Are All Subtypes Created Equal? The Effectiveness of Antiretroviral Therapy against Non–Subtype B HIV-1

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(See the article by Geretti et al. on pages 1296–1305)

Currently, 24 active antiretroviral agents are available for use in the United States. These agents target and interrupt an array of HIV functions, including reverse transcription, proteolysis, envelope fusion, and integration [1]. When used in a variety of combinations, these agents have greatly reduced the morbidity and mortality associated with natural HIV infection in the United States [2]. In this issue of Clinical Infectious Diseases, Geretti et al. [3] demonstrate in an observational study that modern combination antiretroviral therapy works, even when the infecting virus is non–subtype B HIV-1. Specifically, this study examined the rates of viral suppression with antiretroviral therapy during infection with subtypes A, C, and D and with the circulating recombinant form (CRF) 02_AG. This is important, because modern antiretroviral therapy was developed on the basis of investigations of subtype B HIV-1 infection, even though this subtype accounts for only 12% of worldwide infections and is almost nonexistent in many regions [4].

**HIV-1 Diversity**

HIV is a lentivirus with zoonotic origins that can be traced to the simian immunodeficiency virus that infects chimpanzees for HIV-1 and sooty mangabeys for HIV-2 [5–7]. Phylogenetic analyses of viral isolates suggest 3 independent transmission events of primate simian immunodeficiency viruses to humans, each establishing distinct groups of HIV-1: M (main), O (outlier), and N (new). There are currently 9 recognized HIV-1 pure subtypes (A-D, F-H, J, and K) and 43 CRFs [8–10]. In many places in the world where multiple subtypes cocirculate, up to 10% of HIV-1 infections occur with unique recombination forms (URFs), owing to the ease and frequency with which HIV-1 recombines during dual infection [8, 9, 11–13]. Formally, subtypes are defined as phylogenetically separate clusters of strains, and HIV-1 sequences that are the result of recombination among pure subtypes are defined as CRFs if there are at least 3 independent viral strains that show the same recombination structure and as URFs otherwise [10]. The nomenclature of subtypes and recombinant forms is continually evolving (pun intended) as molecular epidemiology and surveillance of HIV-1 throughout the world improves.

The HIV-1 genome is ∼9.8 kb long (compared with ∼3 gigabases in the human genome) and is composed of 9 genetic coding regions, each performing a variety of structural, virologic, and immunologic evasion functions [14]. These coding regions vary in their genetic diversity across group M subtypes. For instance, the env gene, which encodes for the envelope protein, can be >30% different between any 2 subtypes [15], whereas the region that encodes the integrase protein is usually only 3%–8% genetically distant [10]. The high genetic diversity of the HIV-1 M group is due to a number of factors, including mutation rates close to the evolutionary speed limit [16], high recombination rates [17], vigorous heterogeneous cellular [18] and humoral [19] immune responses that leave an imprint on the viral genome [20], and complex population dynamics [21]. Despite this enormous genetic diversity, each subtype, CRF, and URF of the HIV-1 M group can cause the characteristic immunosuppression in the form of AIDS, leading to death. However, the extent of clinically meaningful phenotypical differences among the subtypes in pathogenicity (such as neurologic, cardiovascular, or renal damage), transmissibility, the ability to
evade host immune responses, or cellular tropism remains uncertain.

**ANTIRETROVIRAL THERAPY AND DRUG RESISTANCE**

Because the HIV epidemics found in the wealthiest countries of the world involve predominantly subtype B virus, the development of antiretroviral therapy has been heavily based on the virology of this subtype [22–25]. Similarly, most investigation into HIV drug resistance has been limited to subtype B virus, and little information in genotypic resistance patterns or the rate of resistance development is available for other subtypes [26]. Correspondingly, HIV sequences deposited in public databases and used for retrospective research are disproportionately of subtype B. For instance, the Stanford Drug Resistance Database [27] currently contains \(\sim 17,300\) subtype B reverse-transcriptase sequences but only \(\sim 10,400\) sequences of all other subtypes combined, even though non–subtype B accounts for \(\sim 88\%\) of all HIV-1 infections worldwide [4].

Owing to a high replication rate and error-prone reverse transcription, all subtypes, CRFs, and URFs of HIV-1 can rapidly develop mutations that confer decreased susceptibility (or resistance) to every available antiretroviral therapy agent [27–30]. The rate of developing resistance-associated mutations (RAMs) depends on the maintenance of protein function, replicative fitness advantage in the presence of drug, and ease of the mutational change, which are all influenced by the genetic background of the infecting virus [25]. For example, a single nucleotide substitution from the wild-type codon found in subtype C can generate the mutation V106M, which is associated with nonnucleoside reverse-transcriptase inhibitor resistance, but at least 2 substitutions are needed for the wild-type subtype B codon (figure 1). Table 1 provides other examples of previously characterized RAMs for which the most direct mutational pathway from wild-type codon to RAM is shorter in non-B subtypes. In addition, the observed pattern of RAMs can be different for the same antiretroviral therapy agent among different subtypes, especially for mutations outside the reverse-transcriptase- and protease-coding regions [31], although previous work by Kantor et al. [32] found that HIV-1 resistance patterns are similar across subtypes.

As antiretroviral therapy use becomes more prevalent worldwide, drug-resistant viral strains are likely to increase in frequency among all subtypes because of both de novo adaptation and transmission of resistant variants [33]. Transmitted drug resistance is especially concerning because most non–subtype B infections occur in parts of the world where viral load monitoring during antiretroviral therapy is either unavailable or not routinely used.

**Table 1. Positions in HIV-1 pol where the direct mutational pathway from consensus (wild type) to a resistance-associated mutation (RAM) is shorter in some non-B subtypes than in subtype B.**

<table>
<thead>
<tr>
<th>Position in pol</th>
<th>ART class</th>
<th>RAM residue(^a)</th>
<th>Shortest mutational pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR V82</td>
<td>PI</td>
<td>S</td>
<td>GTC→TCC, G, CRF14: ATC→AGC</td>
</tr>
<tr>
<td>PR V82</td>
<td>PI</td>
<td>T</td>
<td>GTC→AGC, G, CRF14: ATC→ACC</td>
</tr>
<tr>
<td>RT D67</td>
<td>NRTI</td>
<td>N</td>
<td>GAC→AAC, CRF04: AGA</td>
</tr>
<tr>
<td>RT K70</td>
<td>NRTI</td>
<td>G</td>
<td>AAA→GGA, CRF04: AGA→GGA</td>
</tr>
<tr>
<td>RT V106</td>
<td>NRTI</td>
<td>M</td>
<td>GTA→ATG, C, GTG→ATG</td>
</tr>
<tr>
<td>RT V179</td>
<td>NRTI</td>
<td>E</td>
<td>GTT→GAG, G, CRF02, CRF14: GTG→GAG</td>
</tr>
<tr>
<td>RT T215</td>
<td>NRTI</td>
<td>F</td>
<td>ACC→TTC, CRF04: TTC→TTC</td>
</tr>
<tr>
<td>IN E157</td>
<td>INI</td>
<td>Q</td>
<td>GAA→CAA, CRF03: CAA</td>
</tr>
</tbody>
</table>

**NOTE.** Consensus sequences based on the reference sets from Los Alamos National Laboratory (http://www.hiv.lanl.gov). ART, antiretroviral therapy; CRF, circulating recombinant form; IN, integrase; INI, integrase inhibitor; NRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; PR, protease coding region; RT, reverse-transcriptase coding region.

\(^a\) Single-letter amino acid code.

\(^b\) Non-B subtypes are underlined.
SUMMARY AND RECOMMENDATIONS

As demonstrated in the work of Geretti et al. [3], modern antiretroviral therapy works well for the handful of non-subtype B viruses investigated so far and will certainly save lives, independent of the subtype of the infecting virus. To evaluate how infecting subtype influences treatment response as antiretroviral therapy is rolled out to the rest of the world, where most HIV-1 infections are not subtype B, we will need to (1) maintain robust and up-to-date subtype determination procedures [38], (2) routinely monitor for virologic failure of antiretroviral therapy with subsequent surveillance for drug resistance in worldwide populations [34], (3) develop genotypic methods that reliably detect RAMs in sequences of all subtypes, (4) characterize antiretroviral therapy susceptibility (phenotype) for RAMs by subtype [31], and (5) evaluate the impact of host characteristics of the infected population on antiretroviral therapy efficacy and viral subtype. Together, these procedures will help inform antiretroviral therapy guidelines among various populations infected with different subtypes.

Acknowledgments

Potential conflicts of interest. S.L.K.P. and D.M.S.: no conflicts.

References


