Mechanisms of Disease

Development of Antiretroviral Drug Resistance

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Combinations of antiretroviral drugs are efficacious in the treatment of human immunodeficiency virus (HIV) infection, regardless of the viral subtype. However, the level of resistance to antiretroviral drugs differs among HIV variants. Indeed, we have limited knowledge of resistance mutations in non-B subtypes of HIV type 1 (HIV-1) and their clinical relevance, despite the fact that more than 90% of patients with HIV-1 infection worldwide have non-subtype B variants of HIV-1. Most reports on drug resistance deal with subtype B infections in developed countries. Both enzymatic and virologic data indicate that naturally occurring polymorphisms among different HIV subtypes can influence HIV-1 susceptibility to individual antiretroviral drugs and the propensity of HIV to acquire certain resistance mutations. Furthermore, resistance pathways in different subtypes may affect drug cross-resistance and the potential use of specific second-line regimens. This concern may be increased in developing countries.

Substantial natural genetic variation has led to the subclassification of HIV-1 group M (major) into nine subtypes (A through D, F through H, and J and K) and numerous circulating recombinant forms (CRFs), such as CRF01_AE and CRF02_AG.1–3 Although subtype B is most prevalent in Western countries, non-B subtypes predominate elsewhere (e.g., subtype C in sub-Saharan Africa, India, and parts of Brazil; subtype CRF01_AE in Southeast Asia; subtype CRF02_AG in West Africa; and subtype A in eastern Europe and northern Asia.1,4,5 Because of immigration, the proportion of non-B subtypes in North and South America and western Europe is increasing.6–9

Despite advances in antiretroviral therapy that have revolutionized HIV management and the control of the spread of regional epidemics,10–12 resistance to antiretroviral drugs has emerged in all locales in which such drugs are used. This topic has been less well studied in subtypes other than subtype B, because of the predominance of the latter in the wealthy countries in which antiretroviral drugs were first introduced, as well as the availability of genotypic and phenotypic testing for resistance to antiretroviral drugs in such locations.13 However, the potential for genetic differences among subtypes to yield different patterns of resistance-conferring mutations is supported by natural variation among HIV subtypes in genetic content—for example, 40% variation in the viral envelope (env) gene and 8 to 10% variation in the polymerase (pol) and group-specific-antigen (gag) genes. This issue acquires special relevance in view of the fact that the HIV pol gene encodes each of the reverse-transcriptase, protease, and integrase enzymes that are the major targets of antiretroviral therapy. The distribution of HIV subtypes among immigrants to Quebec from African countries at the epicenter of the HIV pandemic illustrates intersubtype and intrasubtype diversity in the reverse-transcriptase–protease region.14
The global expansion and diversification of the pandemic reveal major epidemics of subtypes C (48%), A and CRF01_AE (12% and 5%, respectively), and G and CRF02_AG (8% and 5%, respectively) (Fig. 1B).

Differences in codon sequences at positions associated with drug-resistance mutations might predispose viral isolates of different subtypes to encode different amino acid substitutions, which might affect the rate of emergence of resistance (Table 1). Such diversity might also affect cross-resistance to antiretroviral drugs within the same class, potentially affecting antiviral responsiveness and clinical outcomes (see the interactive graphic, available with the full text of this article at NEJM.org).

Biochemical and virologic data indicate that natural variation in amino acids can affect the magnitude of resistance conferred by certain resistance mutations. For example, the related HIV type 2 (HIV-2) virus and group O HIV-1 viruses show high-level innate resistance to some nonnucleoside reverse-transcriptase inhibitors (NNRTIs) as a result of mutations in a reverse transcriptase that are present as natural polymorphisms (Table 1). In addition, subtype differences in nucleotide and mutational motifs, which are defined as the number of transitions or transversions needed to develop resistance to different classes of antiretroviral drugs, may affect the genetic barrier for resistance. For example, the signature codon 106 polymorphism that is unique to subtype C facilitates the development of the V106M mutation.

**NUCLEOSIDE REVERSE-TRANSCRIPTASE INHIBITORS**

Patients with subtype C HIV infection who were treated with a combination of nucleoside reverse-transcriptase inhibitors (NRTIs) zidovudine and didanosine in Botswana were found to have a thymidine analogue mutations (TAM) pathway (67N/70R/215Y) that was not commonly seen in patients with subtype C in India, South Africa, or Malawi. Of concern, patients in areas in which subtype C was endemic had a high rate (approximately 20%) of the K65R multinoleside-resistance mutation, the K70E mutation, or both mutations after receiving drug regimens based on stavudine or didanosine.

K65R with treatment failure in subtype C viruses was detected in 7 to 15% of patients in South Africa who did not have a response to first- or second-line regimens with stavudine, didanosine, or zidovudine as the nucleoside backbone. In addition, studies from Israel reported high frequencies of K65R with treatment failure in subtype C viruses from Ethiopian immigrants, and 10 to 12% of patients in India who received combination therapy with stavudine, lamivudine, and nevirapine as first-line therapy carried K65R.

Some of these differences in rates of acquisition of K65R or TAMs are doubtless due to treatment regimens and disease stage, as well as access to viral-load testing in many developing countries. This is underscored by the fact that timely introduction of second-line therapy after the failure of first-line therapy, which is commonly associated with resistance to M184V or NNRTI mutations (K103 N/S, G190A, Y181V, K101E, and V106A/M), should prevent the acquisition of TAMs or K65R. Regional differences among subepidemics of subtype C virus in Ethiopia, Brazil, and sub-Saharan Africa may also influence rates of resistance, as observed for resistance to NNRTIs. These differences in K65R mutational profiles are related to subtype and the use of inappropriate drug regimens rather than to geographic considerations.

Newer work now suggests that increased rates of K65R acquisition in subtype C may be due to the nature of the subtype C RNA template and not, for example, to the subtype origin of the viral reverse transcriptase. In particular, subtype C viruses may be especially prone to pausing events at codon 65, facilitating the acquisition of K65R during reverse transcription. In contrast, subtype B templates are prone to frequent pausing at codon 67, facilitating the generation of D67N and TAMs instead of K65R.

Indeed, ultrasensitive pyrosequencing methods have also shown that K65R can be selectively transmitted as minority species in some populations that have not received antiretroviral therapy. Patients with newly acquired subtype C viruses were significantly more likely to have K65R than were those with subtype B infection who had not been treated (1.04% vs. 0.25%, P<0.001). It is also true that K65R seems to develop more frequently in populations of patients with subtype C in whom regimens containing stavudine, didanosine, or tenofovir have failed. The occur-
rence of K65R in subtypes C and CRF01_AE has also been associated with the Y181C NNRTI mutation in some instances. In contrast, K65R may be less common in subtype A than in other subtypes. Patients in Burkina Faso carrying CRF06_cpx recombinant viruses had a higher propensity for the acquisition of TAMs than did those carrying CRF02_AG recombinant viruses.

### Nonnucleoside Reverse-Transcriptase Inhibitors

Initial guidelines from the World Health Organization (WHO) recommended the use of single-dose nevirapine for the prevention of mother-to-child transmission of HIV. High frequencies of drug resistance were observed in 69% of women with subtype C, 36% of those with subtype D, 19% of those with subtype A, and 21% of those with subtype CRF02, despite the absence of resistance before the administration of antiretroviral therapy. The use of ultrasensitive detection procedures, which reveal minority-species resistance, has shown even higher percentages of patients with nevirapine-resistance mutations (K103N and Y181C), reaching 70 to 87% of patients with subtype C infection, as compared with 42% of patients with subtype A who have resistance mutations. These findings underscore the role of viral subtype in facilitating the development of drug resistance, which is exacerbated by the fact that resistance to NNRTIs can also be transmitted through breast-feeding.

Current guidelines for the prevention of maternal transmission recommend that triple-drug combinations be used to prevent the occurrence of drug resistance. A V106M mutation is commonly selected in subtype C viruses (in approximately 30% of patients) after exposure to nevirapine or efavirenz, whereas a V106A substitution is only rarely selected (in approximately 5% of patients) by the same NNRTIs in other subtypes. This is due to a subtype-C–specific polymorphism in reverse transcriptase at codon 106 and has been shown to be clinically relevant in regions in which subtype C is endemic (Table 1). Nevertheless, K103N and Y181C mutations remain important in both subtypes B and C, with K103N occurring in 40% of subtype B and 29% of subtype C viruses and Y181C occurring in 23% of subtype B and 12% of subtype C viruses. Another substitution that

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**Figure 1. Distribution of HIV Subtypes among Immigrants to Quebec from Africa and Global Distribution of Subtypes.**

Panel A shows a phylogenetic analysis of the reverse-transcriptase–protease region of non-B subtype infections in samples obtained from 909 immigrants to Quebec (approximately 15% of patients affected by the provincial epidemic), revealing 10% intersubtype viral diversity from francophone African countries at the epicenter of the pandemic. Subtypes C1, C2, and C3 reflect intrasubtype C regional variations from southern regions (Zimbabwe and Botswana), central regions (Burundi and Rwanda), and eastern regions (Ethiopia and Kenya), respectively. Subtypes A, G, CRF02_AG, CRF06_A/G/J/K, and other circulating recombinant forms predominate in western regions (Benin and Ivory Coast) and central regions (Congo and Cameroon). Panel B shows how the distribution of subtypes in Quebec parallels the global prevalence of non-B subtypes worldwide. Data are from the World Health Organization UNAIDS HIV Vaccine Initiative.
Table 1. Potential Effect of Subtype Diversity on Drug Resistance. *

<table>
<thead>
<tr>
<th>Type of Resistance and Subtype</th>
<th>Drug Class</th>
<th>Resistance Mutations and Polymorphisms</th>
<th>Protease Inhibitors</th>
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<tbody>
<tr>
<td></td>
<td>NRTIs</td>
<td>NNRTIs</td>
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<td>Primary resistance</td>
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<td></td>
<td></td>
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<tr>
<td>O</td>
<td>Multidrug</td>
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<td>Y181C, A98S, K103R,</td>
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<td></td>
<td></td>
<td></td>
<td>E138A, V179E,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>L10I/V, K20I, V32I,</td>
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<td>M36I, I47V, L63E/K,</td>
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<td>V82L</td>
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<td>V777T, V82L</td>
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<td>Secondary resistance</td>
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<td>Protease</td>
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</tr>
<tr>
<td>F</td>
<td>Protease</td>
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<td>M36I, K57R, L89M</td>
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**Frequency of Natural Mutation**

<table>
<thead>
<tr>
<th>Frequency of PI Pathways in Nelfinavir Failure†</th>
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<tbody>
<tr>
<td>L89M</td>
</tr>
<tr>
<td>percent</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>A and AE</td>
</tr>
<tr>
<td>AG</td>
</tr>
<tr>
<td>G</td>
</tr>
<tr>
<td>C</td>
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<tr>
<td>F</td>
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**Backbone for V106M (ATG) Selection**

<table>
<thead>
<tr>
<th>Frequency of V106M in NNRTI Failure</th>
<th>Natural Changes Needed</th>
<th>percent</th>
</tr>
</thead>
</table>

**Nucleotide polymorphisms affecting genetic barrier**

| B | GTA | 2 | <1 |
| C | GTG | 1 | 20–30 |

**64–65–66 Codon Motif**

<table>
<thead>
<tr>
<th>K65R Frequency in Failure of Stavudine, Didanosine, Abacavir, or Tenofovir</th>
<th>percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>AAG-AAA-AAA</td>
</tr>
<tr>
<td>C</td>
<td>AAA-AAG-AAG</td>
</tr>
</tbody>
</table>

* The percentages of each mutation at the time of treatment failure are dependent on the backbone regimen used and the extent to which undetected treatment failure has persisted. NA denotes not applicable, NRTI nucleoside reverse-transcriptase inhibitor, NNRTI nonnucleoside reverse-transcriptase inhibitor, and PI protease inhibitor.

† PI resistance pathways in nelfinavir failure are based on data accessed from the Stanford University HIV Drug Resistance Database.
is seen more frequently among patients with subtype C virus is G190A, which is also a result of naturally occurring G190A/S polymorphisms.55 Reverse-transcriptase polymorphisms at residue 98, which are common in subtype G, are also associated with NNRTI resistance in subtype B.60 Only minor differences in drug-resistance pathways among subtypes A, B, and C have been observed with etravirine, a second-generation NNRTI.54

**PROTEASE INHIBITORS**

Among patients in whom therapy with nelfinavir (a drug with a low genetic barrier for resistance) fails, the D30N mutation, which is associated with treatment failure in subtype B viruses, is not commonly observed in subtypes G, CRF02_AG, and CRF02_AE isolates. Rather, the L90M pathway is favored in the latter subtypes.64 Although subtype C isolates from Ethiopian immigrants to Israel favored the L90M pathway, patients with subtype C viruses in Botswana did have D30N, suggesting that subtype C viruses from Ethiopia and southern Africa might be different.62,63 The basis for the higher preponderance of D30N in subtype B than in other subtypes may be related to the flexibility of the protease flap region and destabilization of the protease-inhibitor complex in subtype B, whereas an accessory N83T mutation may be needed to rescue fitness and confer resistance in subtype C.64,65

L89M polymorphisms that are observed in subtypes C, F, and G can also lead to M89I/V mutations, and a V82I polymorphism in subtype G is of apparent importance in the emergence of I82M/T/S resistance after treatment failure66 (Table 1). The L90M resistance mutation is common in subtype B from Brazil but rare in subtype F.67 Polymorphisms at position 36 in protease may play ancillary roles in determining the emergence of specific resistance mutations among viruses of different subtypes.68

Differences in polymorphisms in the protease gene have been reported among non-B subtypes; these include protease residues 10, 20, and 63 in subtype A; residues 20, 53, 63, 74, and 82 in subtype C; residues 13 and 20 in subtype D; residues 10, 14, 20, and 77 in subtype F; residues 20, 67, 73, 82, and 88 in subtype G; residues 20, 63, 82, and 89 in subtype CRF01_AE; and residue 20 in subtype CRF02_AG.69,70 Increased rates of emergence of NRTI and protease-inhibitor resistance mutations and equal rates of emergence of NNRTI mutations in subtype B, as compared with subtype C, have also been reported.71 In southern Brazil, scientists reported a lower relative frequency of primary resistance to protease inhibitors in subtype C than in subtype B.72 However, subtype diversity may not limit the initial benefits of antiretroviral therapy, despite clear evidence for the preferential emergence of some mutations, such as V82M in proteases in some non-B subtypes, V82M in subtype G versus V82A/F/S in other subtypes, or N88D in subtype B versus N88S in subtypes C and CRF02_AG.73

Major mutations also compromise the efficacy of NRTIs, NNRTIs, and protease inhibitors in the related HIV-2 virus, which has innate resistance to several NNRTIs (Table 1).74,75 Some minor mutations in subtype B protease may appear as frequent natural polymorphisms in several non-B subtypes (e.g., M36I and L89M),67,68 and the L89M polymorphism can lead to the M89I major resistance mutation for protease inhibitors (Table 1).

Diminished susceptibilities among wild-type isolates have been found for CRF02_AG recombinant viruses in three different studies of nelfinavir and atazanavir.60,70,76 One study suggested that distortions in the K26 pocket of the A/G protease may be responsible for a lower binding energy of nelfinavir and lower susceptibility of A/G viruses.76 Although CRF02_AG isolates with lower susceptibilities to certain protease inhibitors (nelfinavir and atazanavir) have been identified, only one study detected diminished atazanavir susceptibilities among wild-type isolates.77 In regard to nelfinavir resistance, competition assays support a lower fitness of subtype C viruses bearing D30N, which could explain the absence of this mutation in some subtype C isolates.65

The protease and gag genes coevolve as a functional unit when HIV is subjected to drug pressure from protease inhibitors. Mutations in gag can act as compensatory substitutions that can increase both rates and levels of resistance to protease inhibitors, as well as viral replication capacity.78 No genotypic system for the determination of drug resistance to protease inhibitors currently monitors gag, despite the fact that relevant mutations in gag can increase resistance by a factor of 2 to 2.5, depending on the subtype. It is
likely that different subtypes could develop compensatory gag mutations at different rates; this might ultimately justify the genotyping of gag in resistance testing.

INTEGRASE INHIBITORS

Resistance to integrase inhibitors in patients in whom raltegravir- and elvitegravir-based regimens fail is associated with three main pathways involving key mutations at positions N155H, Q148K/R/H, and Y143R/C within the integrase gene, with polymorphisms among subtypes that may affect resistance and viral-replication capacity.\textsuperscript{20,79-84} Given a modest genetic barrier to resistance for these compounds, clinical failure may result from the use of suboptimal regimen backbones or interactive effects of reverse-transcriptase and protease resistance.\textsuperscript{85,86}

Signature subtype differences in integrase at codons 140, 148, 151, 157, and 160 among HIV subtypes may affect the genetic barrier for resistance.\textsuperscript{20} These variations predict higher genetic barriers to the development of G140S and G140C mutations in subtypes C, CRF02_AG, and A/CRF01_AE, as well as higher genetic barriers to V151I in subtypes CRF02_AG and CRF01_AE.\textsuperscript{20,87} The E157Q and E160Q mutational motifs were observed in 35% of subtype C isolates, indicating intrasubtype variations.\textsuperscript{87} Nucleotide motifs at codons 155 and 143 are highly conserved among subtypes.\textsuperscript{20} These findings suggest that some sequence variations might not promote resistance through the Q148R/H/K and G140S pathways in subtypes A, CRF02_AG, and C.\textsuperscript{20,87} Despite a 40% difference in integrase sequence between HIV-2 and HIV-1, the pathways to raltegravir resistance are similar.\textsuperscript{88} If it is confirmed that the genetic barrier for resistance to integrase inhibitors is higher in non-B subtypes than in subtype B, this finding may have clinical relevance in many developing countries.\textsuperscript{20,87}

ENTRY INHIBITORS

Although drugs that target viral entry are still in various phases of development, the high level of diversity (20 to 40%) in the env region predicts that this class of drugs will probably have higher potential for natural and emergent drug resistance. Clinical data have shown that the fusion inhibitor enfuvirtide is active against non-B subtypes owing to a highly conserved binding domain, although HIV-2 and HIV-1 class O viruses have natural resistance against this drug.\textsuperscript{89,90} The CCR5 inhibitor maraviroc also has activity against multiple subtypes.

BIOLGIC AND CLINICAL RELEVANCE

Compelling biochemical and virologic data illustrate the differential effect of genetic background on both the type and degree of HIV-1 resistance to antiretroviral drugs, as has been documented for resistance to NRTIs, NNRTIs, and protease inhibitors. For protease inhibitors, genetic background, including polymorphisms in each subtype, can affect the extent to which primary mutations alter protein binding or protease function. Hence, some polymorphisms can act as the equivalent of secondary resistance mutations.

It is important to continue to do research on the role of polymorphisms in the development of drug resistance. In some cases, drug exposure may lead to amplification of such polymorphisms as A98G/S in reverse transcriptase and M36I, K20I, and L89M in protease, leading to a potential for resistance.\textsuperscript{91} In parts of Africa, treatment failure has been reported in as many as 40% of patients after 2 years.\textsuperscript{92} Resistance rates of more than 80% to two drug classes have been reported in India after failure of first-line regimens using combinations of NRTIs and NNRTIs.\textsuperscript{93} Studies are needed to assess genotypes both before and after therapy in the context of possible associations between polymorphisms and drug resistance. This area of research could include polymorphism variability in variants of the same subtype in different geographic regions. This information might improve the efficacy of certain drug combinations over others in the context of second- or third-line therapeutic strategies.

As access to antiretroviral therapy in resource-poor countries increases, it remains imperative to establish appropriate treatment strategies for long-term clinical benefit that limit the emergence of drug resistance. The use of nontoxic, effective antiretroviral drugs should yield excellent clinical responsiveness, regardless of the viral subtype. Subtype differences, suboptimal therapies, and deficiencies in health care delivery systems can create conditions for accelerated development of
resistance. There also remains an urgent need for low-cost viral-load monitoring to prevent and detect drug resistance, as well as to avoid unnecessary treatment switches.\textsuperscript{94-96}

Unfortunately, pooling of resistance data often masks the role of regional differences in viral subtypes and antiretroviral therapies in the development of drug resistance.\textsuperscript{13} In resource-poor settings, such studies have used different NRTI backbones (e.g., combinations of zidovudine and didanosine, zidovudine and lamivudine, or stavudine and lamivudine). Larger longitudinal studies are needed to determine the response to first-line combinations of antiretroviral drugs. The availability of genotypic resistance testing both before and after therapy needs to be expanded to include all countries in which antiretroviral drugs are used.

Phenotypic assays have not detected significant differences in antiretroviral-drug susceptibility between B subtypes and non-B subtypes, findings that are consistent with biochemical data obtained with recombinant reverse transcriptase and protease. This is doubtless the reason that all HIV subtypes should respond in more or less equivalent fashion to good drug regimens. However, some polymorphisms in non-B viruses may act as secondary resistance mutations on the basis of their emergence in subtype B viruses after exposure to antiretroviral drugs, and it may often be difficult to extrapolate the effect of such polymorphisms in non-B subtypes. For example, the I93L substitution causes hypersusceptibility to some protease inhibitors in subtype C but is a secondary resistance mutation in subtype B.\textsuperscript{65}

Although it is tempting to speculate that rates of acquisition of resistance could have important implications for the durability of treatment efficacy, this is likely to be true only for the use of substandard drug regimens. As an example, the K65R mutation emerges faster in subtype C than in subtype B,\textsuperscript{19,27} and biochemical mechanisms explain that this difference relates to the manner in which subtype C templates are processed by HIV-1 reverse transcriptase.\textsuperscript{31-33,97} K65R has also been seen in approximately 70% of patients in whom didanosine-containing regimens fail in Botswana\textsuperscript{25} and in high proportions (approximately 20%) of patients who do not have a response to stavudine, lamivudine, and nevirapine in Malawi, India, and South Africa.\textsuperscript{38,98,99}

In contrast, K65R is uncommon among patients with subtypes B and C who have received either tenofovir or a combination of tenofovir and emtricitabine as part of triple antiretroviral-drug therapy.\textsuperscript{27} Although this reflects the use of well-tolerated, effective drugs that have long intracellular half-lives and that act in combination to suppress viral replication and prevent the emergence of resistance mutations, larger numbers of patients and follow-up will be required to determine whether any consistent effect of the emergence of K65R in subtype C is clinically relevant. The strong association between K65R selection and nevirapine is also of concern in regard to the synergistic fitness interactions that have been observed for the K65R, Y181C, and G190A/S mutations.\textsuperscript{100-102} The use of tenofovir- or zidovudine-based regimens can offset the development of K65R in subtype C HIV infections.\textsuperscript{103,104}

Cross-resistance among drugs is important, especially in settings in which treatment options may be limited. Relatively few in vitro comparative data are available for protease inhibitors in non-B subtypes, yet such data may be crucial for an understanding of cross-resistance to protease inhibitors.\textsuperscript{67,68} Such data are important, since protease inhibitors are often the only available option for drug sequencing in resource-limited settings after the failure of first- or second-line treatment. The fact that resistance to protease inhibitors usually requires the presence of large numbers of resistance mutations may mean that the contribution of any single mutation to drug resistance is minor, an advantage of using drugs with a high genetic barrier for the development of resistance. Hence, differences among subtypes with regard to drug resistance are likely to be more important for NRTIs, NNRTIs, and integrase inhibitors than for protease inhibitors.

**SUMMARY**

An urgent global priority is the optimization of treatment strategies for HIV infection, regardless of geographic locale. It is reassuring that current antiretroviral strategies appear to be effective against a broad spectrum of HIV subtypes. Suboptimal therapies that include such drugs as stavudine and didanosine can facilitate the selection of the K65R mutation, which, in turn, may limit many secondary treatment options. In addi-
tion, suboptimal regimens put patients at risk for the development of NNRTI-resistance patterns. An understanding of drug-resistance patterns among non-B subtype infections may help to optimize the selection of first-line regimens and limit the acquisition of resistance.

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