Broad Nucleoside Reverse-Transcriptase Inhibitor Cross-Resistance in Human Immunodeficiency Virus Type 1 Clinical Isolates

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Nucleoside reverse-transcriptase inhibitors (NRTIs) are important components of most antiretroviral combination treatment regimens. Using a large collection of clinical isolates, we characterized patterns of cross-resistance among all NRTIs. Drugs were grouped by the effect of the M184V mutation: susceptibility to group 1 drugs (zidovudine, stavudine, tenofovir, and adefovir) increased when M184V was present, whereas susceptibility to group 2 drugs (didanosine, zalcitabine, abacavir, and lamivudine) decreased. Significant cross-resistance was observed among all NRTIs and was most notable when samples with or without M184V were analyzed separately. An increasing number of thymidine-analogue mutations (TAMs) was associated with a progressive reduction in drug susceptibility for all NRTIs. The modulating effect of M184I/V on drug susceptibility was present regardless of the number of TAMs. The broad range of susceptibility observed for viruses containing the same number of TAMs indicates that the genetic correlates of NRTI resistance remain to be fully elucidated.

The introduction of highly active antiretroviral therapy (HAART) for the treatment of human immunodeficiency virus (HIV) type 1–infected individuals has greatly reduced the morbidity and mortality associated with this disease [1]. However, HIV has the ability to develop resistance to all available antiretroviral (ARV) agents [2]. As a consequence, an ongoing challenge for clinicians is the appropriate selection and sequencing of treatment regimens to achieve long-term virus suppression. Thus, the selection of active drugs after the failure of prior regimens is a critical issue for optimal patient management.

Nucleoside reverse-transcriptase inhibitors (NRTIs) were the first ARV drugs to be approved for the treatment of HIV, with zidovudine (ZDV) receiving Food and Drug Administration (FDA) approval in 1987. Although 7 protease inhibitors and 3 nonnucleoside reverse-transcriptase inhibitors (NNRTIs) are now available for use in treatment regimens, NRTIs continue to be the cornerstone of HAART [3]. Members of the NRTI class that are currently available in the United States include abacavir (ABC), didanosine (ddI), lamivudine (3TC), stavudine (d4T), zalcitabine (ddC), ZDV, emtricitabine, and tenofovir (TDF), a nucleotide reverse-transcriptase (RT) inhibitor. A number of investigational NRTI drugs are currently in development.

RT mutations frequently identified in viruses from patients who have received ZDV (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) were thought initially to be associated only with ZDV resistance [4–7]. However, the response to other NRTIs after ZDV failure is often muted [8], and ZDV mutations emerge during therapy with d4T or ddI in the absence of ZDV [9]. As a result, ZDV mutations are now commonly included among the thymidine analogue mutations (TAMs), to indicate their broader impact on resistance to the NRTI class. The magnitude of reduced ZDV...
susceptibility conferred by TAMs can be modulated by mutations selected for by other drugs. First described for the 3TC resistance mutation M184V, a total of 3 NRTI mutations (K65R, L74V, and M184V) and 2 NNRTI mutations (L100I and Y181C) are now recognized to increase ZDV susceptibility by suppressing resistance or resensitizing HIV to ZDV in the presence of ≥1 TAMs [10–17].

The availability of highly sensitive phenotypic assays has resulted in an appreciation of the extent of cross-resistance among NRTIs. For example, a recent study that used the Phenosense HIV assay [18] examined the clinical relevance of d4T cross-resistance in patients who had received ZDV [19]. In that study, patients who had received ZDV monotherapy for >3 years and then switched to d4T were more likely to have a virological response if the baseline susceptibility to d4T was not >1.4-fold higher than that of the susceptible wild-type reference virus.

Cross-resistance among NRTI drugs has been found to be associated with certain multidrug resistance (MDR) mutations in RT, such as Q151M and T69 insertion mutations [20–24]. However, these MDR mutations are seen relatively infrequently [25, 26] and cannot account for the much higher rates of cross-resistance among NRTIs that is seen in clinical settings. The optimum use and sequencing of NRTI drugs is dependent on a better understanding of cross-resistance among these drugs. The purpose of the present study was to characterize the extent, patterns, and etiology of cross-resistance among NRTI drugs in the absence of previously defined MDR mutations, using a large database of clinical samples submitted for routine phenotypic and genotypic testing.

MATERIALS AND METHODS

Phenotypic drug susceptibility was determined using the Phenosense HIV assay [18], and the results were expressed as the fold change (FC), calculated as the IC50 of the patient virus sample divided by the IC50 of the NL4-3 reference strain tested in the same assay batch. Bivariate scatter plots of log-transformed FC data were generated for each pair of NRTIs. In each plot, samples were divided into 2 groups on the basis of the absence or presence of a mutation at position 184 in RT (1 or V).

RT genotypes were determined using GeneSeq HIV (ViroLogic), which uses the same resistance test vector as that in the Phenosense assay. Deduced amino-acid sequences of patient viruses were compared with a reference virus strain (NL4-3). Nucleotide sequences were determined using dideoxy nucleotide dye terminator chemistry and resolved on ABI 3700 automated sequencers. The GeneSeq HIV assay can detect most minor virus populations in plasma samples when they are present at 10%–20% of the total virus population (GeneSeq HIV validation data; ViroLogic; data not shown).

A database containing NRTI susceptibilities from 5932 clinical HIV-1 samples with matched phenotypic and genotypic measurements was evaluated. All available phenotypic data for 7 of the 8 FDA-approved NRTIs and adefovir (ADV) were included. Samples were excluded from the analyses if the isolates lacked any nucleoside analogue resistance-associated mutation, contained MDR mutations (Q151 complex or T69 insertions), or genotypic mixtures at the following positions in RT: 41, 67, 70, 184, 210, 215, and 219. When the IC50 of the patient virus exceeded the highest drug concentration tested, the FC was assigned a fixed value that was determined by dividing the highest drug concentration tested by the IC50 of the wild-type reference virus. TAMs were defined as M41L, D67N, K70R, L210W, T215F or Y, and K219E, H, N, Q, or R. On the basis of existing data, M184I and V were considered to have equivalent effects on NRTI susceptibilities [18, 27]. The M184I variant was present in 2% of samples with any mutation at position 184.

Provided that sufficient clinical outcome data are available, a threshold (or cutoff) can be derived that defines the drug susceptibility value above which the virological response to treatment with that drug significantly declines. Clinical cutoffs have been defined for 5 of 8 FDA-approved NRTIs: 4.5-fold for ABC [28], 1.7-fold for ddI and d4T [29–32], 1.4-fold for TDF [33], and 3.5-fold for 3TC [34]. Cutoffs for ZDV, ddC, and ADV were 2.5, 1.7, and 1.4-fold, respectively, and were derived from assay reproducibility data [35]. All cutoffs were derived using the Phenosense HIV assay and may not be directly applicable to other phenotypic assays. Pairwise comparisons of NRTI susceptibilities as continuous variables were done for each drug using the nonparametric Spearman’s rank test or linear correlation using Statview software (version 5.0; SAS).

RESULTS

Patterns of cross-resistance. Susceptibilities of patient viruses to each NRTI were evaluated using phenotypic assays. Results were expressed as the FC in IC50 compared with the NL4-3 reference. Bivariate scatter plots of log-transformed FC data were generated for each pair of NRTIs and are shown in figures 1 and 2. The scatter plots of NRTI pairs exhibiting weaker correlations (figure 2) suggested the existence of 2 distinct populations that, if evaluated separately, might exhibit stronger correlations. The subset of NRTI pairs that included 3TC displayed exaggerated separations and suggested that the M184V mutation might distinguish the 2 apparent populations.

To test this hypothesis, we reexamined the correlations for each NRTI pair using subpopulations segregated on the basis of the presence or absence of the M184I or V mutations. This analysis revealed 2 groups of NRTIs: group 1 included ZDV, d4T, TDF, and ADV, which showed increased susceptibility in the presence of M184I/V; and group 2 included 3TC, ddI, ddC, and ABC, which showed reduced susceptibility in the presence
Figure 1. Scatter plots displaying phenotypic cross-resistance ($\log_{10}$-transformed fold change [FC]) among pairs of nucleoside reverse-transcriptase inhibitors (NRTIs): within-group comparisons are shown. Samples with multiple NRTI resistance mutations (Q151M or T69 insertions), mixtures at M184, or thymidine-analogue mutations were excluded. Samples with M184I or V are in black; those lacking such mutations are in gray. Points at the extreme high end of the lamivudine (3TC) or abacavir (ABC) scale represent samples with high-level resistance that were assigned a fixed FC value that reflects the highest measurable level of resistance in the assay (see Materials and Methods). The oval in the zidovudine (ZDV)–tenofovir (TDF) plot indicates a group of samples containing the K65R mutation. Group 1 NRTIs: ZDV, stavudine (d4T), TDF, and adefovir (ADV); group 2: 3TC, ABC, didanosine (ddI), and zalcitabine (ddC).

of M184I/V. NRTI pairs within the same group all exhibited strong correlations that were independent of M184I/V (figure 1), as shown by the relatively small differences in the Spearman’s rank $\rho$ value among all samples, compared with those that did not have M184I/V mutations (table 1). NRTI pairs from different groups all exhibited weaker correlations if M184I/V was not considered (figure 2), and the Spearman’s rank $\rho$ value increased dramatically in samples without M184I/V (table 1). For the within-group comparisons (figure 1), with the exception of pairs involving 3TC, the data points fell along a single diagonal line with a high correlation coefficient; samples containing or lacking M184I/V clustered at either end of the line. This is most striking for the ZDV:TDF and ADV:TDF plots, whereas somewhat more scatter was seen for pairs such as d4T:ZDV and TDF:d4T.

Conversely, for between-group comparisons, 2 separate but parallel linear clusters of samples were usually observed that were defined by the presence or absence of the M184I/V mutation (figure 2). Samples with 184 mutations tended to cluster along a shifted diagonal line parallel to the samples without
Figure 2. Scatter plots displaying phenotypic cross-resistance (log_{10}-transformed fold change) among pairs of nucleoside reverse-transcriptase inhibitors (NRTIs): between-group comparisons are shown. Samples with multiple NRTI resistance mutations (Q151M or T69 insertions), mixtures at M184, or thymidine-analogue mutations were excluded. Samples with M184I or V are in black; those lacking such mutations are in gray. Points at the extreme high end of the lamivudine (3TC) or abacavir (ABC) scale represent samples with high-level resistance that were assigned a fixed FC value that reflects the highest measurable level of resistance in the assay (see Materials and Methods). Group 1 NRTIs: zidovudine (ZDV), stavudine (d4T), tenofovir (TDF), and adefovir (ADV); group 2: 3TC, ABC, didanosine (ddI), and zalcitabine (ddC).

184 mutations, as exemplified by the ABC:d4T or ddI:TDF plots. Because the M184I/V mutation causes very high-level resistance to 3TC, a more dramatic separation of the samples with and without 184 mutations was observed in the 3TC scatter plots. However, strong correlations ($\rho = 0.62–0.81$) in susceptibility between 3TC and other NRTIs was readily apparent from the samples without 184 mutations (table 1). Although the susceptibilities among all NRTIs were correlated, the range of reduced susceptibility varied dramatically among NRTIs.

Although most of the scatter plots revealed linear relationships between the log-transformed FC data for each pair of NRTIs, there were a few subtle, nonlinear patterns that could be discerned. For example, in the ABC:ddI and ABC:ddC plots, the cluster of samples with M184I/V appeared to lie on a diagonal line that was slightly shifted, compared with samples without M184 mutations (figure 1), which demonstrates the greater impact of the 184 mutation on ABC susceptibility than on the other drugs. Also, in the TDF:ZDV plot, a small cluster of samples with decreased TDF susceptibility but increased ZDV susceptibility can be seen. These samples all have the K65R mutation (oval in figure 1). Similarly, clusters of samples in plots involving ZDV or TDF with ddI or ABC could be seen...
positive correlations (all). Notably, comparisons, both within and between groups, showed strong agreement with Spearman’s rank test results (data not shown).

TDF:ADV ( ), and that within group 2 was ddI:ABC ( ). Linear correlation coefficients were highly consistent except TDF:3TC; however, within-group correlations ( ) existed for all pairwise comparisons (figure 2) that tended to contain other mutations such as L74I/H11002.

<table>
<thead>
<tr>
<th>Table 1. Correlation coefficients (Spearman’s $\rho$) of nucleoside reverse-transcriptase inhibitor susceptibility.</th>
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<td>Comparison, drug 1 and drug 2</td>
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<td>ZDV and ddl</td>
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NOTE. All lamivudine (3TC) fold-change values in samples with M184I or V were >100. ABC, abacavir; ADV, adefovir; d4T, stavudine; ddC, zalcitabine; ddl, didanosine; NA, not applicable; TDF, tenofovir; ZDV, zidovudine.

Correlation of NRTI susceptibilities. To more accurately quantify the correlation among NRTI susceptibilities and the degree of cross-resistance between drugs, Spearman’s rank correlation coefficient was determined for all pairs of NRTIs (table 1). The results for all samples indicated that significant positive correlations ($P < .0001$) existed for all pairwise comparisons except TDF:3TC; however, within-group correlations ($\rho = 0.79–0.95$) were all stronger than between-group correlations ($\rho = 0.13–0.58$). The strongest correlation within group 1 was TDF:ADV ($\rho = 0.95$), and that within group 2 was ddl:ABC ($\rho = 0.90$). Linear correlation coefficients were highly consistent with Spearman’s rank test results (data not shown).

In subset analyses of viruses without M184I/V, all pairwise comparisons, both within and between groups, showed strong positive correlations ($\rho = 0.47–0.90$; all $P < .0001$). Notably, between-group correlations within samples without M184I/V improved significantly compared with all samples (mean $\rho$ change, +0.34), whereas within-group correlations were unchanged (mean $\rho$ change, −0.08). The TDF:ADV comparison had the highest Spearman rank correlation coefficient in 184 wild-type samples ($\rho = 0.90$), and the ZDV:TDF, ABC:3TC, and d4T:ABC comparisons had linear correlation coefficients >0.90 in the same samples (table 1 and data not shown). Correlations were evident between susceptibilities to ZDV and all other NRTIs in M184 wild-type samples, with all $\rho$ values >0.5 except that for ZDV:ddC.

**Effect of TAMs and M184V on NRTI susceptibility distributions.** Because strong correlations were observed between ZDV susceptibility and that of the other NRTIs, the impact of TAMs on susceptibility to each NRTI was assessed by comparing the NRTI susceptibility of virus populations containing increasing numbers of TAMs (figure 3). The effect of the M184I/V mutation on susceptibility to NRTIs in the context of various numbers of TAMs was also examined. Invariably, increasing numbers of TAMs were correlated with decreased susceptibility to all NRTIs. Given equal numbers of TAMs, virus populations containing the M184I/V mutation were more susceptible to group 1 NRTIs than virus populations without M184I/V. Viruses with NRTI hypersusceptibility ($FC < 0.4$) for all group 1 NRTIs were observed in M184I/V virus populations without TAMs. In some cases, NRTI hypersusceptibility was observed in M184I/V viruses that had up to 2 TAMs (e.g., TDF; figure 3). Virus populations containing the M184I/V mutation were always less susceptible to group 2 NRTIs than virus populations without M184I/V that had the same number of TAMs. The effect of TAMs on 3TC susceptibility in M184I/V viruses could not be evaluated under these assay conditions (i.e., 3TC concentrations).

The likelihood of a virus to exhibit reduced susceptibility to a given NRTI was evaluated by tabulating the percentage of samples over the cutoff for each NRTI within genotypic groups, defined by the presence or absence of M184I or V or TAMs (table 2). Viruses with the M184I/V mutation were less likely to have an FC that exceeded the cutoffs of group 1 NRTIs. Viruses with the M184I/V mutation were much more likely to have an FC that exceeded the cutoffs of group 2 NRTIs.

**DISCUSSION**

We describe the existence of broad cross-resistance among all members of the NRTI class. Two distinct groups of NRTIs were identified on the basis of the impact of the M184I or V mutation on drug susceptibility. The etiology of the broad NRTI cross-resistance is clearly associated with, but not completely explained by, mutations in RT that are typically considered to be associated with thymidine nucleoside analogue drugs (ZDV and d4T).

The extent of NRTI cross-resistance has been underappreciated for at least 3 reasons. First, phenotypic assays with sufficient accuracy and precision to measure low-level reductions...
in susceptibility for some NRTIs—such as ddl, d4T, and TDF—have only recently become available. Because subtle (<2-fold) reductions in drug susceptibility are associated with the treatment failure of these drugs, less-precise phenotypic assays were unable to fully characterize the clinically relevant levels of drug susceptibility. Second, inadequate sample numbers hindered prior evaluations of cross-resistance. The large data set used in the present study provided adequate power for cross-resistance analyses and was generated by a single laboratory by use of well-controlled phenotypic and genotypic assays. In addition, samples that contain mixtures of wild-type and mutant amino acids at certain resistance-associated positions were eliminated, further minimizing noise in the data. Mixtures of wild-type and resistant viruses can dilute the level of resistance observed and act as an important cause of phenotype-genotype discordance [36, 37]. Finally, the ability of the M184I/V mutation to increase susceptibility to some NRTIs and decrease susceptibility to others masks correlations between many NRTI pairs and must be taken into account in order to reveal the relationships between NRTIs of different groups.

Reductions in drug susceptibility beyond certain thresholds (the clinical cutoff) are associated with an increased likelihood of a poor virological response during treatment with that drug [28, 29, 33, 34, 38]. Thus, the findings of the present study may have important implications for the sequencing of NRTIs in treatment regimens. NRTIs remain a cornerstone of most antiretroviral treatment regimens and must be used prudently to sustain virus suppression. For NRTIs with defined clinical cutoffs, such as TDF (1.4-fold), ABC (4.5-fold), ddI and d4T (1.7-fold), and 3TC (3.5-fold), it is clear that clinically relevant
also have higher numbers of TAMs, and many cross-resistant mutations at positions 44 and 118 have been proposed to contribute to high-level resistance to zidovudine (ZDV) [43], were introduced into the NL4-3 reference isolate [44]. Alterations in NRTI susceptibility by mutations beyond the PhenoSense assay is a potential limitation of our study, because these mutations may have similar resensitization effects as K65R, L74V, L100I, and Y181C. It is important to consider both the phenotypic susceptibility (to determine presence or absence of NRTI resistance) and the genotype (to determine the presence of detrimental or potentially beneficial mutations) when deciding whether to change a drug regimen in the face of a rebound in virus load. The presence of beneficial mutations when M184I or V is present is not fully understood. The clinical relevance of increases in susceptibility to the group 1 NRTIs when M184I or V is present is not fully understood. However, the presence of M184I/V, a 3TC resistance mutation, has been reported to preserve the activity of ZDV even though multiple TAMs are also present, which suggests that the continuation of 3TC therapy may provide a clinical benefit during ZDV therapy [39]. TAMs emerge more slowly in patients receiving ZDV/3TC combination therapy than in patients receiving ZDV alone [40]. Similar data have also suggested that virological responses to TDF therapy are greater in the presence of the M184V mutation [41]. Thus, for optimal NRTI sequencing, it is important to consider both the phenotypic susceptibility (to determine presence or absence of NRTI resistance) and the genotype (to determine the presence of detrimental or potentially beneficial mutations) when deciding whether to change a drug regimen in the face of a rebound in virus load. The presence of other mutations that can also increase ZDV susceptibility (such as K65R, L74V, L100I, and Y181C) is also important to assess, because these mutations may have similar resensitization effects on other group 1 NRTIs [42].

The inability to evaluate RT sequences beyond aa 305 with the PhenoSense assay is a potential limitation of our study, because alterations in NRTI susceptibility by mutations beyond aa 305 would be missed. However, when mutations in this region, which have been reported to be involved in ZDV-3TC resistance [43], were introduced into the NL4-3 reference vector, alone or in combination with various TAMs or M184V, significant changes in NRTI susceptibility were not seen [27].

Mutations at positions 44 and 118 have been proposed to play a subtle modulatory role. Our observations have important implications for the selection of ARV therapy regimens that contain NRTIs and indicate that cross-resistance among NRTIs is far more common than has been previously appreciated. The loss of activity to a single NRTI, especially ZDV or d4T, can have significant implications for the activity of many or all NRTIs. These results provide an explanation for the findings from many clinical trials that the failure of the first NRTI-containing regimen is associated with a suboptimal response to subsequent NRTI regimens. Phenotypic assays can detect clinically relevant cross-resistance that results from TAMs or other mutations in RT in cases where genotypic correlates are not well defined.

Table 2. Percentage of samples with or without M184I or V that are over the fold-change (FC) cutoff for each nucleoside analogue inhibitor.

<table>
<thead>
<tr>
<th>TAMs</th>
<th>ZDV</th>
<th>d4T</th>
<th>TDF</th>
<th>ADV</th>
<th>3TC</th>
<th>ddI</th>
<th>ddC</th>
<th>ABC</th>
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<tbody>
<tr>
<td>M or V</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>0.0</td>
<td>0.0</td>
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<tr>
<td>I or V</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>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>M</td>
<td>0.3</td>
<td>0.3</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>I or V</td>
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<td>0.0</td>
<td>0.7</td>
<td>0.9</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>87</td>
<td>70</td>
<td>74</td>
<td>77</td>
<td>48</td>
<td>30</td>
<td>21</td>
<td>69</td>
</tr>
</tbody>
</table>

**NOTE.** FC cutoffs were 2.5 for zidovudine (ZDV); 1.7 for didanosine (ddI), stavudine (d4T), and zalcitabine (ddC); 1.4 for adefovir (ADV) and tenofovir (TDF); 3.5 for lamivudine (3TC), and 4.5 for abacavir (ABC). TAMs, thymidine-analogue mutations.

reductions in susceptibility can result when TAMs accumulate during prior NRTI exposure. Clinical data support the notion that cross-resistance to a previously unused NRTI can occur after exposure to other NRTIs [9, 19, 28, 33, 34].

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