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Distribution of Human Immunodeficiency Virus Type 1 Protease and Reverse Transcriptase Mutation Patterns in 4,183 Persons Undergoing Genotypic Resistance Testing

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In a sample of 6,156 sequences from 4,183 persons, the top 30 patterns of protease inhibitor, nucleoside reverse transcriptase (RT) inhibitor, and nonnucleoside RT inhibitor mutations accounted for 55, 46, and 66%, respectively, of sequences with drug resistance mutations. Characterization of the phenotypic and clinical significance of these common patterns may lead to improved treatment recommendations for a large proportion of patients for whom antiretroviral therapy is failing.

The optimal regimens for the initial treatment of human immunodeficiency virus type 1 (HIV-1) infection have become increasingly well defined (6). However, the management of persons who develop HIV-1 drug resistance or who are infected primarily with a drug-resistant virus remains a clinical challenge. Genotypic testing for HIV-1 drug resistance is useful for selecting antiretroviral drugs for patients developing treatment failure, but the optimal means for interpreting genotypic tests is not known because many HIV-1 protease and reverse transcriptase (RT) mutations contribute to drug resistance.

To identify common combinations of drug resistance mutations and to determine their contribution to the burden of HIV-1 drug resistance, we examined HIV-1 protease and RT sequences from a clinic-based population tested at Stanford University Hospital. Identifying common patterns of drug resistance mutations is important for determining which mutation patterns should be examined for their phenotypic and clinical significance.

Patients, sequences, mutations, and drug susceptibility data. Between July 1997 and September 2003, 6,153 protease sequences and 6,156 RT sequences were determined for HIV-1 isolates from 4,183 persons in Northern California at the request of their physicians. Two thousand, nine hundred forty-seven persons had one sequence. Seven hundred ninety-eight persons had 2 sequences, 257 persons had 3 sequences, and 181 persons had 4 or more sequences. Forty-nine sequences from 32 persons belonged to a non-B subtype, including 27 subtype C sequences, 15 subtype A sequences, and 7 subtype D sequences.

Protease inhibitor (PI) resistance mutation patterns were defined by mutations at 14 nonpolymorphic protease positions associated with PI resistance: positions 24, 30, 32, 46, 47, 48, 50, 53, 54, 73, 82, 84, 88, and 90. Nucleoside RT inhibitor (NRTI) resistance mutation patterns were defined by mutations at 18 RT positions associated with NRTI resistance: positions 41, 44, 62, 65, 67, 69, 70, 74, 75, 77, 115, 116, 118, 151, 184, 210, 215, and 219. Nonnucleoside RT inhibitor (NNRTI) resistance mutation patterns were defined by mutations at 15 positions associated with NNRTI resistance: positions 98, 100, 101, 103, 106, 108, 179, 181, 188, 190, 225, 227, 230, 236, and 238.

Drug resistance mutations at polymorphic protease positions (positions10, 20, 33, 36, 63, 71, 77, and 93) were not used to define PI mutation patterns. Two common polymorphisms at NNRTI resistance positions, A98S and V179I (5), were not used to define NNRTI mutation patterns. Drug resistance mutations consisting of mixtures of wild-type and mutant variants were classified as mutant. Sequences with a mixture of more than one drug resistance mutation at the same position were excluded from analysis.

Drug susceptibility data obtained with the PhenoSense assay (ViroLogic, South San Francisco, Calif.) (4) on isolates matching specific mutation patterns were obtained from the Stanford HIV RT and Protease Sequence Database (5).

Summary of drug resistance mutations. Of 6,153 isolates, 21.3% had no drug resistance mutations, 22.6% had mutations associated with resistance to one drug class (15.4% NRTI, 5.7% NNRTI, and 1.5% PI), 34.3% had mutations associated with resistance to two drug classes (20.8% NRTI and PI, 12.4% NRTI and NNRTI, and 1.1% NNRTI and PI), and 21.8% had mutations associated with resistance to three drug classes.

PI patterns. Among the 6,153 protease sequences, 2,934 (47.7%) had a mutation at one or more of the 14 nonpolymorphic PI resistance positions. Of these sequences, 139 (4.7%) had a mixture of two mutations at the same position and were excluded from analysis. The top 30 PI patterns accounted for 54.5% of the 2,795 mutant sequences (Table 1), and 523 additional patterns accounted for the remaining 45.5% mutant sequences (Fig. 1). Of these additional 523 patterns, 204 (677 sequences) had one of the top 30 patterns plus one additional drug resistance mutation.

The top 30 PI patterns were associated with decreased susceptibility (>2.5-fold increase in the 50% inhibitory concentration [IC_{50}] of drug) to a median of five PIs (Table 1). These patterns included mutations at 12 of 14 nonpolymorphic PI resistance positions and had a median of 2.5 PI resistance mutations: 7 patterns with 1 mutation, 8 patterns with 2 mu-

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TABLE 1. Top 30 HIV-1 PI resistance patterns in 2,795 sequences from 2,275 persons with PI resistance mutations, 1997 to 2003

Mutation pattern	No. (%) of sequences[a]	No. of persons[a]	Cumulative %	Susceptibility to drug ($fold_n$)[b]						
				NFV	SQV	IDV	RTV	APV	LPV	ATV
D30N, N88D	249 (8.9)	210	8.9	**52_{18}**	2.0_{17}	1.7_{18}	1.4_{18}	0.9_{15}	0.9_{5}	**3.6_{10}**
L90M	245 (8.8)	206	17.7	**3.2_{9}**	1.4_{10}	1.3_{10}	**2.6_{10}**	1.2_{6}	0.3_{3}	**3.0_{2}**
D30N	130 (4.7)	117	22.3	**14_{10}**	0.5_{10}	0.9_{10}	0.6_{10}	0.5_{8}	0.6_{2}	1.8_{5}
M46I, L90M	89 (3.2)	71	25.5	**8.0_{9}**	2.1_{9}	**11_{8}**	**7.0_{7}**	**4.8_{6}**	**2.6_{2}**	2.1_{1}
G73S, L90M	66 (2.4)	54	27.9	**27_{4}**	**9.2_{4}**	**7.9_{4}**	**5.3_{4}**	1.3_{4}	1.3_{3}	2.0_{1}
I54V, V82A, L90M	60 (2.1)	45	30.0	**37_{9}**	**7.9_{9}**	**16_{9}**	**83_{9}**	**3.0_{7}**	**20_{6}**	**5.0_{3}**
L24I, M46L, I54V, V82A	52 (1.9)	35	31.9	**39_{6}**	**7.1_{6}**	**20_{5}**	**80_{4}**	**4.0_{4}**	**34_{3}**	**19_{1}**
V82I	51 (1.8)	40	33.7	**3.6_{5}**	1.3_{5}	0.7_{5}	1.7_{5}	1.1_{5}	0.8_{3}	1.3_{2}
G73S, I84V, L90M	50 (1.8)	41	35.5	**34_{3}**	**70_{3}**	**19_{3}**	**44_{3}**	**4.5_{2}**	**7.2_{3}**	**15_{1}**
M46L, I54V, V82A, L90M	49 (1.8)	34	37.2	**39_{4}**	**9.1_{4}**	**22_{4}**	**78_{4}**	**5.6_{4}**	**33_{2}**	
I84V, L90M	39 (1.4)	31	38.6	**19_{6}**	**18_{6}**	**9.6_{6}**	**17_{5}**	**3.8_{6}**	**3.1_{4}**	**10.0_{1}**
M46I, N88S	37 (1.3)	30	40.0	**19_{7}**	1.4_{7}	**6.1_{7}**	1.7_{7}	0.2_{6}	0.8_{1}	
M46I, G73S, L90M	31 (1.1)	26	41.1	**22_{3}**	**3.4_{3}**	**8.3_{3}**	**4.4_{3}**	1.6_{2}	**3.0_{3}**	
I54V, V82A	30 (1.1)	29	42.1	**12_{9}**	1.4_{9}	**8.3_{9}**	**28_{8}**	**3.0_{7}**	2.3_{1}	**6.0_{4}**
M46L	29 (1.0)	24	43.2	**4.4_{1}**	0.9_{1}	**2.8_{1}**	**3.1_{1}**	1.4_{1}	1.7_{1}	
M46I, I84V, L90M	29 (1.0)	22	44.2	**16_{5}**	**10.0_{5}**	**9.7_{5}**	**19_{4}**	**5.0_{4}**	**7.9_{4}**	
M46I	26 (0.9)	21	45.1	**3.4_{3}**	0.8_{3}	**7.8_{3}**	**5.9_{3}**	2.2_{3}		**6.9_{1}**
V82A	26 (0.9)	20	46.1	**3.4_{1}**	0.9_{1}	**2.7_{1}**	**4.0_{1}**	1.7_{1}	**4.7_{1}**	1.9_{1}
M46I, I54V, V82A, L90M	26 (0.9)	18	47.0	**75_{2}**	**23_{2}**	**37_{2}**	**148_{2}**	**11_{2}**	**64_{1}**	
M46I, G73S, I84V, L90M	24 (0.9)	19	47.9	**62_{3}**	**88_{3}**	**53_{3}**	**43_{3}**	**11_{3}**	**21_{3}**	**24_{2}**
D30N, N88D, L90M	21 (0.8)	20	48.6	**74_{10}**	**5.4_{10}**	**3.0_{10}**	**3.5_{10}**	1.3_{10}		**4.0_{1}**
N88S	21 (0.8)	19	49.4	**8.9_{13}**	1.2_{13}	**2.5_{13}**	0.8_{13}	0.1_{13}	0.5_{1}	**10.0_{2}**
G48V, I54V, V82A	21 (0.8)	15	50.1	**28_{3}**	**147_{3}**	**25_{3}**	**41_{3}**	**3.0_{3}**	**32_{3}**	**29_{3}**
V32I, M46I, V82A, L90M	20 (0.7)	14	50.8	**25_{2}**	**4.5_{2}**	**27_{2}**	**45_{2}**	**14_{2}**	**12_{2}**	**20_{2}**
L24I, M46I, I54V, V82A	18 (0.6)	15	51.5	**14_{6}**	1.4_{6}	**19_{5}**	**50_{3}**	2.1_{3}	**17_{1}**	
F53L, I54V, V82A, L90M	18 (0.6)	13	52.1	**35_{2}**	**24_{2}**	**14_{2}**	**107_{2}**	**3.1_{2}**	**30_{2}**	
L24I, M46L, V82A	18 (0.6)	12	52.8	**6.1_{1}**	1.3_{1}	**7.4_{1}**	**45_{1}**	**5.8_{1}**	**7.0_{1}**	
M46L, V82A	17 (0.6)	12	53.4	**5.5_{2}**	1.1_{2}	**6.3_{2}**	**13_{2}**	**4.5_{2}**	**6.6_{2}**	**2.5_{2}**
M46L, L90M	17 (0.6)	11	54.0	**12_{2}**	**3.3_{2}**	**8.8_{2}**	**7.1_{2}**	**4.1_{2}**		**4.0_{1}**
D30N, M46I, N88D	15 (0.5)	15	54.5	**25_{1}**	0.9_{1}	1.2_{1}	1.0_{1}	0.8_{1}		

[a] Of 4,183 persons, 2,275 had 2,795 mutant sequences with 553 different PI mutation patterns. The top 30 patterns accounted for 54.5% of 2,795 mutant sequences.
[b] Median susceptibility results (n-fold) for isolates with matching patterns of mutations. The subscript is the number of samples for which susceptibility results are available. Results that are ≥2.5-fold the susceptibility of the wild-type control are shown in bold. Abbreviations: NFV, nelfinavir; SQV, saquinavir; IDV, indinavir; RTV, ritonavir; APV, amprenavir; LPV, lopinavir; ATV, atazanavir.

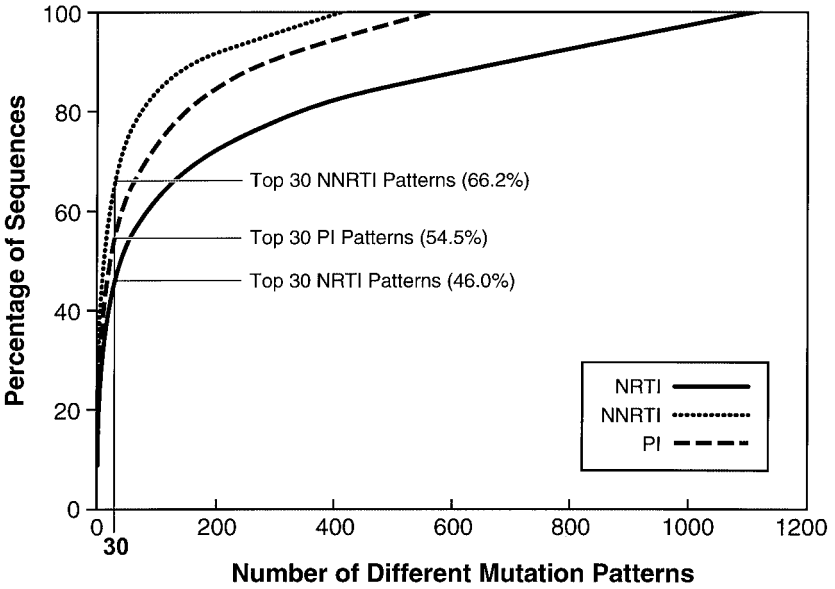

FIG. 1. Percentage of mutant sequences explained by the 553 different PI resistance mutation patterns (dashed line), 1,120 NRTI resistance mutation patterns (solid line), and 411 NNRTI resistance mutation patterns (dotted line). The top 30 PI, NRTI, and NNRTI resistance mutation patterns accounted for 55, 46, and 66%, respectively, of all sequences with drug resistance mutations.

TABLE 2. Top 30 HIV-1 NRTI resistance patterns in 4,089 sequences from 3,550 persons with NRTI resistance, 1997 to 2003

Mutation pattern	No. (%) of sequences[a]	No. of persons[a]	Cumulative %	Susceptibility to drug ($fold_n$)[b]					
				ZDV	D4T	TDF	ABC	DDI	3TC
M184V	710 (17.4)	609	17.4	0.5_{30}	0.8_{32}	0.6_{4}	3.1_{32}	1.5_{30}	**$>200_{31}$**
M41L, M184V, T215Y	156 (3.8)	125	21.2	**5.5_{13}**	1.5_{13}	1.0_{3}	**5.1_{15}**	1.5_{13}	**$>200_{13}$**
M41L, M184V, L210W, T215Y	100 (2.4)	88	23.7	**15_{9}**	**1.8_{9}**	1.2_{4}	**6.1_{10}**	**1.7_{9}**	**$>200_{9}$**
M41L, T215Y	82 (2.0)	71	25.7	**12_{3}**	**1.8_{3}**		2.6_{3}	1.2_{3}	2.0_{3}
D67N, K70R, M184V, K219Q	79 (1.9)	61	27.6	**7.5_{2}**	1.4_{2}	**1.6_{1}**	**5.2_{2}**	1.6_{2}	**$>200_{2}$**
K70R, M184V	65 (1.6)	55	29.2	1.1_{1}	0.7_{1}		2.2_{1}	1.5_{1}	**$>200_{2}$**
M41L, L210W, T215Y	56 (1.4)	48	30.6	**263_{2}**	**2.1_{2}**	**3.4_{2}**	3.0_{2}	1.2_{2}	1.8_{2}
M184V, T215Y	50 (1.2)	42	31.8	1.1_{4}	1.2_{4}	0.5_{2}	**5.2_{4}**	**1.9_{4}**	**$>200_{4}$**
V118I	48 (1.2)	44	33.0	1.0_{1}	0.9_{1}		1.0_{1}	1.1_{1}	1.0_{1}
T215Y	38 (0.9)	31	33.9	**11_{7}**	1.5_{7}	**1.4_{6}**	1.3_{7}	1.1_{7}	1.7_{7}
M41L, V118I, M184V, L210W, T215Y	37 (0.9)	31	34.8	**5.5_{3}**	**2.3_{3}**	**1.8_{2}**	**5.5_{3}**	**1.7_{3}**	**$>200_{3}$**
M41L, D67N, V118I, L210W, T215Y	35 (0.9)	30	35.6	**$2{,}400_{1}$**	**6.9_{1}**	**5.6_{1}**	**6.6_{1}**	**2.3_{1}**	**7.8_{1}**
L74V, M184V	33 (0.8)	31	36.5	0.3_{1}	1.0_{1}		**5.3_{2}**	**2.6_{1}**	**$>200_{1}$**
D67N, K70R, M184V	32 (0.8)	27	37.2	1.1_{2}	1.0_{2}	0.7_{1}	3.0_{2}	1.3_{2}	**$>200_{2}$**
D67N, T69N, K70R, M184V, K219Q	28 (0.7)	22	37.9	**7.9_{1}**	**2.3_{1}**		**7.7_{1}**	**1.8_{1}**	**$>200_{1}$**
M41L, D67N, M184V, L210W, T215Y	27 (0.7)	24	38.6	**30_{6}**	**2.6_{6}**	**2.1_{2}**	**6.4_{5}**	**1.9_{6}**	**$>200_{6}$**
M41L, M184V	27 (0.7)	19	39.2	0.5_{1}	0.6_{1}	0.4_{1}	1.6_{1}	1.4_{1}	**$>200_{1}$**
A62V, M184V	26 (0.6)	22	39.9	0.3_{1}	0.7_{1}	0.4_{1}	3.8_{1}	1.9_{1}	**$>200_{1}$**
M41L, E44D, D67N, V118I, M184V, L210W, T215Y	25 (0.6)	20	40.5	**54_{1}**	**3.2_{1}**	**2.0_{1}**	**6.6_{1}**	**2.0_{1}**	**$>200_{1}$**
D67N, K70R, M184V, T215F, K219Q	25 (0.6)	19	41.1	**7.7_{1}**	1.5_{1}	1.1_{1}	**6.5_{1}**	**1.7_{1}**	**$>200_{1}$**
D67N, K70R, K219Q	24 (0.6)	24	41.7	**26_{2}**	**1.8_{2}**		1.8_{2}	0.9_{2}	1.4_{3}
D67N, K70R	24 (0.6)	20	42.3	**17_{2}**	0.9_{2}	**1.5_{2}**	1.0_{2}	0.8_{2}	1.4_{2}
L74V	21 (0.5)	19	42.8	1.1_{1}	0.9_{1}			**1.8_{1}**	2.6_{1}
M41L, M184V, T215F	21 (0.5)	17	43.3	**4.6_{3}**	1.6_{3}		**5.8_{3}**	**2.0_{3}**	**$>200_{3}$**
M41L, V118I, L210W, T215Y	21 (0.5)	16	43.8	**13_{1}**	**1.9_{1}**		2.0_{1}	1.1_{1}	1.4_{2}
M41L, D67N, L210W, T215Y	18 (0.4)	18	44.3	**$1{,}000_{3}$**	**2.4_{3}**	**5.0_{3}**	**4.5_{3}**	1.6_{3}	**4.0_{3}**
T69N, K70R	18 (0.4)	17	44.7	**7.0_{2}**	0.8_{2}	1.3_{2}	0.8_{2}	0.8_{2}	0.8_{2}
M41L, E44D, D67N, V118I, L210W, T215Y	18 (0.4)	17	45.1	**119_{1}**	**3.6_{1}**		2.3_{1}	1.6_{1}	**4.4_{1}**
M41L, L74V, M184V, T215Y	18 (0.4)	17	45.6	0.7_{1}	1.2_{2}		**6.3_{1}**	**1.8_{2}**	**$>200_{2}$**
T69N	18 (0.4)	16	46.0	0.5_{2}	0.9_{2}	0.8_{2}	1.1_{2}	1.1_{2}	2.3_{2}

[a] Of 4,183 persons, 3,550 had 4,089 mutant sequences with 1,120 different NRTI mutation patterns. The top 30 patterns accounted for 46.0% of the mutant sequences.
[b] Median susceptibility results (n-fold) for isolates with matching patterns of mutations. The subscript is the number of samples with available susceptibility results. Results above the PhenoSense reduced susceptibility cutoff (≥1.9 for ZDV, ≥1.7 for D4T, ≥1.4 for TDF, ≥4.5 for ABC, ≥1.7 for DDI, and ≥3.5 for 3TC [fold]) are shown in bold. Abbreviations: ZDV, zidovudine; D4T, stavudine; TDF, tenofovir; ABC, abacavir; DDI, didanosine; 3TC, lamivudine.

tations, 8 patterns with 3 mutations, and 7 patterns with 4 mutations. The remaining 523 patterns had a median of 4 nonpolymorphic PI resistance mutations (data not shown).

L90M was the most common mutation, occurring in 15 patterns and 28.1% of viruses. Each of the top 30 patterns was common in the first and second halves of the study (data not shown), except for G48V/I54V/V82A, which decreased from 18 sequences between 1997 and 2000 to 3 sequences between 2001 and 2003 ($P < 0.001$).

NRTI patterns. Among the 6,156 RT sequences, 4,517 (73.4%) had a mutation at 1 or more of the 18 NRTI resistance positions. Of these sequences, 428 (9.5%) had a mixture of two mutations at the same position and were excluded from analysis. The top 30 NRTI patterns accounted for 46.0% of the 4,089 mutant sequences (Table 2), and 1,090 additional patterns accounted for the remaining 54.0% of mutant sequences (Fig. 1). Of these additional 1,090 patterns, 250 (784 sequences) had 1 of the top 30 patterns plus 1 additional drug resistance mutation.

The top 30 NRTI patterns were associated with decreased susceptibility (>1.4-fold to >4.5-fold increase in IC_{50} depending on the drug) to a median of three of six NRTIs (Table 2). These patterns had a median of three NRTI resistance mutations: five with one mutation, eight with two mutations, five with three mutations, five with four mutations, five with five mutations, and one each with six and seven mutations. The remaining 1,090 patterns had a median of 5 NRTI-resistance mutations (data not shown).

M184V was the most common NRTI resistance mutation, occurring alone in 17.4% of mutant sequences and in 16 patterns. T215Y occurred with the next-highest frequency and was in 14 patterns. Mutations at positions 65, 75, 77, 115, 116, and 151 did not occur among the top 30 patterns. Each of the top 30 patterns was common in the first and second halves of the study (data not shown), although significant increases were observed in the patterns A62V/M184V ($P < 0.001$) and T69N ($P = 0.001$). K65R was in 1.6% of mutant sequences, occurring alone in 10 sequences and in combination with M184V in 18

TABLE 3. Top 30 HIV-1 NNRTI resistance patterns in 2,526 sequences from 2,168 persons with NNRTI resistance, 1997 to 2003

Mutation pattern	No. (%) of sequences[a]	No. of persons[a]	Cumulative %	Susceptibility to drug ($fold_n$)[b]		
				NVP	DLV	EFV
K103N	459 (18.2)	379	18.2	**46_{21}**	**34_{21}**	**19_{20}**
K103N, Y181C	149 (5.9)	126	24.1	**400_{7}**	**250_{7}**	**46_{8}**
Y181C	116 (4.6)	100	28.7	**104_{6}**	**30_{6}**	1.0_{6}
L100I, K103N	116 (4.6)	99	33.3	**78_{9}**	**103_{9}**	**274_{9}**
K103R	93 (3.7)	74	36.9	0.5_{2}	0.9_{2}	0.5_{2}
Y188L	51 (2.0)	32	39.0	**500_{5}**	**9.0_{5}**	**109_{5}**
V106I	50 (2.0)	46	40.9	0.3_{3}	0.1_{3}	0.2_{3}
A98G	46 (1.8)	44	42.8	**3.6_{6}**	0.7_{6}	0.8_{5}
K103N, V108I	44 (1.7)	41	44.5	**218_{2}**	**65_{2}**	**79_{2}**
K101E, G190A	44 (1.7)	33	46.2	**500_{1}**	2.0_{1}	**123_{1}**
K101Q	38 (1.5)	35	47.7	2.2_{1}	1.4_{1}	2.1_{1}
K101R	34 (1.3)	31	49.1	0.3_{2}	0.3_{2}	0.3_{2}
K103N, P225H	34 (1.3)	28	50.4	**95_{4}**	**10_{4}**	**104_{4}**
K103N, Y181C, G190A	33 (1.3)	29	51.7	**240_{1}**	**190_{1}**	**240_{1}**
K103N, G190A	31 (1.2)	29	53.0	**500_{1}**	**37_{1}**	**213_{1}**
V108I	30 (1.2)	25	54.2	**3.0_{1}**	1.3_{1}	1.7_{1}
Y181C, G190A	29 (1.1)	25	55.3	**490_{3}**	**7.2_{3}**	**11_{3}**
K101E	29 (1.1)	20	56.5	**12_{1}**	**4.9_{1}**	**5.0_{1}**
V179D	27 (1.1)	22	57.5	0.7_{1}	**2.9_{1}**	1.4_{1}
K103N, K238T	26 (1.0)	24	58.6	**152_{2}**	**25_{2}**	**47_{2}**
K238R	23 (0.9)	21	59.5	0.5_{1}	0.2_{1}	0.2_{1}
G190A	22 (0.9)	21	60.3	**75_{5}**	0.4_{5}	**7.0_{5}**
K101P, K103N	22 (0.9)	16	61.2	**400_{1}**	**250_{1}**	**700_{1}**
V108I, Y181C	20 (0.8)	18	62.0	**400_{2}**	**40_{2}**	**4.9_{2}**
K101E, Y181C, G190A	20 (0.8)	15	62.8	**547_{2}**	**21_{2}**	**103_{2}**
A98G, K103N	19 (0.8)	16	63.5	**121_{4}**	**25_{4}**	**32_{4}**
G190S	18 (0.7)	16	64.3	**206_{3}**	0.4_{3}	**47_{3}**
K103N, V108I, Y181C	17 (0.7)	15	64.9	**400_{1}**	**250_{1}**	**700_{1}**
K103N, Y188L	17 (0.7)	12	65.6	**680_{1}**	**190_{1}**	**270_{1}**
K103N, M230L	16 (0.6)	16	66.2	**690_{2}**	**250_{2}**	**360_{2}**

[a] Of the 4,183 persons in this study, 2,168 had 2,526 mutant sequences with 411 different NNRTI mutation patterns. The top 30 patterns accounted for 66.2% of the 2,526 mutant sequences.

[b] Median susceptibility results (*n*-fold) for isolates with matching patterns of drug resistance mutations. The subscript is the number of samples for which susceptibility results are available. Results that are ≥2.5-fold the wild-type control result are shown in bold. Abbreviations: NVP, nevirapine; DLV, delavirdine; EFV, efavirenz.

sequences, in combination with Q151 M in 15 sequences, and in combination with M184V and Q151 M in 8 sequences. The frequency of K65R increased from 1.2 to 1.9% between the first and second halves of the study (*P* value not significant).

NNRTI patterns. Among the 6,156 RT sequences, 2,658 (43.2%) had a mutation at one or more of the 15 NNRTI resistance positions. Of these sequences, 132 (5.0%) had a mixture of two mutations at the same position and were excluded from analysis. The top 30 NNRTI mutation patterns accounted for 66.2% of mutant sequences (Table 3), and 381 additional patterns accounted for the remaining 33.8% of mutant sequences (Fig. 1). Of these additional 381 patterns, 210 (503 sequences) had 1 of the top 30 patterns plus 1 additional drug resistance mutation.

The top 30 NNRTI patterns were associated with decreased susceptibility (>2.5-fold increase in IC_{50} of drug) to a median of three NNRTIs (Table 3). These patterns had a median of 2 NNRTI resistance mutations: 14 with 1 mutation, 13 with 2 mutations, and 3 with 3 mutations. The remaining 381 patterns had a median of 3 NNRTI resistance mutations (data not shown).

K103N was the most common NNRTI resistance mutation, occurring alone in 18.2% of sequences and in 12 of the remaining patterns. The top 30 patterns included mutations at 13 of the 15 NNRTI resistance positions. Mutations at positions 227 and 236 were uncommon, occurring in 62 and 4 sequences, respectively. Four of the patterns—K103R, V106I, K101R, and K238R—are polymorphisms that do not occur with increased frequency in persons receiving NNRTIs and do not confer phenotypic resistance (Table 3). Three of the top 30 patterns included mutations (K101P, M230L, and K238T) that have only recently been recognized as causing NNRTI resistance (W. Huang, N. T. Parkin, Y. S. Lie, T. Wrin, R. Haubrich, S. Deeks, N. Hellmann, C. J. Petropoulos, and J. M. Whitcomb, abstract from the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy 2000, Antivir. Ther. **5**(Suppl. 3)**:**24-25, 2000; C. J. Petropoulos, C. Chappey, and N. T. Parkin, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. H-451, 2003). There was no significant change in the NNRTI resistance patterns between the first and second halves of the study (data not shown).

Consistency of drug susceptibility results within each pattern. With the exception of atazanavir and tenofovir, multiple drug susceptibility results were available for most patterns of drug resistance mutations (Table 4). The mean absolute deviation in resistance (*n*-fold) from the median susceptibility for each pattern ranged from 0.05 $\log_{10}$ (1.1-fold) for stavudine and didanosine to 0.32 $\log_{10}$ for delavirdine (2.1-fold), suggesting that results were consistent within most patterns of drug-resistance mutations.

TABLE 4. Consistency of drug susceptibility results within the top 30 patterns of drug resistance mutations for each drug class

Drug class	Drug	Isolates with patterns for which more than one susceptibility result is available		Mean absolute deviation in fold resistance from the median value of each pattern (log scale)[a]
		No. of patterns	No. of isolates	
NRTI	ZDV	17	95	0.21
	D4T	18	99	0.05
	TDF	12	34	0.10
	ABC	18	101	0.09
	DDI	18	97	0.05
	3TC	20	103	ND
NNRTI	NVP	19	90	0.23
	DLV	19	90	0.32
	EFV	19	89	0.24
PI	NFV	26	155	0.22
	SQV	26	155	0.19
	IDV	26	153	0.18
	RTV	26	146	0.16
	APV	26	131	0.15
	LPV	18	55	0.12
	ATV	11	37	0.17

[a] For 67% of mutant isolates, the 3TC IC_{50} was above the limit of detection of the assay and was censored at 200-fold, making it impossible to examine the consistency of results for most patterns. Abbreviations: ZDV, zidovudine; D4T, stavudine; TDF, tenofovir; ABC, abacavir; DDI, didanosine; 3TC, lamivudine; NVP, nevirapine; DLV, delavirdine; EFV, efavirenz; NFV, nelfinavir; SQV, saquinavir; IDV, indinavir; RTV, ritonavir; APV, amprenavir; LPV, lopinavir; ATV, atazanavir.

Conclusions. In this sample of >6,000 sequences from nearly 4,200 persons, the top 30 PI, NRTI, and NNRTI mutation patterns accounted for 55, 46, and 66%, respectively, of all sequences with drug resistance mutations. A much larger number of mutation patterns, however, were required to account for the remaining mutant sequences. Studies that examine the clinical significance of drug resistance mutations should focus on the commonly occurring patterns of mutations that we identified in this analysis, because they affect the largest numbers of patients and form the foundation for many of the more complex patterns.

Although about one-third of patients had more than one sequence, clustering of patterns within patients did not explain the observed patterns, because nearly identical patterns were observed in analyses that considered only one sequence per patient (Tables 1 to 3, footnotes). All the HIV-1 isolates in this study were from northern California; however, we have previously shown with heavily treated persons that the patterns of drug resistance mutations in northern California are similar to those in subtype B sequences from other parts of the world (3). Although each of the known protease and RT drug resistance mutations occurs in non-B-subtype isolates (R. Kantor, D. Katzenstein, R. Camacho, P. R. Harrigan, A. Tanuri, D. Pillay, A.-M. Vandamme, P. Phanuphak, W. Sugiura, V. Soriano, L. Morris, Z. Grossman, L. F. Brigido, J. Schapiro, and R. W. Shafer, Abstr. 10th Conf. Retrovir. Opportun. Infect., abstr. 623, 2003), preliminary data suggest that the patterns of these mutations may be different in other subtypes (1, 2; Z. Grossman, E. Paxinos, D. Auerbuch, S. Maayan, N. Parkin, D. Engelhard, M. Lorber, E. Kedem, F. Mileguir, N. Vardinon, Z. Bentwich, C. Petropoulos, and J. M. Schapiro, abstract from the 11th International HIV Drug Resistance Workshop 2002, Antivir. Ther. **7:**S39, 2002).

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