrast, others have reported an increased rate of TAM-2 pathway in certain non-B clades, as subtypes C and F. A relatively low use of thymidine analogues in our study population could account for our findings.

The examination of resistance mutations and patterns that may compromise susceptibility to the most recently marketed NNRTIs and PIs in HIV-1 non-B subtypes was the main objective of our study. Although information about rilpivirine resistance is still preliminary, it seems that the antiviral activity of this drug is still preserved in the presence of the majority of single NNRTI RAMs, as supported by in vitro studies. It must be noted that rilpivirine and etravirine largely share their respective resistance profile, which includes the novel changes recently proposed for etravirine resistance. In our study population, the prevalence of mutations E138G/K/Q, V179E/I, G190A and H221Y was very low in both B and non-B viruses. Moreover, there was no significant difference in the prevalence of rilpivirine/etravirine resistance changes, apart from V108I and G190A, which were significantly more frequent in B than non-B subtypes. In this regard, no differences in the distribution of etravirine RAMs were found comparing B and non-B subtypes in a recent retrospective study. Etravirine being equally effective in suppressing viral replication in patients infected with B or non-B viruses. As expected, mutation V90I, which is a natural polymorphism in certain non-B subtypes, was more prevalent in those viruses. CRF02_AG variants exhibited the greatest rate of V90I. Finally, we found a high rate of V179E in non-B subtypes, mainly in CRF02_AG and G variants, which supports the assertion that it is a naturally occurring polymorphism. In our study, changes L10I, M36I and L89I/V were the most frequent change selected in patients who failed on rilpivirine in the ECHO and THRIVE trials. In our database, the prevalence of this change was very low among subtype B viruses (0.5%), being completely absent in non-B variants. Prior reports have already highlighted that mutation E138K does not seem to be selected by CRF01_AE viruses from patients failing on NNRTIs.

The latest PIs approved for the treatment of HIV infection have been tipranavir and darunavir. They are the most potent within this drug family and display antiviral activity against most viruses exhibiting resistance to other PIs, reflecting their greater barrier to resistance. Several polymorphisms frequently found in non-B subtypes are part of the list of changes included in the genotypic resistance scores for tipranavir and darunavir. In our study, changes L10I, M36I and L89I/V were the most frequent tipranavir RAMs in non-B subtypes. In spite of these changes, proteases from non-B subtypes are generally fully susceptible to the inhibitory activity of most PIs. Their effect may only be appreciated in terms of shorter time to failure and/or a differential resistance pathway in patients already harbouring other PI RAMs. Furthermore, mutations 154V, V82T and 184V, which confer tipranavir resistance, as already shown in the RESIST trials, were more frequently seen in B than non-B subtypes. Altogether, the estimated overall prevalence of tipranavir resistance in our series was higher in subtype B than in non-B viruses. It should be acknowledged that the interpretation of resistance to tipranavir in non-B subtypes is challenging because information on patterns of resistance in these variants is scarce. The current algorithms might be suboptimal for assessing tipranavir resistance in non-B subtypes. It does not mean that the current interpretation algorithms may be invalid but updated scores should be developed that include information from individuals infected with non-B viruses and, ideally, check the impact of non-polymorphic positions.

For darunavir, the prevalence of 150V in subtype F was higher than among other HIV-1 variants, including B, CRF02_AG, C and G. Of note, 150V is considered to produce tipranavir hypersusceptibility but, conversely, largely compromises darunavir susceptibility. This observation may be of interest when there are plans for PI sequencing in patients infected with subtype F. Overall, however, the presence of darunavir RAMs in our database was largely dependent on prior extensive PI exposure whereas HIV clade did not influence it. This observation is in agreement with the results from other studies.

In summary, the analysis of a relatively large number of HIV-1 pol genotypes derived from clinical specimens collected outside clinical trials suggests that resistance to the newest PIs and NNRTIs is currently rare in antiretroviral-experienced patients. Interestingly, it is more frequent in patients infected with subtype B than non-B variants, despite the recognition of more frequent natural polymorphisms at resistance positions in the latter. A greater antiretroviral exposure in patients infected with subtype B than non-B viruses most likely explains this observation. As antiretroviral prescription patterns and circulating HIV-1 subtypes evolve in any given country, our results highlight the importance of periodic monitoring of drug resistance patterns.

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HIV-1 drug resistance in non-B subtypes

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References


