Reduced Antiretroviral Drug Susceptibility Among Patients With Primary HIV Infection

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Context  The transmission of drug-resistant human immunodeficiency virus (HIV) has been documented, but the prevalence of such transmission is unknown.

Objective  To assess the spectrum and frequency of antiretroviral susceptibility among subjects with primary HIV infection.

Design, Setting, and Patients  Retrospective analysis of 141 subjects identified from clinical research centers in 5 major metropolitan areas, enrolled from 1989 to 1998, with HIV seroconversion within the preceding 12 months and no more than 7 days’ prior antiretroviral (ARV) therapy.

Main Outcome Measures  Phenotypic and genotypic ARV susceptibility of HIV from plasma samples.

Results  The transmission of drug-resistant HIV as assessed by a greater than 10-fold reduction in ARV susceptibility to 1 or more drugs was observed in 3 (2%) of 141 subjects, including to a nonnucleoside reverse transcriptase inhibitor in 1 patient and to a nucleoside reverse transcriptase inhibitor and a protease inhibitor in 2 patients. Population-based sequence analysis of these 3 samples identified multidrug-resistance mutations in reverse transcriptase (M184V, T215Y, K219K/R) and protease (L10I/V, K20R, M36I, M46I, G48V, L63P, A71T, V77I, V82T, I84V, L90M) in the 2 latter patient samples, along with numerous polymorphisms. A reduction in susceptibility of greater than 2.5- to 10-fold was observed in viral isolates from 36 patients (26%). Sequence analysis of these 36 samples identified well-characterized drug resistance mutation in reverse transcriptase and protease in only 1 of these patients.

Conclusions  Reductions in drug susceptibility of more than 10-fold were rare among this cohort of recently HIV-infected subjects and were distributed among each of the 3 major classes of ARV drugs tested. Reductions in susceptibility of more than 2.5- to 10-fold to certain ARV drugs of unknown clinical significance were highly prevalent among newly infected patients. Resistance testing may be warranted to monitor the frequency of drug resistance over time and to assess the potential for geographic variability.
risk for transmission of resistant HIV. Furthermore, the use of a suboptimal initial treatment regimen in a person infected with drug-resistant virus is expected to limit the magnitude and durability of an antiviral response and may preclude the preservation of HIV-specific immune responses associated with early, effective ARV therapy. Prospective studies are needed to evaluate the clinical significance of primary HIV infection with drug-resistant virus and the subsequent virological response to ARV therapy.

The evaluation of drug resistance in HIV-infected persons may include an assessment of viral sequence (genotype) or viral drug susceptibility (phenotype). Consensus guidelines are available to facilitate interpretation of the often complex results of such assays and summarize their potential role in clinical management. In vitro techniques to assess viral susceptibility provide a quantitative assessment of viral growth characteristics in the presence of ARV drugs, which may correlate more directly than genotype results with virological responses. Clinical validation of genotypic and phenotypic assays is ongoing for each of these methods. Sequence analyses have identified amino acid substitutions in reverse transcriptase and protease, which confer varying levels of resistance to specific ARV drugs.

Many well-characterized drug resistance mutations (also called primary mutations) have been identified that are selected in virus exposed to antiretroviral therapy and are often associated with treatment failure. Less well-characterized amino acid substitutions that emerge with treatment have been described; these are often identified as viral polymorphisms in therapy-naïve subjects and are less clearly associated with drug resistance as assessed by in vitro drug susceptibility results. These genetic variants may exist as predominant or minority populations in the patient before the introduction of drug therapy but are selected during ARV therapy.

The clinical and virological consequences of primary HIV infection with drug-resistant virus may include suboptimal treatment responses, reduced viral fitness, and the potential for transmission of drug-resistant virus following defined risk exposures. We report an analysis of the spectrum and frequency of ARV susceptibility among subjects with acute and early HIV infection.

METHODS

Patient Recruitment

We evaluated subjects from a widespread referral network within each of 5 metropolitan cities across the United States (San Diego, Calif; Los Angeles, Calif; Dallas, Tex; Denver, Colo; and Boston, Mass) who had a history of HIV seroconversion during the preceding 12 months or documented evolution of an HIV antibody or Western blot response during study screening. All study participants signed an informed consent approved by the local institutional human subjects committee. Demographic information and an HIV risk assessment for each subject were obtained. Subjects with more than 7 days of prior ARV therapy or plasma viral RNA levels of less than 400 copies/mL were excluded from the study.

Patient Population

Subjects from 5 clinical research centers were identified over a 10-year period from 1989 to 1998 and were retrospectively enrolled in our cohort. Clinical and laboratory features of acute or early HIV infection were documented in all subjects. Subjects who were HIV seropositive at study entry reported a negative HIV test result during the preceding 12 months. Documentation of prior negative HIV test results was generally available if these test results were collected confidentially (ie, not anonymously). For subjects who reported a high-risk exposure followed by the onset of symptoms consistent with an acute retroviral syndrome, we estimated the date of HIV infection as either (1) the date of the HIV risk exposure, if the exposure was reported during the preceding 30 days, or (2) the date of symptom onset, if the exposure date was unknown. For asymptomatic seroconverters, the date of HIV infection was reported as the date of the first documented virological or serologic test result for HIV infection within 12 months of a negative test result.

Study Design

A baseline plasma sample was collected from each subject and stored at −70°C. Human immunodeficiency virus antibody status was determined by enzyme immunoassay (Abbott Laboratories, North Chicago, Ill) with confirmation by Western blot (Cambridge Biotech Corp, Rockville, Md). Quantification of plasma HIV RNA (Amplicor, Roche Molecular Systems, Branchburg, NJ) and analysis of CD4 lymphocyte subsets by dual-color fluorescence-activated cell sorter analysis (FACScan, Becton Dickinson Cytometry Systems, San Jose, Calif) were performed within 30 days of study entry (baseline). Patients identified in the Los Angeles area had plasma HIV RNA detected using the Chiron (Emeryville, Calif) branched-chain DNA assay (Version 2.0).

Phenotypic Drug Susceptibility Testing

The baseline plasma sample was analyzed for phenotypic drug susceptibility by PhenoSense HIV (ViroLogic Inc, South San Francisco, Calif). Reference sensitivity testing for this assay has demonstrated that among 134 patient plasma samples with viral loads of more than 500 copies/mL, 148 samples (96%) were successfully amplified and yielded acceptable phenotypic drug susceptibility results. Recombinant resistance test vectors were constructed by inserting amplified protease and reverse transcriptase gene segments from the plasma virus population into a replication-defective retroviral vector derived from a molecular clone of HIV-1 (pNL4-3) containing a luciferase indicator gene (luciferase). The assay was performed by cotransfecting 293 human embryonic kidney cells with resistance test vector DNA and an expres-
DRUG SUSCEPTIBILITY IN PRIMARY HIV INFECTION

Assay validation studies have demonstrated that IC\textsubscript{50} values 2.5-fold greater than the drug-sensitive reference virus (NL4-3) are indicative of reduced drug susceptibility.\textsuperscript{26} Assay variability (based on 95% confidence intervals) around repeated evaluations of the same sample was less than 3.2-fold for IC\textsubscript{50} values and less than 2.3-fold for fold-change values, and was similar for all tested drugs in the validation studies.\textsuperscript{26}

Although small retrospective studies have demonstrated a correlation between reduced assay susceptibility results and virological outcomes,\textsuperscript{27-31} insufficient clinical data are available to determine what level of reduced susceptibility is reproducibly associated with virological failure for each ARV drug. As a result, arbitrary classifications of reduced susceptibility were proposed for this analysis. Antiretroviral susceptibility results were reported as samples with wild type susceptibility (within 2.5-fold of the NL4-3 reference virus), samples with reductions in susceptibility of more than 2.5- to 10-fold less than reference virus, and samples with reductions in susceptibility of more than 10- to 1000-fold less than reference virus. These categories are provided to distinguish viral isolates with susceptibility differences within an order of magnitude. When a patient sample was noted to have a greater than 10-fold reduction in susceptibility to one drug and a greater than 2.5- to 10-fold reduction in susceptibility to another drug, summary results for that subject were reported among those with a more than 10-fold reduction in susceptibility.

Validation studies of the phenotype assay demonstrate that highly resistant viruses are generally detected at resistant virus concentrations ranging from 10% to 40%, depending on the virus and the drug.\textsuperscript{26}

### Statistical Analysis

Categorical variables are reported as frequency measures. Continuous variables are reported as arithmetic and geometric mean values with ranges. Two sample McNemar binomial exact tests were used to compare the frequency of reduced susceptibility among patient samples among each of the drug classes tested. A 2-tailed \( P < .05 \) was considered significant.

### RESULTS

A total of 141 subjects infected with HIV-1 between 1989 and 1998 were evaluated; 120 (85%) of these since 1996. Eighteen subjects infected during this period were not included in the analysis, including 4 for having HIV RNA of less than 400 copies/mL, which precluded susceptibility testing; 7 for failed amplification reactions despite having an HIV RNA of at least 400 copies/mL; and 7 for prior ARV therapy of more than 7 days’ duration.

Study volunteers were referred to participating study centers from local urgent care clinics, medical care providers, inpatient hospital services, community-based organizations, and by self-referral. Eighty percent of subjects reported symptoms consistent with an acute retroviral syndrome (fever, fatigue, sore throat, myalgias, headache) within 30 days of recognized high-risk HIV exposure(s). Documentation of primary HIV infection was available in 71% of the study cohort, including 62 subjects (44%) who presented with an evolving HIV antibody response (ie, acute HIV infection) and 38 subjects (27%) who had documented seroconversion within 12
months of presentation (ie, early HIV infection). Primary HIV infection was presumed in the remaining 41 subjects (29%) who reported symptoms consistent with an acute retroviral syndrome following a high-risk exposure within 12 months of a negative anonymous (undocumented) HIV antibody test. The patients were predominantly men with an average age of 32 years whose HIV risk factor was having sex with men (TABLE). Because initial plasma HIV RNA results were greater than the upper assay limit (750,000 copies/mL) in 13 patients (9%), the calculated mean baseline RNA represents a minimum estimate.

A plasma sample for ARV susceptibility testing was collected an average of 64 days (range, 0-279 days) after the estimated date of HIV infection. The mean interval between the first documented positive HIV test result (serologic or virological) and the collection of a drug resistance plasma sample was 40 days. At the time of baseline specimen collection, 6 subjects had received prior ARV therapy for a mean of 6 days (range, 4-7 days). Forty-eight (34%) of the 141 study subjects were from San Diego, 48 (34%) from Los Angeles, 19 (14%) from Dallas, 13 (9%) from Boston, and 13 (9%) from Denver.

Virus with reduced susceptibility to 1 or more nucleoside reverse transcriptase inhibitor (NRTI) was present in 5 samples (3%) (FIGURE 1). Two of these samples (1%) exhibited a greater than 10-fold reduction in susceptibility and 3 (2%) showed a greater than 2.5- to 10-fold reduction. The percentage of samples with reduced susceptibility to each NRTI was, for zidovudine, 2%; lamivudine, 2%; stavudine, 1%; didanosine, 0%; and zalcitabine, 1% (P > .05). Virus from 1 subject had reduced susceptibility to more than 1 NRTI tested.

Twenty-four patient samples (17%) had virus with reduced susceptibility to a nonnucleoside reverse transcriptase inhibitor (NNRTI), although only 1 sample (1%) exhibited a greater than 10-fold reduction in drug susceptibility (Figure 1). The observed reductions in susceptibility to this class were generally less than the reductions previously reported from nevirapine-treated patients. Reduced susceptibility to either nevirapine (10%) or delavirdine (14%) was observed in a significantly greater percentage of samples compared with efavirenz (1%; P < .001).

Among the 24 samples with reduced susceptibility to NNRTIs, 9 (38%) had reduced susceptibility to both nevirapine and delavirdine, while 2 (8%) had reduced susceptibility to all 3 NNRTIs.

The observed reductions in protease inhibitor susceptibility were generally between 2.5- and 10-fold that of the reference virus (Figure 1). Greater than 10-fold reductions in protease inhibitor susceptibility were observed in only 2 subjects (1%). Virus from both subjects had reduced susceptibility to all 4 tested protease inhibitors (FIGURE 2). In contrast, more than 2.5- to 10-fold reductions in susceptibility to a protease inhibitor were observed in 10% of patients, including 1% to saquinavir, 2% to indinavir, 5% to ritonavir, and 9% to nelfinavir (Figure 1). The number of subjects with reduced susceptibility to nelfinavir was significantly greater than observed for saquinavir or indinavir (P = .002). Comparisons among other drugs were not statistically significant.

Reductions in drug susceptibility of more than 10-fold to 1 or more ARV drugs were observed in 3 (2%) of 141
patient samples (Figure 2). Patient 97-546 from San Diego had 4- to 20-fold reductions in susceptibility to each of the NNRTIs tested and responded well to a protease inhibitor–NRTI–based treatment regimen (without use of an NNRTI). Patient 98-1093 from Los Angeles had a 12-fold reduction in susceptibility to zidovudine and 4- to 121-fold reductions in susceptibility to the protease inhibitors. The patient was initially treated with nelfinavir-stavudine-lamivudine and hydroxyurea but showed incomplete virological suppression (HIV RNA >400 copies/mL) at 24 weeks of therapy. After assessing the drug susceptibility of the patient’s virus, his treatment regimen was changed to an NNRTI-NRTI–based regimen (efavirenz-didanosine-stavudine-abacavir with hydroxyurea added 54 days later) with subsequent sustained suppression of viral load to less than 50 copies/mL.

Population-based sequence analysis was used to evaluate the reverse transcriptase and protease sequence of all recombinant virus pools with reduced drug susceptibility (n = 39). In 2 of 3 subjects with more than 10-fold reduction in drug susceptibility, drug resistance mutations in reverse transcriptase (M41L, M184V, T215Y) and protease (L10I/V, K20R, M36I, M46I, G48V, L63P, A71T, V77I, V82T, I84V, L90M) were observed in a background of numerous polymorphisms not characteristically associated with drug resistance. In patient 97-546, who had up to 20-fold reduced susceptibility to the NNRTIs (Figure 2), amino acid substitutions in reverse transcriptase were identified (ie, I135M, E138A), which may have accounted for the observed reduction in susceptibility to the NNRTIs. However, none of the well-characterized mutations in the binding pocket of reverse transcriptase were identified. A single resistance mutation to zidovudine (K219K/R) was identified in this subject, associated with a 2.2-fold reduction in susceptibility (below the threshold of a more than 2.5-fold reduction in susceptibility). Among the 36 patient samples (26%) with more than 2.5- to 10-fold reductions in susceptibility, numerous

Figure 2. Antiretroviral Drug Resistance in 3 Patients With Reductions in Drug Susceptibility of Greater Than 10-Fold

Reductions in drug susceptibility for the 3 patients with greater than 10-fold reduced susceptibility to at least 1 drug compared with the NL4-3 reference are shown. Drugs not listed in the figure had wild-type drug susceptibility results. NRTI indicates nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; and PI, protease inhibitor.
polymorphisms were detected, but only 1 well-defined drug resistance mutation (T215Y) was found, which corresponded to an 8.4-fold reduction in susceptibility to zidovudine.

No geographic clustering was observed among patients with reduced susceptibility to the antiretroviral drugs tested (data not shown); however, this study did not have power to detect significant geographic variability. Although 70% of these patients were identified after the release of the first potent protease inhibitors (1997), the proportion of patients with moderately reduced susceptibility to the protease inhibitors and NNRTIs did not significantly increase between 1989 and 1998 (data not shown). However, both subjects with more than 10-fold reductions in protease inhibitor susceptibility were identified in 1998. Similarly, samples with more than 10-fold reductions in susceptibility to either NRTIs or NNRTIs were collected during 1997 (n = 1) or 1998 (n = 2). Virus with more than 10-fold reductions in susceptibility to 2 classes of ARV drugs (multidrug-resistant virus) were present in 2 subjects (1%). No subject had a more than 10-fold reduction in susceptibility to all 3 classes of drugs.

**COMMENT**

The observation of preserved HIV-specific CD4+ T-cell proliferative responses in subjects who initiated potent ARV therapy during acute HIV seroconversion has resulted in modification of the consensus guidelines for ARV therapy to include a recommendation for prompt therapy in the setting of primary HIV infection. Studies from Europe and the United States have reported the transmission of drug-resistant variants in up to 10.5% to 15% of subjects with primary HIV infection and 13% of ARV therapy-naïve subjects. We identified a smaller proportion of subjects (2%) from 5 metropolitan US cities infected with drug-resistant virus. These differences do not appear to be related to selection bias or delay between HIV infection and testing in our study cohort. Although we cannot exclude the possible reversion of transmitted drug-resistant mutants prior to performance of study sequence analyses, persistence of transmitted or acquired drug resistance mutations for zidovudine and nevirapine in the absence of selective drug pressure has been demonstrated for 12 months and 3.5 months, respectively. Rather, regional differences in ARV treatment practices or risk behaviors among treatment-experienced patients from previously published cohorts (San Francisco, Switzerland, and Spain), which were not observed within our cohort, may account for this difference.

We believe it is important to monitor the prevalence of drug resistance for epidemiological reasons and to assess the need for routine drug resistance testing to guide clinical management of subjects with primary HIV infection. Multiple studies have demonstrated an increased frequency of treatment failure in subjects with established infection and drug-resistant virus. Similar studies of virological outcomes among subjects infected with drug-resistant virus may require the screening of very large numbers of patients with primary HIV infection.

Reductions in susceptibility of more than 10-fold to ARV drugs were confirmed in 2 of 3 subjects by the identification of well-characterized drug resistance mutations in reverse transcriptase and protease. The initial response to a protease inhibitor–NRTI–based treatment regimen was suboptimal in these 2 subjects. Complete viral suppression was observed in the third subject with greater than 10-fold reduced susceptibility to delavirdine, although his treatment regimen did not include an NNRTI. In contrast, among a subset of 13 patients from this Los Angeles cohort with wild-type drug susceptibility, all had viral suppression (plasma HIV RNA <500 copies/mL) by week 12 of potent therapy.

**Figure 3. Response to Therapy for 1 Patient With A Drug-Resistant Human Immunodeficiency Virus (HIV) Strain Compared With A Patient With Wild-type HIV**

The virological response to therapy for patient 98-1186 (red triangle), with a greater than 10-fold reduction in drug susceptibility, is compared with a typical patient (97-513, blue diamond) with wild-type drug susceptibility. Both subjects initiated combination antiretroviral therapy with zidovudine-lamivudine-indinavir within 7 days of study entry. Genotypic sequence analysis for patient 98-1186 was performed on a sample collected 49 days after the start of therapy (study day 53). Well-recognized drug resistance mutations for zidovudine, lamivudine, and multiple protease inhibitors were identified. Antiretroviral therapy was changed on study day 89 to didanosine-stavudine-efavirenz-abacavir, with hydroxyurea added 54 days later (day 143). Complete suppression of viral load (HIV RNA <50 copies/mL) was first documented approximately 11 weeks after changing antiretroviral therapy. Gray line indicates lower limit of detection of viral load.

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Because the first therapeutic regimen is the most important in terms of producing a maximal and durable virological response, suboptimal initial therapy in subjects infected with drug-resistant virus may be associated with the outgrowth of increasingly drug-resistant mutants and more rapid disease progression. Poor adherence related to drug toxicities may further confound our ability to identify subjects in whom suboptimal treatment responses may be related to infection with drug-resistant virus. The cost of frequent viral load testing to identify subjects with slow treatment-induced declines in plasma viral load should be compared with that of routine drug resistance testing in patients with primary HIV infection. Drug resistance testing in newly infected subjects might be expected to limit the stepwise accumulation of drug resistance mutations associated with incomplete viral suppression in patients who receive an initial therapeutic regimen that contains only 1 or 2 active drugs.

The high prevalence of reduced drug susceptibility of more than 2.5- to 10-fold to certain ARV drugs in this population (26%) was not associated with the presence of recognized drug resistance mutations. The absence of a significant delay between HIV seroconversion and drug susceptibility testing in this population does not suggest selective outgrowth of a more fit virus. However, we cannot exclude the possibility that minor subpopulations of more highly resistant virus were present and not detected by population-based sequencing. Greater natural variability in the susceptibility of wild-type virus to NNRTIs and some protease inhibitors compared with NRTIs may represent another explanation for the higher proportion of samples in this cohort with moderately reduced susceptibility to these drugs. Assay validation studies support the highly reproducible low-level reductions in NNRTI susceptibility (more than 2.5- to 10-fold) among clinical isolates that lack well-characterized resistance mutations, such as were observed in this cohort, and suggest that additional mutations that confer reduced NNRTI susceptibility have not yet been defined. The high prevalence of more than 2.5- to 10-fold reductions in drug susceptibility also may be related to the use of new, more precise recombinant assays. Lower levels of reduced drug susceptibility may be detected with these assays compared with conventional peripheral blood mononuclear cell assays used in the past. The prevalence of NRTI drug resistance in our population was lower than previously reported. The higher prevalence of NRTI drug resistance previously reported may be attributed to inclusion of mutations that represent polymorphisms and do not confer reduced drug susceptibility or more widespread use of these drugs among unique study cohorts. Reductions in drug susceptibility of more than 2.5- to 10-fold to certain ARVs may have treatment implications in newly infected patients; however, further studies are needed to determine the clinical significance of such reductions in susceptibility and to determine whether the presence of more resistant subpopulations account for some of these observations.

These data demonstrate that the transmission of multidrug-resistant HIV has occurred in multiple cities across the United States. We were unable to identify the source partner to ascertain ARV treatment histories among most subjects or a particular exposure history in patients infected with drug-resistant virus. The cost-effectiveness of resistance testing should be evaluated in the context of efforts to rapidly identify and treat patients infected with drug-resistant virus.

Extrapolation of these findings to include screening of drug-naive patients with established infection will require demonstration that resistance mutations persist in the absence of drug selection pressure. Transmitted resistant virus may be outcompeted over time by subpopulations of more fit wild-type virus. Available resistance assays do not readily detect minor populations of resistant virus, which might subsequently be selected with initiation of ARV therapy. Longitudinal studies are needed to monitor changes in the frequency of primary drug resistance, the utility and limitations of phenotypic and genotypic testing in this setting, the extent to which each ARV drug class is affected, and the clinical consequences of primary infection with drug-resistant virus.

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