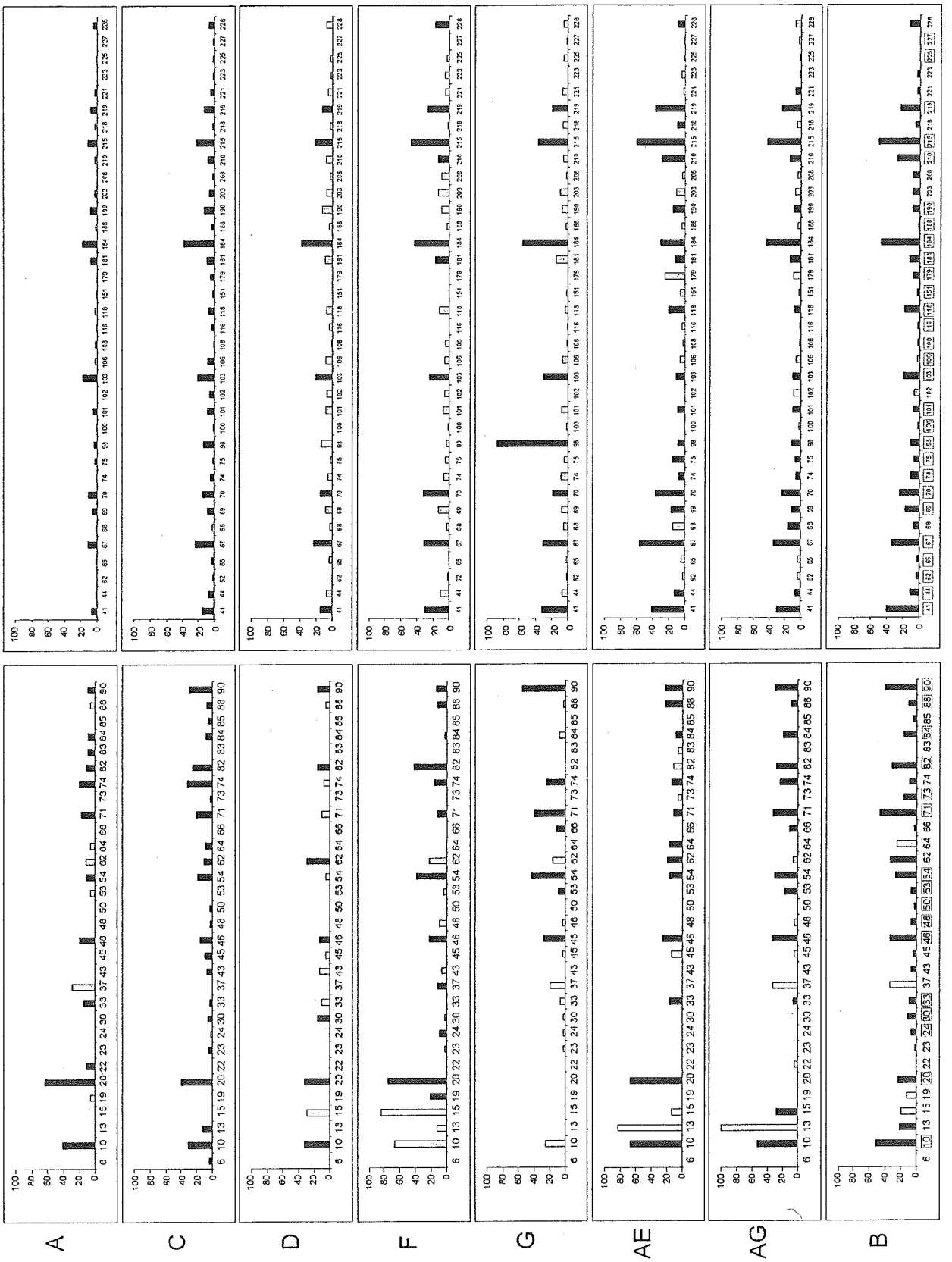
Protease
Treatment Related Mutations
Reverse Transcriptase
A
C
D
F
G
AE
AG
B

(position 15), subtype F (position 19), subtype A (position 37), and CRF01_AE (position 64).

Of the eight treatment-related RT positions at sites not known to be associated with drug resistance, seven were also significantly associated with treatment in subtype B viruses (positions 68, 203, 208, 218, 221, 223, and 228) and one (position 102) was associated with treatment in subtype C but not B.

Subtype–treatment interactions. The subtype of the sequence significantly influenced the effect of treatment (significant θ_3; see Methods) on 20 protease positions (10, 12, 13, 14, 15, 20, 37, 53, 62, 63, 64, 65, 67, 71, 73, 74, 77, 82, 88, and 89) and 11 RT positions (35, 39, 48, 98, 104, 106, 121, 162, 166, 179, and 238). For example, RT position 98 was mutant in 7% of untreated and 16% of treated persons with subtype B viruses (approximately 2-fold difference) and in 1% of untreated and 14% of treated persons with CRF01_AG viruses (14-fold difference). Other positions less likely to be mutated in subtype B than in non-B viruses in response to treatment included protease residues 14 (subtype A); 13 and 64 (subtype C); 37 and 65 (subtype F); 71 (subtype G); 62 and 64 (CRF01_AE); and 15 and 71 (CRF02_AG); and RT residues 35 (subtype A); 98 and 106 (subtype C); 35 and 98 (subtype G); and 98 (CRF02_AG).

At other positions, treatment had a larger effect on subtype B viruses than on one or more non-B subtypes. For example, protease position 20 was mutant in 2% of untreated and 24% of treated persons with subtype B viruses (approximately 12-fold increase with treatment) and in 11% of untreated and 42% of treated persons with subtype C viruses (approximately 4-fold increase with treatment). These positions included protease residues 10, 20, and 63 (subtype A); 20, 53, 63, 74, and 82 (subtype C); 13 and 20 (subtype D); 10, 14, 20, and 77 (subtype F); 20, 67, 73, 82, and 88 (subtype G); 20, 63, 82, and 89 (CRF01_AE); and 20 (CRF02_AG); and RT residues 39 and 179 (subtype A); 35, 48, 121, and 166 (subtype C); 39 (subtype D); 39 (subtype F); 39 and 104 (subtype G); 162 and 238 (CRF01_AE); and 39 (CRF02_AG).

These 31 positions with subtype–treatment interactions included 12 known drug-resistance positions. Of these, seven protease (10, 20, 53, 63, 77, 82, and 88) and two RT (179 and 238) resistance positions were more likely to be mutated in subtype B than in one or more non-B subtypes in response to treatment. One protease position (71) and two RT positions (98 and 106) were more likely to be mutated in one or more non-B subtypes.

Known Drug-Resistance Mutations

Figure 6 shows the amino acid substitutions present at drug-resistance positions in protease and RT sequences from untreated and treated persons infected with B and non-B subtypes. Fourteen of the 22 known PI-resistance positions occurred in subtype A, 20 in subtype C, 16 in subtype D, 20 in subtype F, 18 in subtype G, 17 in CRF01_AE, and 17 in CRF02_AG. Thirteen of the 18 known NRTI-resistance positions occurred in subtype A, 18 in subtype C, 13 in subtype D, 15 in subtype F, 18 in subtype G, 18 in CRF01_AE, and 16 in CRF02_AG. Ten of the 15 known NNRTI-resistance positions occurred in subtype A, 15 in subtype C, 11 in subtype D, 13 in subtype F, 14 in subtype G, 13 in CRF01_AE, and 12 in CRF02_AG.

In all, 106 of 113 (94%) different amino acid substitutions at 55 known subtype B drug-resistance positions (22 protease and 33 RT) were also present in at least one non-B subtype. In an exploratory analysis, which was not controlled for multiple comparisons, the frequencies of 24 mutations at 14 protease positions and 32 mutations at 19 RT positions differed between subtype B and one or more non-B subtypes.

Discussion

This collaborative analysis was designed to determine whether and to what degree the genetic mechanisms of HIV drug resistance are shared between subtype B and non-B viruses. Mutations responsible for drug resistance in subtype B viruses have been characterized by three types of studies: (i) those that identify mutations selected in viruses of persons receiving antiretroviral therapy, (ii) those that quantify the effect of specific mutations on in vitro drug susceptibility, and (iii) those that examine the effectiveness of treatment regimens in persons with viruses containing known or suspected drug-resistance mutations. This study, which identifies mutations arising in non-B viruses during antiretroviral therapy, is a necessary step for designing laboratory and clinical studies of potential drug-resistance mutations.

Do the known subtype B drug-resistance mutations also occur in non-B subtypes? We found that each of the 55 known subtype B drug-resistance mutations occurred in at least one non-B isolate. Of these, 44 (80%) were significantly associated with drug therapy in non-B isolates. The remaining 11 mutations were uncommon in subtype B and all non-B subtypes, making it difficult to determine whether they were also significantly associated with therapy. Phenotypic susceptibility testing of non-B viruses with treatment-selected mutations is necessary to confirm and quantify the contribution of these mutations to drug resistance in the genetic context in which they arise.

Do non-subtype B viruses from persons with virologic failure develop novel mutations? Fifteen protease and eight RT positions not generally considered to be drug-resistance positions were significantly associated with treatment in at least one non-B subtype. However, mutations at 17 of these 23 positions were also associated with treatment in subtype B viruses. Therefore, of the 67 mutations associated with

Figure 6. Amino Acid Differences from Consensus B Sequence at Drug-Resistance Positions in Protease and RT according to Subtype

(A) shows data for protease, and (B) shows data for RT. In both, the first line lists the drug-resistance positions. The second line shows single-letter amino acid codes for the consensus B sequence. For each subtype (left column), the percentage of specific mutations in untreated persons is shown above the dashed line, whereas the percentage of specific mutations in treated persons is shown below the dashed line. Positions with significant differences in mutation frequency between B and non-B subtypes ($p < 0.01$, according to χ^2 test with Yate's correction) are circled. A pound sign indicates an insertion.

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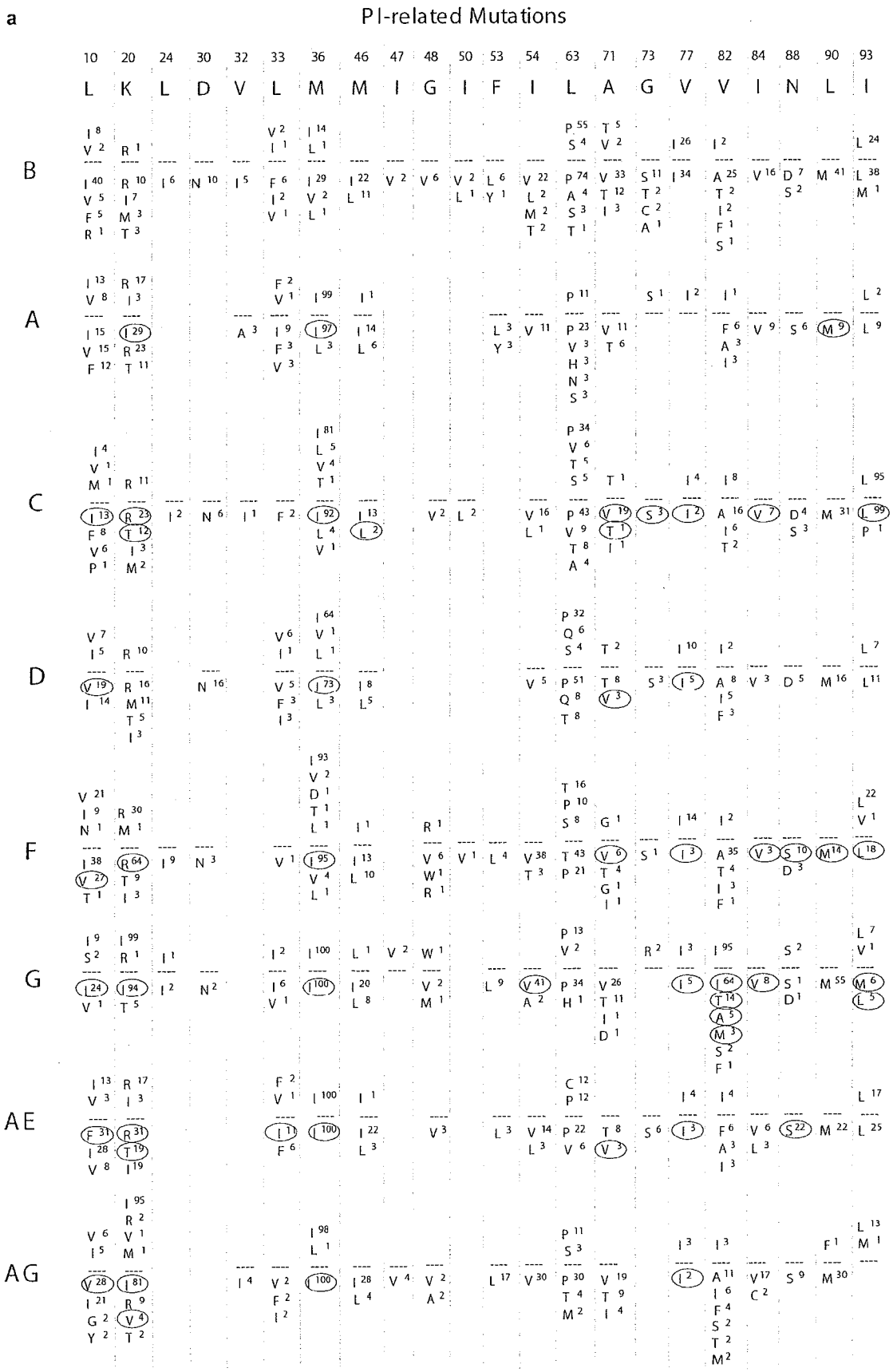
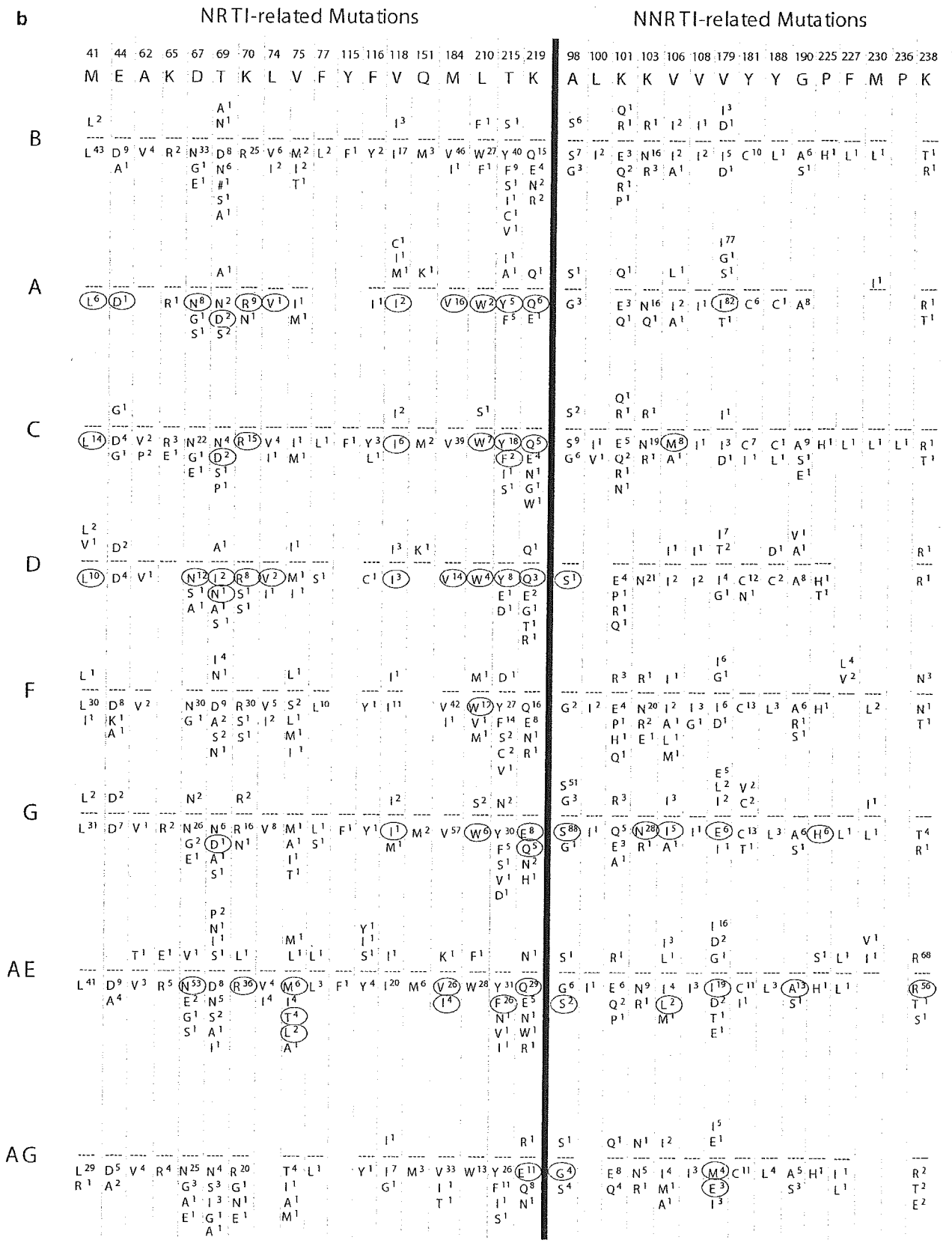

a
PI-related Mutations
10 20 24 30 32 33 36 46 47 48 50 53 54 63 71 73 77 82 84 88 90 93
L K L D V L M M I G I F I L A G V V I N L I
B
A
C
D
F
G
AE
AG


b
NRTI-related Mutations
NNRTI-related Mutations
41 44 62 65 67 69 70 74 75 77 115 116 118 151 184 210 215 219
M E A K D T K L V F Y F V Q M L T K
98 100 101 103 106 108 179 181 188 190 225 227 230 236 238
A L K K V V V Y Y G P F M P K
B
A
C
D
F
G
AE
AG

treatment in at least one non-B subtype, 61 were also associated with treatment in subtype B. For the six mutations associated with therapy in at least one non-B subtype but not in subtype B, the associations were at the borderline of significance and require confirmation.

Among untreated persons, non-B subtype-specific polymorphisms occurred at 37 protease and 41 RT positions. Most of these non-B polymorphic positions are also polymorphic in subtype B viruses, and several act as accessory drug-resistance mutations in subtype B viruses. Phenotypic susceptibility testing of non-B viruses with such polymorphic accessory mutations is needed to confirm that these naturally occurring viruses are fully susceptible to current antiretrovirals—a supposition that appears be true based on the excellent virologic responses of non-B viruses to antiretroviral treatment in observational studies.

We made two simplifications in this study to increase the statistical power of our analyses. These will become unnecessary in future analyses as sufficient numbers of sequences from persons with well characterized treatment histories become available. First, we did not distinguish between different substitutions at the same position; all differences from consensus B were considered mutations. Second, viruses were classified only by the classes of drugs to which they were exposed rather than by individual drugs or drug regimens. Therefore, our analyses could not detect differences between subtype B and other subtypes that depend on specific mutations or specific drugs. Indeed, two such differences have been reported: (i) V106M is the most common substitution at RT position 106 in subtype C viruses whereas V106A predominates in subtype B viruses [33,35,46], and (ii) although the protease mutations D30N and L90M both develop in non-B viruses during nelfinavir therapy, D30N occurs more commonly in subtype B, whereas L90M occurs more commonly in subtypes C, G, and CRF01_AE [17,34,47,48].

Although the clinical samples in this study were originally obtained for a variety of purposes, including clinical management, the sequences of these samples represent experiments of nature that reveal the mutations associated with continued HIV-1 replication in the presence of selective antiretroviral therapy. The accurate identification of treatment-related mutations in such a cross-sectional analysis is challenging, however, because misclassification can result from the transmission of drug-resistant viruses, differences in specific HIV-1 variants among different human populations (population stratification), and the many statistical comparisons required as a result of HIV-1 sequence variability.

The transmission of drug-resistant HIV-1 viruses weakens cross-sectional analyses because some untreated persons may have been infected with viruses already containing treatment-related mutations. To mitigate this effect, we excluded isolates from untreated persons containing two or more non-polymorphic known drug-resistance mutations, because this pattern is not consistent with natural sequence variation. However, as noted in the Methods, an analysis that included these isolates did not alter any of the significant findings in the study. Conversely, the possibility that resistance mutations transmitted between persons in our dataset inflated the amount of resistance among persons receiving treatment was mitigated by excluding any isolate differing from another isolate at less than 1% of its nucleotides.

HIV-1 evolution is driven by genetic drift, immunologic pressure, and selective drug pressure. Population stratification can be a confounding factor when viral lineages with different founder mutations (resulting from drift or immunologic pressure) are exposed to different degrees of antiretroviral selection pressure. To distinguish mutations developing in multiple individuals as a result of selective drug pressure from mutations originating in a fewer number of founder viruses, we reconstructed the ancestral sequences at each node of a phylogenetic tree for each subtype and counted the number of times each mutation was predicted to have developed within that subtype. Because of the limited ability of phylogenetic methods to estimate accurate trees for large numbers of related sequences (i.e., belonging to the same HIV-1 subtype), only those positions for which the majority of mutations (≥75%) appeared to result from new mutations were considered to be selected by antiretroviral therapy.

Because this analysis was, to our knowledge, the first to simultaneously examine all protease and most polymerase-coding RT positions in multiple subtypes, and because multiple associations between mutation and treatment were expected, we used a relatively lenient correction for multiple comparisons in order to minimize the number of missed associations. Nonetheless, of the 67 positive associations detected in this study, 61 were also present in persons with subtype B viruses and have previously been reported [45,49].

In conclusion, most of the protease and RT positions associated with drug resistance in subtype B viruses are selected by antiretroviral therapy in one or more non-B subtypes as well. Conversely, we found no evidence that non-B viruses develop resistance by mutations at positions that are not associated with resistance in subtype B viruses. Based on currently available data, global surveillance efforts and genotypic assessments of drug resistance should focus primarily on the known subtype B drug-resistance mutations.

Supporting Information

Dataset S1. List of GenBank Accession Numbers for Non-Subtype-B Sequences Used in This Study

Found at DOI: 10.1371/journal.pmed.0020112.sd001 (59 KB PDF).

Accession Numbers

The GenBank (http://www.ncbi.nlm.nih.gov/Genbank/) isolates and accession numbers for the reference subtype specimens discussed in this paper are U455/subtype A (M62320), HXB2/subtype B (K03455), C2220/subtype C (U46016), NDK/subtype D (M27323), 93BR020/subtype F (AF005494), SE6165/subtype G (AF061642), 90CR056/subtype H (AF005496), SE9173c/subtype J (AF082394), 97EQTB11C/subtype K (AJ249235), CM240/CRF01_AE (U54771), IbNG/CRF02_AG (L39106), YBF30/Group N (AJ006022), and ANT70C/Group O (L20587). The accession numbers for the non-subtype-B sequences used in this study are listed in Dataset S1.

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Author contributions. R. Kantor, D. A. Katzenstein, B. Efron, J. M. Schapiro, and R. W. Shafer designed the study. R. Kantor, D. A. Katzenstein, B. Efron, A. P. Carvalho, B. Wynhoven, P. Cane, J. Clarke, S. Sirivichayakul, M. A. Soares, J. Snoeck, C. Pillay, H. Rudich, R. Rodrigues, A. Holguin, K. Ariyoshi, M. B. Bouzas, and R. W. Shafer analyzed the data. R Kantor, D. A. Katzenstein, P. Cahn, W. Sugiura, V. Soriano, L. F. Brigido, Z. Grossman, L. Morris, A.-M. Vandamme, A. Tanuri, P. Phanuphak, J. N. Weber, D. Pillay, P. R. Harrigan, R. Camacho, and R. W. Shafer interpreted the data. R. Kantor, D. A. Katzenstein, and R. W. Shafer contributed to writing the paper. ∎

References

1. Gao F, Bailes E, Robertson DL, Chen Y, Rodenburg CM, et al. (1999) Origin of HIV-1 in the chimpanzee *Pan troglodytes troglodytes*. Nature 397: 436–441.
2. Hahn BH, Shaw GM, De Cock KM, Sharp PM (2000) AIDS as a zoonosis: Scientific and public health implications. Science 287: 607–614.
3. Korber B, Muldoon M, Theiler J, Gao F, Gupta R, et al. (2000) Timing the ancestor of the HIV-1 pandemic strains. Science 288: 1789–1796.
4. Robertson DL, Anderson JP, Bradac JA, Carr JK, Foley B, et al. (2000) HIV-1 nomenclature proposal. Science 288: 55–56.
5. Osmanov S, Pattou C, Walker N, Schwardlander B, Esparza J (2002) Estimated global distribution and regional spread of HIV-1 genetic subtypes in the year 2000. J Acquir Immune Defic Syndr 29: 184–190.
6. Gonzales MJ, Machekano RN, Shafer RW (2001) HIV-1 reverse transcriptase and protease subtypes: Classification, amino acid mutation patterns, and prevalence in a Northern California clinic-based population. J Infect Dis 184: 998–1006.
7. Dumans AT, Soares MA, Machado ES, Hue S, Brindeiro RM, et al. (2004) Synonymous genetic polymorphisms within Brazilian human immunodeficiency virus type 1 subtypes may influence mutational routes to drug resistance. J Infect Dis 189: 1232–1238.
8. Gonzalez LM, Brindeiro RM, Aguiar RS, Pereira HS, Abreu CM, et al. (2004) Impact of nelfinavir resistance mutations on in vitro phenotype, fitness, and replication capacity of human immunodeficiency virus type 1 with subtype B and C proteases. Antimicrob Agents Chemother 48: 3552–3555.
9. Shafer RW, Eisen JA, Merigan TC, Katzenstein DA (1997) Sequence and drug susceptibility of subtype C reverse transcriptase from human immunodeficiency virus type 1 seroconverters in Zimbabwe. J Virol 71: 5441–5448.
10. Shafer RW, Chuang TK, Hsu P, White CB, Katzenstein DA (1999) Sequence and drug susceptibility of subtype C protease from human immunodeficiency virus type 1 seroconverters in Zimbabwe. AIDS Res Hum Retroviruses 15: 65–69.
11. Toni T, Masquelier B, Bonard D, Faure M, Huet C, et al. (2002) Primary HIV-1 drug resistance in Abidjan (Cote d'Ivoire): A genotypic and phenotypic study. AIDS 16: 488–491.
12. Palmer S, Margot N, Gilbert H, Shaw N, Buckheit R Jr, et al. (2001) Tenofovir, adefovir, and zidovudine susceptibilities of primary human immunodeficiency virus type 1 isolates with non-B subtypes or nucleoside resistance. AIDS Res Hum Retroviruses 17: 1167–1173.
13. Apetrei C, Descamps D, Collin G, Loussert-Ajaka I, Damond F, et al. (1998) Human immunodeficiency virus type 1 subtype F reverse transcriptase sequence and drug susceptibility. J Virol 72: 3534–3538.
14. Adje C, Cheingsong R, Roels TH, Maurice C, Djomand G, et al. (2001) High prevalence of genotypic and phenotypic HIV-1 drug-resistant strains among patients receiving antiretroviral therapy in Abidjan, Cote d'Ivoire. J Acquir Immune Defic Syndr 26: 501–506.
15. Weidle PJ, Malamba S, Mwebaze R, Sozi C, Rukundo G, et al. (2002) Assessment of a pilot antiretroviral drug therapy programme in Uganda: Patients' response, survival, and drug resistance. Lancet 360: 34–40.
16. Vergne L, Malonga-Mouellet G, Mistoul I, Mavoungou R, Mansaray H, et al. (2002) Resistance to antiretroviral treatment in Gabon: Need for implementation of guidelines on antiretroviral therapy use and HIV-1 drug resistance monitoring in developing countries. J Acquir Immune Defic Syndr 29: 165–168.
17. Cane PA, de Ruiter A, Rice PA, Wiselka M, Fox R, et al. (2001) Resistance-associated mutations in the human immunodeficiency virus type 1 subtype C protease gene from treated and untreated patients in the United Kingdom. J Clin Microbiol 39: 2652–2654.
18. Pillay D, Walker AS, Gibb DM, De Rossi A, Kaye S, et al. (2002) Impact of human immunodeficiency virus type 1 subtypes on virologic response and emergence of drug resistance among children in the Paediatric European Network for Treatment of AIDS (PENTA) 5 trial. J Infect Dis 186: 617–625.
19. Frater AJ, Dunn DT, Beardall A, Ariyoshi K, Clarke JR, et al. (2002) Comparative response of African HIV-1-infected individuals to highly active antiretroviral therapy. AIDS 16: 1139–1146.
20. Grossman Z, Vardinon N, Chemtob D, Alkan ML, Bentwich Z, et al. (2001) Genotypic variation of HIV-1 reverse transcriptase and protease: Comparative analysis of clade C and clade B. AIDS 15: 1453–1460.
21. Kebba A, Atwine D, Mwebaze R, Kityo C, Nakityo R, et al. (2002) Therapeutic responses to AZT + 3TC + EFV in advanced antiretroviral naive HIV type 1-infected Ugandan patients. AIDS Res Hum Retroviruses 18: 1181–1187.
22. Landman R, Schiemann R, Thiam S, Vray M, Canestri A, et al. (2003) Once-a-day highly active antiretroviral therapy in treatment-naive HIV-1-infected adults in Senegal. AIDS 17: 1017–1022.
23. Alexander CS, Montessori V, Wynhoven B, Dong W, Chan K, et al. (2002) Prevalence and response to antiretroviral therapy of non-B subtypes of HIV in antiretroviral-naive individuals in British Columbia. Antivir Ther 7: 31–35.
24. Weidle PJ, Downing R, Sozi C, Mwebaze R, Rukundo G, et al. (2003) Development of phenotypic and genotypic resistance to antiretroviral therapy in the UNAIDS HIV Drug Access Initiative—Uganda. AIDS 17 (Suppl 3): S39–S48.
25. Djomand G, Roels T, Ellerbrock T, Hanson D, Diomande F, et al. (2003) Virologic and immunologic outcomes and programmatic challenges of an antiretroviral treatment pilot project in Abidjan, Cote d'Ivoire. AIDS 17 (Suppl 3): S5–S15.
26. Laurent C, Kouanfack C, Koulla-Shiro S, Nkoue N, Bourgeois A, et al. (2004) Effectiveness and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1-infected adults in Cameroon: Open-label multicentre trial. Lancet 364: 29–34.
27. Palmer S, Alaeus A, Albert J, Cox S (1998) Drug susceptibility of subtypes A, B, C, D, and E human immunodeficiency virus type 1 primary isolates. AIDS Res Hum Retroviruses 14: 157–162.
28. Loemba H, Brenner B, Parniak MA, Ma'ayan S, Spira B, et al. (2002) Genetic divergence of human immunodeficiency virus type 1 Ethiopian clade C reverse transcriptase (RT) and rapid development of resistance against nonnucleoside inhibitors of RT. Antimicrob Agents Chemother 46: 2087–2094.
29. Caride E, Brindeiro R, Hertogs K, Larder B, Dehertogh P, et al. (2000) Drug-resistant reverse transcriptase genotyping and phenotyping of B and non-B subtypes (F and A) of human immunodeficiency virus type 1 found in Brazilian patients failing HAART. Virology 275: 107–115.
30. Caride E, Hertogs K, Larder B, Dehertogh P, Brindeiro R, et al. (2001) Genotypic and phenotypic evidence of different drug-resistance mutation patterns between B and non-B subtype isolates of human immunodeficiency virus type 1 found in Brazilian patients failing HAART. Virus Genes 23: 193–202.
31. Velazquez-Campoy A, Vega S, Freire E (2002) Amplification of the effects of drug resistance mutations by background polymorphisms in HIV-1 protease from African subtypes. Biochemistry 41: 8613–8619.
32. Ariyoshi K, Matsuda M, Miura H, Tateishi S, Yamada K, et al. (2003) Patterns of point mutations associated with antiretroviral drug treatment failure in CRF01_AE (subtype E) infection differ from subtype B infection. J Acquir Immune Defic Syndr 33: 336–342.
33. Brenner B, Turner D, Oliveira M, Moisi D, Detorio M, et al. (2003) A V106M mutation in HIV-1 clade C viruses exposed to efavirenz confers cross-resistance to non-nucleoside reverse transcriptase inhibitors. AIDS 17: F1–F5.
34. Grossman Z, Paxinos EE, Averbuch D, Maayan S, Parkin NT, et al. (2004) Mutation D30N is not preferentially selected by human immunodeficiency virus type 1 subtype C in the development of resistance to nelfinavir. Antimicrob Agents Chemother 48: 2159–2165.
35. Grossman Z, Istomin V, Averbuch D, Lorber M, Risenberg K, et al. (2004) Genetic variation at NNRTI resistance-associated positions in patients infected with HIV-1 subtype C. AIDS 18: 909–915.
36. Lole KS, Bollinger RC, Paranjape RS, Gadkari D, Kulkarni SS, et al. (1999) Full-length human immunodeficiency virus type 1 genomes from subtype C-infected seroconverters in India, with evidence of intersubtype recombination. J Virol 73: 152–160.
37. Shafer RW, Jung DR, Betts BJ (2000) Human immunodeficiency virus type 1 reverse transcriptase and protease mutation search engine for queries. Nat Med 6: 1290–1292.
38. D'Aquila RT, Schapiro JM, Brun-Vezinet F, Clotet B, Conway B, et al. (2003) Drug resistance mutations in HIV-1. Top HIV Med 11: 92–96.
39. Rhee SY, Gonzales MJ, Kantor R, Betts BJ, Ravela J, et al. (2003) Human immunodeficiency virus reverse transcriptase and protease sequence database. Nucleic Acids Res 31: 298–303.
40. Hue S, Clewley JP, Cane PA, Pillay D (2004) HIV-1 pol gene variation is sufficient for reconstruction of transmissions in the era of antiretroviral therapy. AIDS 18: 719–728.
41. Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B 57: 289–300.
42. Lan NT, Recordon-Pinson P, Hung PV, Uyen NT, Lien TT, et al. (2003) HIV type 1 isolates from 200 untreated individuals in Ho Chi Minh City (Vietnam): ANRS 1257 study. Large predominance of CRF01_AE and presence of major resistance mutations to antiretroviral drugs. AIDS Res Hum Retroviruses 19: 925–928.
43. Tovanabutra S, Beyrer C, Sakkhachornphop S, Razak MH, Ramos GL, et al.

(2004) The changing molecular epidemiology of HIV type 1 among northern Thai drug users, 1999 to 2002. AIDS Res Hum Retroviruses 20: 465–475.
44. Rose PP, Korber BT (2000) Detecting hypermutations in viral sequences with an emphasis on G –> A hypermutation. Bioinformatics 16: 400–401.
45. Wu TD, Schiffer CA, Gonzales MJ, Taylor J, Kantor R, et al. (2003) Mutation patterns and structural correlates in human immunodeficiency virus type 1 protease following different protease inhibitor treatments. J Virol 77: 4836–4847.
46. Morris L, Pillay C, Chezzi C, Lupondwana P, Ntsala M, et al. (2003) Low frequency of the V106M mutation among HIV-1 subtype C-infected pregnant women exposed to nevirapine. AIDS 17: 1698–1700.
47. Gomes P, Diogo I, Goncalves MF, Carvalho P, Cabanas J, et al. (2002) Different pathways to nelfinavir genotypic resistance in HIV-1 subtypes B and G [abstract]. Ninth Conference on Retroviruses and Opportunistic Infections; 2002 February 24–28; Seattle, Washington. Abstract number 46. Available: http://www.retroconference.org//2002/Abstract/12937.htm. Accessed 14 March 2005.
48. Sugiura W, Matsuda Z, Yokomaku Y, Hertogs K, Larder B, et al. (2002) Interference between D30N and L90M in selection and development of protease inhibitor-resistant human immunodeficiency virus type 1. Antimicrob Agents Chemother 46: 708–715.
49. Gonzales MJ, Wu TD, Taylor J, Belitskaya I, Kantor R, et al. (2003) Extended spectrum of HIV-1 reverse transcriptase mutations in patients receiving multiple nucleoside analog inhibitors. AIDS 17: 791–799.

Patient Summary

Background There are many different subtypes of HIV-1. The most common one in more developed countries is subtype B and that is the one which has been studied most and used in drug development. However, worldwide, other subtypes are more frequent. All HIV-1 subtypes acquire mutations, and some of these cause resistance to the drugs used to treat HIV. It is not clear whether the same mutations that cause drug resistance to subtype B virus are also important in causing resistance to non-subtype-B viruses.

What Did the Researchers Do? They compared the viral sequences of 3,686 people with non-subtype-B HIV, and 4,769 with subtype B virus, all with known treatment histories. They found that the mutations known to cause drug resistance in subtype B virus also occur in non-subtype B, and the majority of mutations in non-subtype B also occur in subtype B.

What Do These Findings Mean? It seems that largely the same mutations occur in both subtype B and non-subtype-B viruses. However, some mutations were only present in low numbers, so more work will need to be done before their role is clear. Also, the authors did not look at mutations and their relation to each different drug a patient had—only the general type of drug. Nor did they look at what happens when different mutations occur at one place in a virus. However, for now the current strategy of focusing on assessing the mutations seen in subtype B virus seems a reasonable approach to take when assessing surveillance of drug resistance while more work is done to follow up these findings.

Where Can I Get More Information? TheBody.com has a section on drug resistance: http://www.thebody.com/treat/resistance.html. The Aidsmap Web site has many patient information sheets, including on resistance: http://www.aidsmap.com