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MINIREVIEW

Antiretroviral Drug Resistance in Human Immunodeficiency Virus Type 2

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Scientists established long ago that human immunodeficiency virus type 1 (HIV-1) is the causative agent of AIDS (4, 30, 48). HIV is known to severely damage the immune system by selectively infecting T-helper (CD4+) lymphocytes. This can lead to serious infections by agents that would normally be easily held in check by the immune system (12). In 1986, a second type of HIV, HIV-2, was identified in certain areas of West Africa (11). HIV-2 represents an introduction of simian immunodeficiency virus from the sooty mangabey into the human population, whereas HIV-1 arose from introduction into humans of SIV from the chimpanzee (31, 76, 79, 80). Infection with HIV-2 can ultimately lead to AIDS, although disease progression is much slower than with HIV-1. Whereas HIV-1 is much more widespread than HIV-2, the latter is prevalent at moderate to high rates in such West African countries as Senegal, Guinea-Bissau, Gambia, and Cape Verde; HIV-2 is the leading cause of AIDS in Guinea-Bissau (77). It is relatively rare outside West Africa, although individual cases have been identified in Europe, the Americas, Asia, and other parts of Africa (50).

An increasing body of evidence indicates that HIV-2 is on the decline in countries that were thought to have been affected the most, and this is also true where HIV-1 is on the increase (87). During 16 years of observation in Gambia, the prevalence of HIV-2 decreased from 7 to 4%, while that of HIV-1 increased from 4 to 18%, and dual HIV-1/HIV-2 infections remained stable at ~1% (27). In view of the fact that HIV-1/HIV-2 coinfection can complicate antiretroviral therapy, the decline incidence may simplify HIV treatment programs in affected areas.

At least seven subtypes of HIV-2, termed A through G, exist (10, 28, 32, 91). Subtype A is predominant in Guinea-Bissau, while subtype B is predominant in Cote d’Ivoire (65). Recently, an intersubtype recombinant involving subtypes A and B was described in Cameroon (92). Dambod et al. reported the identification of a highly divergent HIV-2 strain in 2004 and proposed that classification of HIV-2 subtypes be changed by taking into consideration a new subtype, H (21). HIV-2 appears to be less virulent than HIV-1, with slower progression to AIDS (51), lower plasma viral loads, lower rates of heterosexual transmission, and slower declines in CD4+ T-cell count. There have been suggestions that infection with HIV-2 may possibly be protective against HIV-1 (2, 55), but the data on this topic are conflicting (56, 78). Furthermore, recent data from meta-analyses have concluded that HIV-2 infection is a risk factor rather than a protective factor for HIV-1 (37).

HIV-2 DRUG RESISTANCE

HIV-1 and HIV-2 are related but differ by about 50 to 60% at the nucleotide level, with significant differences in amino acid sequences. The two viruses share only about 60% of amino acids in the protein encoded by the pol gene, yet the reverse transcriptase (RT) proteins of the two viruses are similar in overall structure and function (42). Figures 1 and 2 show amino acid differences between HIV-1 and HIV-2 protease (PR) and RT, respectively, with emphasis on positions known to be involved in HIV-1 drug resistance. Although many studies have described the development of HIV-1 resistance to all six classes of antiretroviral drugs, only limited information exists in regard to HIV-2.

HIV-2 RESISTANCE TO PIs

Kinetic studies have shown that PR inhibitors (PIs) bind to HIV-2 but with 10- to 100-fold weaker affinity than for HIV-1, depending on the inhibitor (64, 84). Studies of individual PIs show that nelfinavir (NFV) and saquinavir (SQV) exert similar inhibitory activity against HIV-2 and HIV-1, whereas ritonavir (RTV) and indinavir (IDV) are one- to twofold less inhibitory against HIV-2 (47, 52, 63). Several reports have confirmed that treatment of HIV-2 patients with dual PI or nucleoside RT inhibitor (NRTI)-PI combination regimens results in decreased HIV-2 viral load, increased CD4+ T-cell count, and an improvement in clinical status (1, 81).

Tissue culture drug selection studies with HIV-2 have shown that natural polymorphisms can accelerate the time to development of resistance to certain PIs, with the appearance of the mutations I54M, I82L, I84V, and L90M being responsible for reduced PI susceptibility (57) (Table 1). Recent data have shown that SQV, lopinavir (LPV), and darunavir (DRV) are

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more potent against wild-type HIV-2 isolates than other PIs and might be preferred as treatment options for HIV-2-infected patients (22).

HIV-2 expresses natural polymorphisms in the PR (e.g., 10I/V, 20I/V, 32I, 36I, 46I, 147V, 63E/K, 71V, 73A, 77T, 82I, and 93L) that may be implicated in emergent drug resistance. A recent study showed that 13 mutations in the PR of HIV-2 (W6F, T12A, E21K, I50V, I54M, V62A, I64V, V71I, I82F, I82L, I84V, L90M, and L99F) were selected with a variety of PIs. Three of these mutations (W6F, T12A, and E21K) had not previously been associated with either HIV-2 or HIV-1 drug resistance (57).

Treatment-associated changes occurred in the HIV-2 PR gene at sites corresponding to some of those that confer drug resistance in HIV-1 (15, 18, 66). However, these changes could not be directly associated with a particular PI (18). One group described the selection of I82F, I54M, and V71I in one HIV-2-infected patient who received IDV for 12 months (70). Others have shown that several mutational pathways can be associated with resistance to different PIs (57).

A novel mutational motif involving V62A and L99F, which was selected in several instances under IDV and NFV pressure, confers resistance to PIs in HIV-2 (57). The mutations I54M, I82F, L90M, and V71I have been observed in HIV-2 following NFV selective pressure, under conditions that selected the D30N mutation with HIV-1 (57). The L99F mutation was selected by both NFV and IDV, showing the potential for cross-resistance to these drugs as previously reported (15). The E21K and L99F mutations, selected under drug pressure in the same study, were also present in some HIV-2 subtype B-infected drug-naïve patients (4 to 13%), suggesting that natural polymorphism-based resistance to PIs might occur in certain HIV-2 subtypes (15, 66). However, the effect of L99F on phenotypic susceptibility of HIV-2 to PIs has not been elucidated in site-directed mutagenesis studies. Two HIV-2 isolates were recently shown to develop resistance to NFV via the 90M and 54M/99F pathways, while a third isolate did so via the 82F pathway (57). This contrasts with the predominance of the D30N mutation as a key factor in the development of HIV-1 resistance to NFV (38). This study also demonstrated that one of three HIV-2 isolates selected the D30N mutation under NFV selective pressure after 38 weeks in culture (57), possibly because the L90M change in HIV-2 is more advantageous and/or better tolerated than a change at residue 30 (18). Furthermore, L90M is the preferred NFV resistance mutation in non-B subtypes of HIV-1. Similar fitness explanations may underlie the selection of the I82F and I54M substitutions in HIV-2 isolates exposed to NFV (38). Substitutions at positions 12A and 21K may play roles as compensatory mutations following acquisition of major mutations associated with HIV-2 resistance to PIs.

Published data have shown that the I50V mutation in PR is specific for amprenavir (APV) while I82L is specific for tipranavir (TPV) in HIV-2 (57). Both of these mutations are
selected in vitro and in vivo in HIV-1 clinical isolates exposed to these drugs (26, 85). The I82L substitution may also develop faster in HIV-2 than in HIV-1 in tissue culture selections (57).

The mutation I54M was the most frequently selected in HIV-2 isolates, suggesting its association with broad cross-resistance to PIs. This mutation was selected by APV, NFV, and IDV. I54M is also selected in HIV-1 subtype B viruses under APV drug pressure (24).

Some natural polymorphisms in HIV-2 may confer baseline resistance to APV. HIV-2 naturally harbors 46I and 47V, which are associated with resistance to APV in HIV-1. Numerous studies have shown that wild-type HIV-2 isolates manifest reduced susceptibility to APV and NFV compared to HIV-1 (1, 72, 90; J. Goncalves, F. Antunes, and J. Moniz-Pereira, 11th International Workshop on HIV Drug Resistance: Basic Principles and Clinical Implications, Seville, Spain, 2002).

Other studies have reported that the acquisition of the 54M and 82F mutations in HIV-2-infected patients may result in cross-resistance to multiple PIs and high-level resistance (33- to 1,000-fold) to LPV (71). Tissue culture selections, however, failed to select these two mutations in the same virus, perhaps for reasons of diminished fitness; 54M also yielded more extensive cross-resistance than 82F (57). All mutations selected resulted in resistance (18- to 131-fold) to LPV. The acquisition of 54M alone or together with 84V, 90M, or 99F may result in multiple-PI resistance (57).

Almost all HIV-1 PR mutations have been shown to decrease viral fitness (67). Furthermore, enzymatic assays have shown that such mutations result in reduced catalytic activity (6, 17, 53). Although there are no published studies on the impact of these resistance mutations in HIV-2, an analogy with HIV-1 renders likely the assumption that decreased viral fitness and enzymatic efficiency also occur in PI-resistant HIV-2.

Multidrug-resistant HIV-1 may have reduced pathogenicity. Indeed, many patients with such viruses who remain on treatment seem to recover CD4 cells despite detectable viral load (34). It is not known whether similar findings will be obtained in the case of HIV-2.

The baseline phenotypes of HIV-2 isolates are generally similar to those of HIV-1, suggesting that the 13 polymorphisms in the HIV-2 PR do not have a major impact on drug susceptibility. Nonetheless, such polymorphisms may shorten the time to development of resistance in HIV-2 to PIs. Moreover, the viral backbone of HIV-2 may lead to selection of novel mutations such as 99F. These findings underscore the importance of these resistance mutations in facilitating the development of resistance to PIs as a public health concern. Other studies have shown that the differences in phenotypes between wild-type HIV-2 and HIV-1 may depend on the PI being tested.

HIV-2 have now been observed in patients (J. Cavaco Silva, J. Cabanas, M. F. Goncalves, K. Van Laethem, A.-M. Vандамме, P. Gomes, and R. J. Camacho, XVI International HIV Drug Resistance Workshop, Barbados, 2007). These include I54M, I82F, I84V/F, L90M, and I50V (Table 1). In a small set of HIV-2-infected persons, five of six who had L90M also carried the L99F and V71I mutations (Cavaco Silva et al., XVI International HIV Drug Resistance Workshop). Similarly, five of six with A62V also carried the L99F mutation. To date, no study has investigated whether mutations at Gag-PR cleavage sites may have an effect on HIV-2 drug resistance, as is the case for HIV-1 (25).

Table 1 presents a summary of selected studies on HIV-2 drug resistance showing the different mutational pathways observed.

### HIV-2 Resistance to NRTIs

Although most in vitro studies have shown that similar concentrations of NRTIs are needed to block both HIV-1 and HIV-2 replication (13, 16, 82), some published data suggest that some drugs may not be as effective against HIV-2 (57, 89, 90). Genotypic analysis of HIV-2 patients on antiretroviral therapy has shown that many of the same amino acid substitutions that are associated with NRTI resistance in HIV-1 also seem to be implicated in the case of HIV-2.

In regard to zidovudine (ZDV), several studies have reported that HIV-2 and HIV-1 are equally sensitive both in culture (16, 54, 89) and in cell-free biochemical assays (44, 88), while others suggest that HIV-2 may be relatively resistant to this NRTI (7, 68, 69). Such natural resistance has been attributed to HIV-2 polymorphisms at positions similar to those that are implicated in HIV-1 resistance to ZDV (e.g., L210N, T215Y, and K219E). A recent report showed that the only polymorphism at position 215 in 71 drug-naive patients was 215T, although other changes became evident after therapy (J. Cavaco Silva, A. Miranda, J. Cabanas, M. Goncalves, E. Valadas, K. Mansinho, K. Van Laethem, A-M. Vандамме, P. Gomes, and R. J. Camacho, presented at the 16th Conference on Retroviruses and Opportunistic Infections, Montreal, Canada, 2009 [abstr. 663]).

It has been suggested that the mechanisms responsible for ZDV resistance are different for HIV-1 and HIV-2 and that diminished incorporation may play a more important role in HIV-2 than selective excision (7). The latter study also showed that HIV-1 more readily incorporates ZDV and is more susceptible to ZDV than HIV-2. These findings are consistent with recent findings that higher concentrations of ZDV are needed to durably suppress replication of HIV-2 than HIV-1 (58).

In regard to the K65R mutation, two clinical studies (Table 1) found a high frequency of this mutation in NRTI-treated patients infected with HIV-2 (20, 23). In other studies, K65R was either rare (one or two patients) (14, 46) or absent (70). In vitro, K65R selection with HIV-2 is not common (58, 68). Recently, however, a clinical study involving 124 patients found a prevalence of K65R of 20.1% (25/124) in patients treated with several combinations of NRTIs; 18 (72%) of these patients had received tenofovir (TDF) at some point of their treatment (J. Cavaco Silva, A. Miranda, J. Cabanas, M. Goncalves, E. Valadas, K. Mansinho, K. Van Laethem, A-M. Vандамме, P. Gomes, and R. J. Camacho, presented at the 16th Conference on Retroviruses and Opportunistic Infections, Montreal, Canada, 2009 [abstr. 663]).

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<table>
<thead>
<tr>
<th>Authors and reference</th>
<th>Subtype(s) (no.) tested</th>
<th>Source</th>
<th>Drugs tested</th>
<th>No. of samples</th>
<th>Mutations selected in:</th>
<th>Findings</th>
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<td></td>
<td>PR</td>
<td>RT</td>
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<tr>
<td>Colson et al. (15)</td>
<td>A (21), B (B), U (5)</td>
<td>Treated and naïve patients</td>
<td>RTV, NFV, SQV, APV, IDV, LPV</td>
<td>31</td>
<td>7R, 46I, 62A, 71I, 90M, 99F</td>
<td>ND</td>
</tr>
<tr>
<td>Damond et al. (18)</td>
<td>A (68), B (25), H (1)</td>
<td>Treated and naïve patients</td>
<td>IDV, NFV, SQV, RTV</td>
<td>111</td>
<td>36V, 46V, 54L, 54M, 62A, 62l, 82F, 82M, 71I, 71A, 90M</td>
<td>ND</td>
</tr>
<tr>
<td>Pieniazek et al. (65)</td>
<td>A (8), B (20)</td>
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<td>ZDV, ddI, 3TC, d4T, IDV, NFV</td>
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<td>ND</td>
<td>ND</td>
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<td>A (52), B (24)</td>
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<td>ZDV, ddI, 3TC, RTV, IDV, NFV, SQV, d4T</td>
<td>76</td>
<td>ND</td>
<td>ND</td>
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<td>Adje-Toure et al. (1)</td>
<td>ND</td>
<td>Treated patients</td>
<td>ZDV, ddI, 3TC, d4T, IDV, NFV</td>
<td>18</td>
<td>90M</td>
<td>151M, 184V, 184I, 215Y</td>
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<tr>
<td>Brandin et al. (8)</td>
<td>ND</td>
<td>Treated patients failing HAART</td>
<td>ZDV, ddI, d4T, NFV</td>
<td>20</td>
<td>43V, 45R, 48A, 50V, 54M, 64V, 71I, 92T, 99F</td>
<td>65R, 151M, 184V, 219D</td>
</tr>
<tr>
<td>Rodes et al. (70)</td>
<td>ND</td>
<td>Treated patients</td>
<td>ZDV, ddI, 3TC, RTV, IDV, NFV, SQV, d4T</td>
<td>12</td>
<td>54M, 71I, 82F</td>
<td>62V, 65R, 69S, 70R, 151 M, 184V</td>
</tr>
<tr>
<td>Rodes et al. (71)</td>
<td>ND</td>
<td>Treated patients failing HAART</td>
<td>LPV, IDV, RTV, TPV, ZDV, 3TC, ABC, d4T, ddI, ddC</td>
<td>2</td>
<td>10I, 33L, 54M, 71I, 82F, 47A</td>
<td>ND</td>
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<tr>
<td>Rodes et al. (71)</td>
<td>ND</td>
<td>Treated patients</td>
<td>ZDV, 3TC, ABC, LPV, ddI, TDF, SQV</td>
<td>5</td>
<td>10I, 33L, 47A, 54M, 71I, 82F, 84V, 90F</td>
<td>ND</td>
</tr>
<tr>
<td>Damond et al. (20)</td>
<td>A (6)</td>
<td>Treated patients</td>
<td>TFV, 3TC, LPV, APV, d4T, ZDV</td>
<td>7</td>
<td>ND</td>
<td>65R, 67N, 70R, 151 M, 184V, 215Y, 219D</td>
</tr>
<tr>
<td>Descamps et al. (23)</td>
<td>A (31), B (2), U (1)</td>
<td>Treated patients</td>
<td>ZDV, d4T, DDI, 3TC, ABC, DDC, TFV</td>
<td>34</td>
<td>ND</td>
<td>65R, 67N, 70R, 151 M, 184V, 215S/Y, 215T/S 219D</td>
</tr>
<tr>
<td>Cavaco Silva et al.b</td>
<td>ND</td>
<td>Treated and naïve patients</td>
<td>ATV, APV, LPV</td>
<td>34</td>
<td>47A, 50L, 50V 54 M, 62A, 82F, 84V/L, 90 M, 99F/Y</td>
<td>ND</td>
</tr>
<tr>
<td>Reid et al. (68)</td>
<td>A (4), B (1)</td>
<td>In vitro selections</td>
<td>ZDV, ZDV/ddI</td>
<td>5</td>
<td>ND</td>
<td>65R, 184I</td>
</tr>
</tbody>
</table>

TABLE 1. Selected studies on HIV-2 drug resistance showing drugs used and mutations selected in PR and RT.
<table>
<thead>
<tr>
<th>Study</th>
<th>Source(s)</th>
<th>Patients</th>
<th>Selections</th>
<th>Resistance Patterns</th>
<th>NRTIs</th>
<th>MDR</th>
<th>Other Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Ende et al. (86)</td>
<td>ND</td>
<td>Biologic clones from 3 patients</td>
<td>ZDV, 3TC, ddl</td>
<td>3</td>
<td>ND</td>
<td>41I, 151I, 184V</td>
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<tr>
<td>Ntemgwa et al. (57)</td>
<td>A (3)</td>
<td>In vitro selections</td>
<td>APV, NFV, IDV, TPV</td>
<td>3</td>
<td>6F, 12A, 21K, 50V, 64V, 54M, 62A, 71L, 82F, 82L, 84V, 90 M, 99F</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Ntemgwa et al. (58)</td>
<td>A (3), B (1)</td>
<td>In vitro selections</td>
<td>ABCd4T, ddl, TFV, ZDV, 3TC, FTC</td>
<td>4</td>
<td>ND</td>
<td>184V, 184I, 134A, 167I, 174V</td>
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<tr>
<td>Jallow et al. (46)</td>
<td>A (8)</td>
<td>Treated patients</td>
<td>ZDV, 3TC</td>
<td>8</td>
<td>ND</td>
<td>69S, 62V, 65R, 151M, 184V, 215Y/F, 214L, 335L</td>
<td></td>
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<tr>
<td>Colson et al. (14)</td>
<td>A (25), B (4), U (3)</td>
<td>Treated patients</td>
<td>ABC, d4T, ddl, ddC, TFV, ZDV, 3TC, NFV, RTV, IDV, LPV, SQV, APV</td>
<td>32</td>
<td>ND</td>
<td>62V, 65R, 70R, 75M, 103R, 115F, 151M, 184V, 215F, 219D</td>
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<td>Ruelle et al. (74)</td>
<td>A (25), B (5), ND (35)</td>
<td>Treated and naïve patients</td>
<td>71I, 89V, 90M</td>
<td>65</td>
<td>89V, 90M</td>
<td>65R, 111I, 151M, 184V</td>
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<tr>
<td>Ruelle et al. (75)</td>
<td>ND</td>
<td>Naïve patients</td>
<td>None</td>
<td>52</td>
<td>None</td>
<td>151M, 184V</td>
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<td>Gottlieb et al. (35)</td>
<td>A (22), B (1)</td>
<td>Treated patients</td>
<td>ZDV, 3TC, DDI, d4T, IDV, NVP</td>
<td>23</td>
<td>7R, 54M, 62A, 82F, 90M, 99F</td>
<td>65R, 70R, 151M, 184V</td>
<td></td>
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</tbody>
</table>

Some mutations at amino acid positions in the HIV-2 RT gene correspond with those involved in HIV-1 resistance, although no conventional mutations associated with ZDV resistance were observed.

NRTIs select in culture for different patterns of drug resistance in HIV-1 and -2; lack of selection of K65R in HIV-2 in vitro using either single or dual drug combinations of NRTIs. Whereas HIV-2 has some equivalent HIV-1 mutations, others either were absent or pre-existing as natural polymorphisms; differences between HIV-1 and -2 should be taken into account in the development of new drugs.

Findings highlight the need for specific guidelines for determining genotypic resistance and treatment of HIV-2-infected patients.

Better treatment outcome for HIV-2-infected patients on a PI-containing regimen; showed for the first time that transmission of drug-resistant HIV-2 occurred.

Either HIV-2-resistant viruses are being transmitted or individuals are taking unsupervised treatment.

HIV-2-infected patients treated with ARV therapy commonly harbor mutations consistent with multiclass drug resistance.

*ND, not determined; U, undefined; FTC, emtricitabine.
HIV-2 RESISTANCE TO NNRTIS

HIV-2 has been described as naturally resistant to all non-nucleoside RT inhibitors (NNRTIs) (43). Natural resistance of HIV-2 to NNRTIs is thought to arise on account of the Y188L polymorphism, which appears naturally in all HIV-2 isolates. Reversion to Y188 renders the RT of HIV-2 sensitive to some mutations at codon 215 selected under drug pressure did not possess K65R, despite subsequent challenge with either TDF, didanosine (ddI), stavudine (d4T), or abacavir (ABC). Clearly, more studies are needed to uncover the mechanisms that may account for the high incidence of K65R in the treated HIV-2-infected patients in this study.

In HIV-1, the appearance of K65R can preclude the development of thymidine analogue mutations (TAMs) and vice versa (60–62). The strongest such antagonism seems to exist between K65R and T215Y (60), due to K65R-mediated reduction of the TAM-related excision process. Of note, HIV-2 has potential drug resistance polymorphisms at TAM positions 210, 215, and 219. However, it is unlikely that HIV-2 RT is similarly affected, since the latter does not apparently enact excision (7).

One group was unable to select for K65R in HIV-2 using cord blood mononuclear cells and MT2 cells, even with drug combinations (i.e., tenofovir [TFV] plus ABC, TFV/ddI, and d4T/ddI) that would usually select for this mutation with HIV-1 (58). Moreover, this result was confirmed using an allele-specific real-time PCR assay to detect K65R in HIV-2 (58). Other studies have shown a more frequent selection of the Q151M mutation in HIV-2 isolates in vivo than in HIV-1 (1, 23, 35). Studies have shown that the M184V mutation is selected easily in both HIV-1 and HIV-2 with lamivudine (3TC) and emtricitabine (46, 58). However, no study has shown the selection of L74V with ddI in HIV-2, nor is there any evidence that either M184V or L74V affects ZDV susceptibility in HIV-2.

Regarding NRTIs, amino acids at six positions in wild-type HIV-2 are analogous to secondary or accessory drug resistance mutations in HIV-1 (69N, 75I, 118I, 210N, 215S and 219E). These residues may predispose HIV-2 to distinct evolutionary pathways in response to drug pressure. Further genotypic and phenotypic analyses of NRTI resistance in HIV-2 are needed, as are larger numbers of isolates for study.

HIV-2 RESISTANCE TO INTEGRASE INHIBITORS

Integrase inhibitors (INIs) are a novel therapeutic option for HIV-1-infected patients (39, 40). Raltegravir (RAL) has been approved for clinical use in HIV-1 infection, and a second INI, elvitegravir (EVG), is undergoing advanced trials (36). However, little is known about the potential use of INIs in HIV-2-infected patients. A recent study showed that the phenotypic susceptibility of clinical HIV-2 isolates to INIs was similar to that of HIV-1 despite a 40% difference in sequence between the HIV-1 and HIV-2 integrase genes (73). This may be because certain key catalytic motifs (i.e., the DDE triad and the HHCC and RKK motifs) were fully conserved in HIV-2 at the genomic positions described for HIV-1 (73). Another recent study described the selection of the Q148R INI resistance mutation in an HIV-2-infected patient failing a RAL-containing regimen (72). This mutation yielded 55-fold and 99-fold resistance to RAL and EVG, respectively. Of note, such mutations have previously been linked to virologic failure in HIV-1-infected patients (83). The N155H mutation has also been found in the integrase gene of an HIV-2-infected patient failing a RAL-containing regimen (33). These findings show that HIV-1 and HIV-2 probably share similar INI resistance pathways and that INI resistance can develop in HIV-2 as in HIV-1 (49). The clinical efficacy of RAL in HIV-2 has been described in two case reports (19, 33).

HIV-2 RESISTANCE TO ENTRY INHIBITORS

Maraviroc works by binding to the CCR5 coreceptor to prevent HIV-1 from entering the cell. However, the activity of maraviroc is limited to patients with CCR5-tropic viruses (29). Primary HIV-2 isolates can use a broad range of coreceptors to attain productive infection in vitro, and these include CXCX4, CCR5, CCR1-5, as well as GPR15 (BOB) and CXCR6 (BONZO) (5, 59). Thus, HIV-2 isolates may be able to access many more coreceptors than HIV-1. Although the activity of maraviroc against HIV-2 has not been evaluated, the potential of HIV-2 to employ a broad range of coreceptors may limit its therapeutic use. HIV-2 also displays natural resistance to the fusion inhibitor enfuvirtide (89).

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