HIV-1 might retard HIV-1 infection of $CD4^+$ T lymphocytes, delaying or preventing subsequent formation of a lymphocytic HIV-1 reservoir.

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Nucleotide and Amino Acid Polymorphisms at Drug Resistance Sites in Non-B-Subtype Variants of Human Immunodeficiency Virus Type 1

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We have compared nucleotide substitutions and polymorphisms at codons known to confer drug resistance in subtype B strains of human immunodeficiency virus type 1 (HIV-1) with similar substitutions in viruses of other subtypes. Genotypic analysis was performed on viruses from untreated individuals. Nucleotide and amino acid diversity at resistance sites was compared with a consensus subtype B reference virus. Among patients with non-subtype B infections, polymorphisms relative to subtype B were observed at codon 10 in protease (PR). These included silent substitutions (CTC→CTT, CTA, TTA) and an amino acid mutation, L10I. Subtype A viruses possessed a V179I substitution in reverse transcriptase (RT). Subtype G viruses were identified by silent substitutions at codon 181 in RT (TAT→TAC). Similarly, subtype A/G viruses were identified by a substitution at position 67 in RT (GAC→GAT). Subtype C was distinguished by silent substitutions at codons 106 (GTA→GTG) and 219 (AAA→AAG) in RT and codon 48 (GGG→GGA) in PR. Variations relative to subtype B were seen at RT position 215 (ACC→ACT) for subtypes A and A/E. These substitutions and polymorphisms reflect different patterns of codon usage among viruses of different subtypes. However, the existence of different subtypes may only rarely affect patterns of drug resistance-associated mutations.

The advent of highly active antiretroviral therapy (HAART) has helped to stabilize the progression of human immunodeficiency virus type 1 (HIV-1) disease in Western countries (19). However, most current knowledge of HIV pathogenesis and responsiveness to antiretroviral therapy is based on work carried out with subtype B viruses, while relatively little information is available with regard to other viral subtypes (13). At the same time, global rates of infection attributable to viruses of other subtypes (A to K) are rapidly increasing (3, 6, 23; K. Fransen, A. Buve, J. N. Nkengasong, M. Laga, and G. van der Groen, Letter, Lancet 347:1403, 1996). There is also evidence for the increased prevalence of non-subtype B infections in Western countries as well as infections caused by recombinant viruses involving subtype B and other viruses (18).

Drug resistance testing has assumed an important role in HIV therapeutics, yet little information is available with regard to the potential effect of subtype diversity on both drug resistance and responsiveness to antiviral therapy (13).

Our goal was to analyze genomic diversity at a number of sites known to be associated with resistance to each of the three major families of antiretroviral drugs (ARVs), i.e., nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). This analysis involved a comparison of known mutational sites among subtype B viruses with the same loci in other viral subtypes. The results illustrate the likelihood that the development of drug resistance among various HIV-1 subtypes may involve different amino acid substitutions and that certain of these changes may result in a variety of phenotypes with regard to the ability of such mutations to confer resistance against individual drugs. This subject is likely to gain in importance as more is learned about HIV genomic diversity at resistance-conferring genomic sites among various subtypes of HIV-1.

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MATERIALS AND METHODS

Patients. The clinical isolates employed in this study included plasma samples from ARV-naive patients provided to our laboratory from sites in Botswana, Kenya, Cote d'Ivoire, Japan, Canada, and Israel (in the final case, the samples evaluated were from patients who had emigrated from Ethiopia). In all instances, samples were obtained with informed consent.

To assist in our analysis of viruses of subtypes A/E, D, G, and A/G, we also studied sequences derived from viruses of untreated patients that are available through the Los Alamos database (http://hiv-web.lanl.gov). We searched only for those mutations relevant to *gag-pol* from among non-subtype B viruses derived from untreated patients. However, some sequences could not be analyzed due to problems of alignment and were excluded. We also analyzed plasma subtype B viral isolates from 50 drug-naive individuals monitored in our clinics. To limit the effect of transmission of drug resistance mutations from treated patients, the presence of more than one major drug resistance-associated mutation in the absence of treatment represented an exclusion criterion. As a result, 12 patients were excluded from the control group. Among them, seven harbored NNRTI-associated mutations, nine harbored thymidine analogue mutations, four possessed the mutation M184V, and six harbored PI-associated mutations. Among the nonexcluded patients, one harbored an L33I mutation, two possessed an A71T mutation, and four harbored an A71V mutation.

Sequencing of the RT and PR genes. To sequence the RT and PR genes, RNA was extracted from plasma viruses using the QIAamp kit and RNA products were amplified by PCR. The sequencing of DNA products was carried out using kits (TruGene) obtained from Bayer Diagnostics Inc. (Toronto, Canada) as described in detail elsewhere (21). Sequencing of both the RT and PR genes also enabled us to determine the subtypes of viral isolates in concert with the Stanford database (http://hivdb.stanford.edu/). Nucleotide and amino acid genomic diversity at resistance sites in the various viral isolates was compared with a consensus subtype B reference virus (http://hiv-web.lanl.gov). The list of resistance sites that were analyzed is as follows: NRTIs: 41, 44, 62, 63, 65, 67, 69, 70, 74, 75, 77, 115, 116, 118, 151, 210, 215, and 219; NNRTIs: 100, 101, 103, 106, 108, 179, 181, 188, 190, 225, 230, and 236; PIs: 10, 20, 24, 30, 32, 33, 36, 46, 47, 48, 53, 54, 71, 73, 77, 82, 84, 88, 89, and 90.

Sequence data. GenBank accession numbers for subtype A/E isolates from Japan are AY211945 to AY211947. Accession numbers for subtype C viruses from Botswana are AF492600 to AF4926004. Accession numbers for subtype C viruses from Ethiopia are AF492618 to AF492622.

GenBank accession numbers from Los Alamos database. (i) Subtype AE. GenBank accession numbers for subtype AE were as follows: AB070352, AB097872, AF164485, AF170545, AF170548, AF170549, AF197339, AF197340, AF259954, AF259955, AY008714, AY125894, U51188, U51189 U54771, and AF197338.

(ii) Subtype D. GenBank accession numbers for subtype D were as follows: AJ320484, K03454, M22639, M27323, U88824, U88822, AJ519489, AJ519488, AJ488926, and AJ488927.

(iii) Subtype G. GenBank accession numbers for subtype G were as follows: AF061642, AF423760, AF450098, and U88826.

(iv) Subtype AG. GenBank accession numbers for subtype AG were as follows: AB049811, AB052867, AF063223, AF063224, AF184155, AJ251056, L39106, and AY271690.

Statistical analysis. Fisher's exact test was employed to compare rates of mutational prevalence among the different subtypes.

RESULTS

Analysis of mutational variations among different viral subtypes from different countries. We analyzed 105 HIV-1 sequences of non-subtype B origin from a variety of countries; of these sequences, 38 are present in the Los Alamos database. The distribution of the different subtypes and circulating recombinant forms of these viruses was as follows: subtype A (n = 20) (Canada, Kenya, and Cote d'Ivoire), A/E recombinant viruses (n = 20) (Canada, Japan, Thailand, China, and Central African Republic), subtype C (n = 32) (Canada, Kenya, Botswana, and Ethiopia), subtype D (n = 12) (Canada, Chad, Kenya, and Japan), subtype G (n = 7) (Canada, Sweden, Nigeria, and Spain), and A/G recombinant viruses (n = 14) (Canada, Cameroon, Cote d'Ivoire, Ghana, Senegal, Nigeria, and France).

Prevalence of substitutions and mutations at resistance sites in nontreated patients. This work focused on differences in baseline nucleic acid sequences and amino acids between subtype B isolates and viral isolates from patients infected with viruses of non-B subtypes. The distribution of changes relative to subtype B at resistance sites is shown in Table 1. However, it is important to realize that the substitutions that were commonly observed among non-B subtypes were also present in a reduced proportion of subtype B viruses; this information is also shown in Table 1.

Indeed, only eight polymorphisms with the potential to yield changes in amino acid (Table 1) were seen in non-subtype B viruses relative to subtype B, and only three of these, i.e., V179I in RT and K20I and V82I in PR, yielded a different amino acid in a significant number of cases. Moreover, these eight polymorphisms tended to be restricted to only one or two viral subtypes. This indicates that even at most positions considered in Table 1, polymorphisms unique to non-B viruses that affect the structure of the target enzymes through amino acid differences are rare.

NRTIs. At position D67, a GAT codon was found to encode D in 78% of subtype A/G viruses, whereas GAC was predominant in the other subtypes. Although K70 is encoded by AAA in almost all subtype B isolates (i.e., >92%), a different codon is generally responsible for encoding K in subtype C and D viruses (>80% express AAG). Also, at codon K219, AAA in subtype B is replaced by AAG in 81% of subtype C viruses. Similarly, ACC is the codon that results in T215 in 86% of subtype B viruses, whereas ACT encodes T215 in 75% of subtype A and all recombinant A/E viruses.

NNRTIs. V106 is encoded by GTG in 97% of subtype C and 42% of subtype D viruses. All of these subtype D viruses originated from Chad (Table 2). Three patterns were observed with regard to position V179, with GTG shown to encode this amino acid in >70% of subtype A/G and G viruses and 4% of subtype B viruses. GTC was identified in 89% of subtype C patients from Botswana but in only 41% of all subtype C samples and in only two samples from subtype B patients (Table 2). V179I has specificity for group A and is present in 75% of these samples. A TAC codon that encodes Y (Y181) was observed in all G patients and in 78% of these with A/G recombinants. In contrast, the codon responsible for Y181 in almost all B, C, and A/E viruses was TAT. A silent nucleotide substitution at position P225 (CCT→CCC) was found in 66% of subtype C viruses and in 20% of subtype B viruses. F227 is encoded by TTT in 67% of non-B subtypes and in only 18% of subtype B viruses.

PR. At position L10, a CTC codon was found to encode L in >80% of subtype B viruses, whereas CTT was predominant in non-B subtypes. Similarly, AAA was found to encode K20 in 44% of non-B subtypes while AAG predominated in the case of subtype B. However, among subtype G and A/G viruses, the polymorphism K20I was predominant. At position M36, most non-B subtypes possessed an I36 polymorphism. A nucleotide substitution at position 48 (GGG→GGA) was present in 84% of subtype C viruses and was present in 12% of subtype B viruses. Among subtype C viruses, a dichotomy was observed between viruses of Ethiopian versus non-Ethiopian origin, with ATT being present at position 54 in almost 100% of the former isolates but in relatively few of the latter, in which ATC was predominant (Table 2). Since both ATC and ATT encode I, the significance of this polymorphism is not apparent, although it may suggest a common ancestral variant for Ethiopian isolates, perhaps related to a founder effect. A V82I polymorphism was observed in 86% of subtype G viruses.

Genetic barrier for resistance. To ascertain whether different coding sequences in non-subtype B viruses could influence the genetic barrier for resistance to certain drugs, we analyzed the numbers of nucleotide transitions or transversions needed to obtain a known resistance mutation in viruses of different subtypes (Table 3). In subtype C, the V106M mutation in RT that confers resistance to efavirenz (EFV), nevirapine (NVP), and delevaridine (DLV) is facilitated by a single transition (GTG→ATG), compared to two transitions needed in viruses of other subtypes (GTA→ATG) (transitions are underlined). Two transitions are needed in subtype G viruses to obtain the secondary NNRTI resistance mutation, V108I, compared to only one transition in other subtypes. In subtypes G and AG, a

TABLE 1. Prevalence of nucleotide changes observed between subtype B and other subtypes in nontreated patients

Codon	Subtype B reference sequence	Amino acid	Nucleotide substitution in non-B viruses	Amino acid[a]	Prevalence of nucleotide substitutions (%) in viral subtype[b]:						
					B (n = 50)	A (n = 20)	A/E (n = 20)	C (n = 32)	D (n = 12)	G (n = 7)	A/G (n = 14)
NRTI related											
62	GCC	A	GCT	A	24	20	80**	13	33		
65	AAA	K	AAG	K	4			47**			
67	GAC	D	GAT	D	6					14	78**
69	ACT	T	ACC	T	8		70**		17		
70	AAA	K	AAG	K	12			81**	92**		
74	TTA	L	TTG	L	0					57**	
77	TTC	F	TTT	F	10				33		
115	TAT	Y	TAC	Y	4					42*	
116	TTT	F	TTC	F	4				8		
118	GTT	V	ATA	I	0				8	28	
151	CAG	Q	CAA	Q	24				50		
210	TTG	L	CTG	L	0					14	
210	TTG	L	TTA	L	22				8	28	
215	ACC	T	ACT	T	14	75**	100**				7
219	AAA	K	AAG	K	2			81**			
NNRTI related											
98	GCA	A	GCG	A	0	60**	5	6		42*	43**
98	GCG	A	TCG	S	0					28	
98	GCA	A	TCA	S	26			9			
100	TTA	L	CTA	L	2	55**	25*	3	42*	42*	
100	TTA	L	CTG	L	0				50**		
106	GTA	V	GTG	V	0			97**	42**		
108	GTA	V	GTG	V	2		5			42*	
179	GTT	V	GTC	V	14			41*			
179	GTT	V	GTG	V	4					71*	78**
179	GTT	V	ATT	I	2	75*	15				
181	TAT	Y	TAC	Y	4	5		3		100**	78**
225	CCT	P	CCC	P	20	5		66	25		7
227	TTC	F	TTT	F	18	55*	10	100**	100**	14	93**
PI related											
10	CTC	L	CTT	L	6	70**	65**	97**	66**		14
10	CTC	L	CTA	L	4					71*	7
10	CTC	L	TTA	L	2						64**
10	CTC	L	ATT/A	I	10	5	20			28	
20	AAG	K	AAA	K	2	75**	80**	25	50**	14	
20	AAG	K	ATA	I	0					86**	100**
20	AAG	K	AGA/AGG	R	0	5	5	19			
48	GGG	G	GGA	G	14			84**			7
54	ATC	I	ATT	I	4	5		25			7
71	GCT	A	GCC	A	4						64**
73	GGT	G	GGG	G	0					28	
82	GTC	V	ATC	I	0	5		3		86**	7
88	AAT	N	AAC	N	8	40*	5	9			
90	TTG	L	TTA/CTG	L	4		15				7

[a] Letters in boldface type refer to amino acid changes. Los Alamos database data include information derived from 16, 10, 4, and 8 patients with subtype A/E, D, G, and A/G infections, respectively.
[b] Symbols for statistical significance: *, $P < 0.05$; **, $P < 0.01$.

single transversion can result in a V179E mutation (GTG→GAG) compared to two transversions in viruses of other subtypes (GTT→GAG or GAA). In contrast, viruses of subtype A that possess a V179I polymorphism require both a transition and transversion to yield the V179D resistance mutation (ATT→GAT), compared to only a single transversion in subtype B viruses (GTT→GAT). In PR, the V82S/T resistance mutations may be facilitated by a V82I polymorphism in subtype G viruses compared to viruses of subtype B. In contrast, V82A may be facilitated in subtype B. The prevalence of differences at position 210 in RT and that at positions 73 and 90 in PR were too low for analysis.

At other positions, at which nucleotide substitutions occurred with high prevalence, no differences were observed between subtype B and other viruses with regard to the number of transitions or transversions needed to generate a specific resistance-associated mutation.

As shown in Table 1, the changes at positions 74, 98, 100, and 106 in RT and 20 and 82 in PR were prevalent in non-B subtypes relative to subtype B. Among these substitutions, only those at positions 74 and 106 in RT and 82 in PR are located in proximity to the active sites of these enzymes (http://hiv-web.lanl.gov).

DISCUSSION

HIV-1 group M subtype nucleotide diversity in the Env protein can range between 20 and 30%. With regard to Gag,

TABLE 2. Substitutions in subtype C and D viruses relative to subtype B based on country of origin

Subtype	Origin	No. of patients with indicated nucleotide substitution				
		PR	RT			
		I54I (ATC→ATT)	A62A (GCC→GCT)	F77F (TTC→TTT)	V106V (GTA→GTG)	V179V (GTT→GTC)
C	Botswana (n = 9)	0	0	0	6	8
C	Ethiopia (n = 6)	6	0	0	6	0
C	Other[a] (n = 17)	2	0	0	1	5
D	Chad (n = 4)	0	4	4	4	0
D	Other[b] (n = 8)	0	1	0	1	0

[a] Viruses of subtype C origin from countries other than Botswana or Ethiopia.
[b] Viruses of subtype D origin from sources other than Chad.

variability ranges between 10 and 15% (4) and divergence at the *pol* gene is ~10%. Our group has previously characterized subtype variation at known resistance sites with regard to subtype B and C viruses (16). In the latter study, we analyzed nucleotide substitutions and amino acid diversity at codons known to confer resistance in each of the PR and RT regions, while other studies had only analyzed amino acid variability in this context (12, 14).

Non-B subtypes were defined as a group as having a polymorphism at codon 10 in PR, an M36I substitution in PR, and a polymorphism at codon 227 in RT. Subtype A was identified by a V179I polymorphism in RT. Subtype G and A/G viruses were identified by a silent substitution at codon 181 in RT. Similarly, subtype A/G viruses were identified by a substitution at position 67 in RT. Subtype C was distinguished by silent substitution at codons 106 and 219 in the RT region and codon 48 in PR. Interestingly, two subgroups were recognized within subtype C. The first included viruses from patients of Ethiopian origin with a specific nucleotide substitution at codon 54 in the PR region. The other subgroup included patients from Botswana with a specific nucleotide substitution at codon 179 in RT that is different from previously identified changes at this codon. In addition, three subtype C viruses from Kenyan patients did not harbor these two nucleotide substitutions. Polymorphisms that were specific to a geographic region were also observed in subtype D viruses from Chad, which contained substitutions at positions 62, 77, and 106 (similar to subtype C viruses) in RT. This suggests the possibility of different ancestral variants for viruses of each subgroup.

We previously described a V106M mutation in samples from three patients infected with a subtype C virus who had failed therapy with EFV (5), and others have now shown that this mutation is also seen in subtype C viruses derived from patients who failed therapy with NVP (17). V106M has also been selected in vitro by EFV in subtype C viruses and confers high-level cross-resistance to all three currently approved NNRTIs (5). The selection of this mutation in subtype C viruses results from a single nucleotide change from wild-type in subtype C viruses (*G*TG→*A*TG). In addition, a G→A nucleotide transition is facilitated in this circumstance.

Interestingly variability in codon usage at position V106 between subtype B (GTA) and subtype C (GTG) occurs at the third position in the triplet; third positions rarely have an impact on mutagenesis. The importance of the V106M substitution with regard to subtype C viruses has been confirmed by other groups that also rarely reported the presence of this mutation in subtypes other than C (Z. Grossman, V. Istomin, D. Averbuck, I. Levy, K. Risenberg, M. Chowers, E. Shahar, M. Lorber, E. Mendelson, D. Ram, Z. Kra-Oz, M. Burk, Z. Bentwich, S, Maayan, and J. M. Shapiro, Abstr. 10th Conf. Retroviruses Opportun. Infect., abstr. 624, 2003). As a result, V106M is now reported as an NNRTI resistance-conferring mutation in most algorithms to complement V106A, which is associated with resistance to NVP. Interestingly, variants at position 103 other than K103N (K103S/H/T) may also confer reduced susceptibility to NNRTIs [P. R. Harrigan, B. Wynhoven, J. Montaner, P. McKenna, and L. Bacheler, abstract

TABLE 3. Codons at which differences exist between subtype B and non-B viruses

Region	Amino acid position	Wild-type codon in subtype B[a]	Amino acid	Subtype(s)	Wild-type codon in non-subtype B	Amino acid[b]	Mutated codon[c]	Resistant amino acid	Drugs affected[d]
RT	106	GTA	V	C	GTG	V	ATG[e]	M	EFV, NVP, DLV
	108	GTA	V	G	GTG	V	ATA	I	EFV, NVP
	179	GTT	V	G, A/G	GTG	V	GAG or GAA	E	EFV, NVP, DLV
	179	GTT	V	A	ATT	I	GAT or GAC	D	EFV, DLV
PR	20	AAG	K	A, A/E	AAA	K	ATG	M	IDV, RTV, LPV, ATZ, TPV
	82	GTC	V	G	ATC	I	GCC	A	Multi-PI
	82	GTC	V	G	ATC	I	TCC or AGC	S	Multi-PI
	82	GTC	V	G	ATC	I	ACC	T	Multi-PI

[a] The underlined nucleotides represent transitions or transversions from wild type to nucleotides that code for a resistance-associated amino acid.
[b] Presumed polymorphism.
[c] Nucleotides that encode resistance-associated amino acids.
[d] Abbreviations: DLV, delevaridine; IDV, indinavir; RTV, ritonavir; LPV, lopinavir; ATZ, atazanavir; TPV, tipranavir.
[e] Differences in numbers of nucleotide changes needed to mutate a particular drug resistance-associated amino acid. Only frequently observed mutations are shown.

from the XII International HIV Drug Resistance Workshop 2003, Antivir. Ther. 8(Suppl. 1):S120, 2003].

The present study also suggests several other possible differences between viral subtypes with regard to nucleotide transitions and transversions at known drug resistance sites. A good example is the NNRTI mutation V179D/E, which may be differentially selected in subtypes G, A/G, and A compared to B. In contrast to V106M, however, 179D/E confers only low-level resistance to NNRTIs. The secondary NNRTI mutation, V108I, may be facilitated in subtype B viruses compared to subtype G. In PR, V82A/S/T may be differentially selected compared to subtype B, because of a V82I polymorphism in the former.

Among polymorphisms unique to non-B subtypes, there are only a limited number of codon positions that might affect enzyme structure. For example, position 82 in PR is in close proximity to the active-site Asp 25 in the normally folded PR, and mutations in this region might compromise substrate-enzyme contact sites (24). In contrast, position 20 in PR is located outside the active site. In RT, positions 74 and 106 are close to the active site but positions 98 and 100 are not (http://hiv-web.lanl.gov). Thus, the opportunity for significant differences among viral subtypes with regard to resistance appears to be limited.

In general the effect of subtype diversity on virological response to therapy, as well as the development of both phenotypic resistance and resistance-conferring mutations, is still a topic of conjecture (11). Other groups have shown differences in resistance profiles among subtypes. Among nelfinavir-treated patients, D30N substitutions are apparently present less frequently in non-subtype B viruses than in subtype B [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 XI International HIV Drug Resistance Workshop 2002, Antivir. Ther. 7(Suppl. 1):S30, 2002]. In addition, a specific mutation at position 88 in A/E circulating recombinant forms has been reported in nelfinavir-treated persons [K. Ariyoshi, M. Matsuda, H. Miura, K. Yamada, N. S. Hellmann, and W. Sugiura, abstract from the XI International HIV Drug Resistance Workshop 2002, Antivir. Ther. 7(Suppl. 1):S150, 2002]. In vitro studies that characterized the enzymatic activity of PR enzymes containing different PI polymorphisms commonly seen in subtypes A and C suggest that the latter may amplify the effect of drug resistance mutations (25). Specific subtype C and intra-C subtype resistance mutations and polymorphisms have also been reported (14, 22), and 55% of group O viruses have a naturally occurring resistance mutation with regard to NNRTIs, i.e., Y181C (7).

Analysis of a large database that included 1,240 non-B-infected persons revealed that virtually all drug resistance mutations known to occur in subtype B can also be found in non-B isolates. However, differences among non-B subtypes were present in untreated individuals, and these included characteristic polymorphisms [R. Kantor, D. Katzenstein, M Gonzales, S. Sirivichayakul, P. Cane, C. Pillay, J. Snoeck, Z. Grossman, A. M. Vandamne, L. Morris, D. Pillay, P. Phanuphak, J. M. Schapiro, and R. W. Shafer, abstract from the XI International HIV Drug Resistance Workshop 2002, Antivir. Ther. 7(Suppl. 1):S142, 2002]. Another study found characteristic minor mutations within the PR region of non-subtype B viruses as well as polymorphisms but no major mutation in either RT or PR (9). A further report from South Africa reported no differences in resistance profiles between subtype B and C viruses (C. Pillay, M. Ntsala, R. Kantor, C. Chezzi, F. Venter, L. Levin, and L. Morris, Abstr. 2nd IAS Conf. HIV Pathog. Treatment, abstr. 775, 2003). Furthermore, several studies of non-B-infected patients have not revealed any association between HIV subtype, adherence to therapy, and virologic response to treatment and disease progression (1, 2, 8, 10, 15, 20; S. De Wit, R. Boulme, B. Poll, J. C. Schmit, and N. Clumeck, Abstr. 2nd IAS Conf. HIV Pathog. Treatment, abstr. 25, 2003). A recent study from Cote d'Ivoire examined 276 patients receiving HAART and found that 50% achieved a viral load of <200 copies/ml, a result similar to that observed in Western countries (15). Among 79 drug-naive African patients who received HAART, 60 had undetectable viral loads after 1 year (10). Another study evaluated ARV therapy in 113 children and did not show evidence of differential in virologic response among viruses of different subtypes (20).

In summary, our analysis of nucleotide substitutions in viruses of various subtypes reveals only limited possibilities for differences with regard to patterns of resistance mutations in comparison to subtype B. This fact as well as the clinical data cited above should be reassuring with regard to the management of HIV disease in populations well represented in non-B subtypes. This is important in the context of efforts to provide ARVs to people in need of treatment in developing countries, while not obviating the need to monitor the emergence of drug resistance-associated mutations in such settings.

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