

Update of the Drug Resistance Mutations in HIV-1: Fall 2006

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The International AIDS Society–USA (IAS–USA) Drug Resistance Mutations Group is marking 6 years as an independent volunteer panel of experts focused on identifying key HIV-1 drug resistance mutations. The goal of the effort is to quickly deliver accurate and unbiased information on these mutations to HIV clinical practitioners.

This version of the IAS–USA Drug Resistance Mutations Figures replaces the version published in this journal in October/November 2005. The IAS–USA Drug Resistance Mutations Figures are designed for use in identifying mutations associated with viral resistance to antiretroviral drugs and in making therapeutic decisions. Care should be taken when using this list of mutations for surveillance or epidemiologic studies of transmission of drug-resistant virus. A number of amino acid substitutions, particularly minor mutations, represent polymorphisms that in isolation may not reflect prior drug selective pressure or reduced drug susceptibility.

In the context of making clinical decisions regarding antiretroviral therapy, evaluating the results of HIV genotypic testing includes: (1) assessing whether the pattern or absence of a pattern in the mutations is consistent with the patient's antiretroviral history; (2) recognizing that in the absence of drug (selection pressure), resistant strains may be present at levels below the limit of detection of the test (analyzing stored samples, collected under selection pressure, could be useful in this setting); and (3) recognizing that virologic failure of the first regimen typically involves HIV-1 isolates with resistance to only 1 or 2 of the drugs in

the regimen (in this setting, resistance most commonly develops to lamivudine or the nonnucleoside reverse transcriptase inhibitors [NNRTIs]).^{2,6} The absence of detectable drug resistance following treatment failure may result from the presence of drug-resistant minority viral populations, patient medication nonadherence, laboratory error, drug-drug interactions leading to subtherapeutic drug levels, and possibly compartmental issues, indicating that drugs may not reach optimal levels in specific cellular or tissue reservoirs.

Revisions to the Figures for the August/September 2006 Update

Nucleoside (or Nucleotide) Reverse Transcriptase Inhibitors

Among the changes in the August/September 2006 version of the figures and user notes, user note 1 has updates about NNRTI hypersusceptibility. On the nucleoside (or nucleotide) reverse transcriptase inhibitor (nRTI) bars, the K70E mutation has been added to tenofovir. User note 4 discusses mutations outside of the reverse transcriptase gene region depicted on the figure bars. These mutations may prove to be important for HIV drug resistance. Also on the nRTI bars, the E44D and V118I mutations have been removed from stavudine and zidovudine because the significance of E44D or V118I when each occurs in isolation is unknown (see user note 5).

Nonnucleoside Reverse Transcriptase Inhibitors

The multi-NNRTI resistance bars have been removed because the presence of 2

or more of the NNRTI mutations depicted on these bars may lead to poorer long-term virologic response (see user note 12).

Protease Inhibitors

In the protease inhibitor (PI) category, the ritonavir bar has been removed because ritonavir is now used only for pharmacologic purposes, not as monotherapy, as discussed in user note 15. The “/ritonavir” designation has been added to atazanavir, fosamprenavir, darunavir, indinavir, and saquinavir to indicate boosting with low-dose ritonavir. User note 16 provides an update on how HIV-1 Gag cleavage site changes can cause PI resistance in vitro.

Based on new data (see user note 17), the following minor mutations have been added to atazanavir with or without ritonavir: L10C, K20T/V, E34Q, F53L/Y, I54A, I64L/M/V, V82F/I, and I93M. A darunavir/ritonavir bar has been added for the fully approved drug formerly known as TMC-114 (see user note 18). The darunavir/ritonavir major mutations on the bar are I50V, I54M, L76V, and I84V and the minor mutations are V11I, V32I, L33F, I47V, I54L, G73S, and L89V. Minor mutations added to saquinavir/ritonavir are: L24I, I62V, and V82F/T/S.

Comments?

The IAS–USA Drug Resistance Mutations Group welcomes comments on the mutations figures and user notes.

(continued, page 130)

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MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (nRTIs)¹

Multi-nRTI Resistance: 69 Insertion Complex² (affects all nRTIs currently approved by the US FDA)



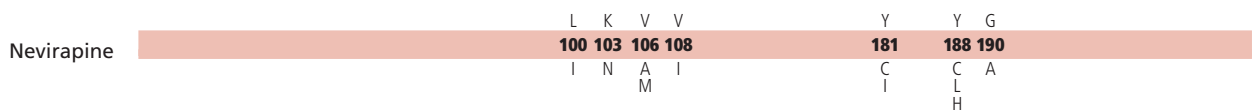
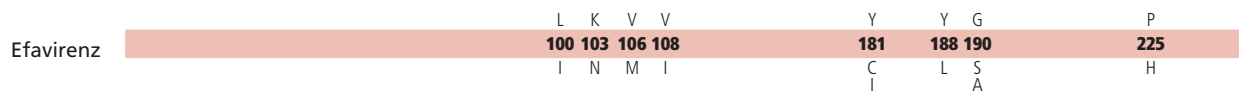
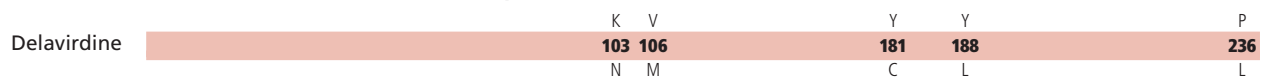
Multi-nRTI Resistance: 151 Complex³ (affects all nRTIs currently approved by the US FDA except tenofovir)



Multi-nRTI Resistance: Thymidine Analogue-associated Mutations^{4,5} (TAMs; affect all nRTIs currently approved by the US FDA)



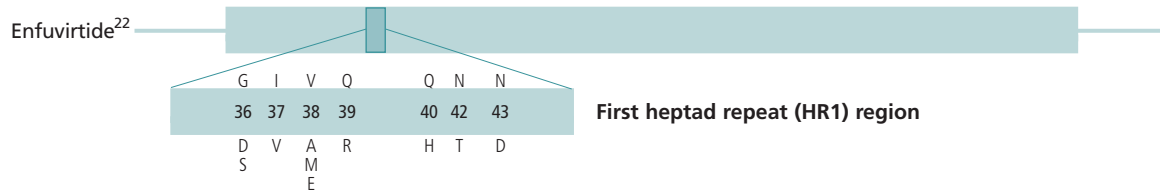
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)^{1,12}



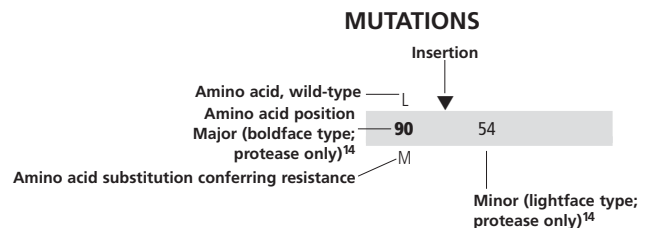
MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS^{13,14,15,16}

Atazanavir +/-ritonavir ¹⁷	L 10 I F V C	G 16 E R M I T V	K 20 R I	L 24 I	V 32 I	L 33 I F V	E 34 Q I L V	M 36 V	M 46 L	G 48 V	I 50 L	F 53 L Y	I 54 L V M T A	D 60 E	I 62 V	I 64 L M V	A 71 V I T L	G 73 C S T A	V 82 A T F I	I 84 V	I 85 V	N 88 S	L 90 M	I 93 L M
Fosamprenavir/ritonavir	L 10 F I R V				V 32 I				M 46 L	I 47 V	I 50 V	I 54 L V M				G 73 S	V 82 A F S T	I 84 V		L 90 M				
Darunavir/ritonavir ¹⁸	V 11 I			V 32 I	L 33 F				I 47 V	I 50 V	I 54 M L				G 73 S	L 76 V	I 84 V		L 89 V					
Indinavir/ritonavir	L 10 I R V	K 20 M R	L 24 I	V 32 I	M 36 I			M 46 L			I 54 V			A 71 T	G 73 S	V 77 I	V 82 A	I 84 V	L 90 M					
Lopinavir/ritonavir ¹⁹	L 10 F I R V	K 20 M R	L 24 I	V 32 I	L 33 F			M 46 L	I 47 A	I 50 V	F 53 L	I 54 V L A M T S		L 63 P	A 71 V	G 73 S	V 82 A F T S	I 84 V	L 90 M					
Nelfinavir ²⁰	L 10 F I		D 30 N		M 36 I			M 46 L						A 71 T	V 77 I	V 82 A	I 84 V	N 88 D	L 90 M					
Saquinavir/ritonavir	L 10 I R V		L 24 I						G 48 V		I 54 V L		I 62 V	A 71 T	G 73 S	V 77 I	V 82 A	I 84 V	L 90 M					
Tipranavir/ritonavir ²¹	L 10 V V	I 13 M R	K 20 R		L 33 F	E 35 G	M 36 I		K 43 T	M 46 L	I 47 V		I 54 A M V	Q 58 E	H 69 K	T 74 P	V 82 L	N 83 D	I 84 V	L 90 M				

MUTATIONS IN THE GP41 ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS



Amino acid abbreviations: A, alanine; C, cysteine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.



The International AIDS Society–USA Drug Resistance Mutations Group reviews new data on HIV drug resistance in order to maintain a current list of mutations associated with clinical resistance to HIV. This list includes mutations that may contribute to a reduced virologic response to a drug.

The mutations listed have been identified by 1 or more of the following criteria: (1) in vitro passage experiments or validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) genetic sequencing of viruses from patients in whom the drug is failing; (4) correlation studies between genotype at baseline and virologic response in patients exposed to the drug. In addition, the group only reviews data that have been published or have been presented at a scientific conference. Drugs that have been approved by the US Food and Drug Administration (FDA) are included (listed in alphabetical order by drug class). User notes provide additional information as necessary. Although the Drug Resistance Mutations Group works to maintain a complete and current list of these mutations, it cannot be assumed that the list presented here is exhaustive. Readers are encouraged to consult the literature and experts in the field for clarification or more information about specific mutations and their clinical impact.

User Notes

1. Numerous nucleoside (or nucleotide) reverse transcriptase inhibitor (nRTI) mutations, such as the M41L, L210W, and T215Y mutations, may lead to viral hypersusceptibility to the nonnucleoside reverse transcriptase inhibitors (NNRTIs) in nRTI-treated individuals. The presence of these mutations may improve subsequent virologic response to NNRTI-containing regimens in NNRTI treatment-naïve individuals (Shulman et al, *AIDS*, 2004; Demeter et al, 11th CROI, 2004; Haubrich et al, *AIDS*, 2002; Tozzi, *J Infect Dis*, 2004; Katzenstein et al, *AIDS*, 2003). NNRTI hypersusceptibility can be conferred by 2 distinct phenotypes: increased enzyme susceptibility to NNRTI (eg, V118I/T215Y) or decreased virion associated levels of reverse transcriptase (eg, H208Y/T215Y and V118I/H208Y/T215Y). The viruses that contained less reverse transcriptase replicated less efficiently than those with wild-type levels of reverse transcriptase. (Clark et al, *Antivir Ther*, 2006). The clinical relevance of all these mutations has not been assessed.

2. The 69 insertion complex consists of a substitution at codon 69 (typically T69S) and an insertion of 2 or more amino acids (S-S, S-A, S-G, or others). The 69 insertion complex is associated with resistance to all nRTIs currently approved by the US FDA when present with 1 or more thymidine analogue-associated mutations (TAMs) at codons 41, 210, or 215 (Miller et al, *J Infect Dis*, 2004). Some other amino acid changes from the wild-type T at codon 69 without the insertion may also be associated with broad nRTI resistance.

3. Tenofovir retains activity against the Q151M complex of mutations (Miller et al,

J Infect Dis, 2004).

4. Multi-nRTI resistance mutations, also known as nucleoside analogue-associated mutations (NAMs), are associated with resistance to numerous nRTIs. The M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E are known as TAMs. TAMs are a subset of NAMs that are selected by the thymidine analogues zidovudine and stavudine and are associated with cross-resistance to all nRTIs currently approved by the US FDA (Larder et al, *Science*, 1989; Kellam et al, *Proc Natl Acad Sci USA*, 1992; Calvez et al, *Antivir Ther*, 2002; Kuritzkes et al, *J Acquir Immune Defic Syndr*, 2004). Mutations at the C-terminal reverse transcriptase domains (amino acids 293–560) outside of regions depicted on the figure bars may prove to be important for HIV drug resistance. Mutations in the connection (A371V) and RNase H (Q509L) domains of reverse transcriptase are co-selected on the same genome as TAMs and increase significantly zidovudine resistance when combined with TAMs. They also increase, although to a much lesser extent, cross-resistance to lamivudine, abacavir, and tenofovir but not to stavudine or didanosine (Brehm et al, *Antivir Ther*, 2006). In zidovudine-experienced patients, it has been shown by drug susceptibility testing that, in the C-terminal domain, the mutations G335C, N348I, and A360I exhibited 30-, 35-, and 30-fold increases in zidovudine resistance, respectively. (Nikolenko et al, *Antivir Ther*, 2006.) Three mutations (N348I, T369I, and E399D) in the reverse transcriptase C-terminus are associated with the increased resistance to zidovudine and to NNRTIs.

Mutations at this level could modulate NNRTI resistance by affecting dimerization of p66/p51 heterodimers (Gupta et al, *Antivir Ther*, 2006). The clinical relevance of these mutations has not been assessed.

5. The E44D and the V118I mutations increase the level of resistance to zidovudine and stavudine in the setting of TAMs, and correspondingly increase cross-resistance to the other nRTIs. The significance of E44D or V118I when each occurs in isolation is unknown (Romano et al, *J Infect Dis*, 2002; Walter et al, *Antimicrob Agents Chemother*, 2002; Girouard et al, *Antivir Ther*, 2002).

6. The M184V mutation alone does not appear to be associated with a reduced virologic response to abacavir in vivo (Harrigan et al, *J Infect Dis*, 2000; Lanier et al, *Antivir Ther*, 2004). When present with 2 or 3 TAMs, M184V contributes to reduced susceptibility to abacavir and is associated with impaired virologic response in vivo (Lanier et al, *Antivir Ther*, 2004). The M184V plus 4 or more TAMs resulted in no virologic response to abacavir in vivo (Lanier et al, *Antivir Ther*, 2004).

7. The K65R mutation may be selected by didanosine and is associated in vitro with decreased susceptibility to the drug (Winters et al, *Antimicrob Agents Chemother*, 1997). The impact of the K65R mutation in vivo is unclear.

8. The presence of 3 of the following—M41L, D67N, L210W, T215Y/F, and K219Q/E—has been associated with resistance to didanosine (Marcelin et al, *Antimicrob Agents Chemother*, 2005). The K70R and M184V mutations are not associated with a decreased virologic response to didanosine in vivo (Molina et al, *J Infect Dis*, 2005).

9. The presence of the M184V mutation appears to delay or prevent emergence of TAMs (Kuritzkes et al, *AIDS*, 1996). This effect may be overcome by an accumulation of TAMs or other mutations. The clinical significance of this effect of M184V is not known.

10. The T215A/C/D/E/G/H/I/L/N/S/V substitutions are revertant mutations at codon 215, conferring increased risk of virologic failure of zidovudine or stavudine in antiretroviral-naïve patients (Riva et al, *Antivir Ther*, 2002; Chappey et al, *Antivir Ther*, 2003; Violin et al, *AIDS*, 2004). In vitro studies and preliminary clinical studies suggest that the T215Y

mutant may emerge quickly from one of these mutations in the presence of zidovudine or stavudine (Garcia-Lerma et al, *J Virol*, 2004; Lanier et al, *Antivir Ther*, 2002; Riva et al, *Antivir Ther*, 2002).

11. The K65R mutation is associated with a reduced virologic response to tenofovir in vivo (Miller et al, *J Infect Dis*, 2004). A reduced response occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W (Miller et al, *J Infect Dis*, 2004). Slightly increased treatment responses to tenofovir in vivo were observed if M184V was present (Miller et al, *J Infect Dis*, 2004).

12. The long-term virologic response to sequential NNRTI use is poor, particularly when 2 or more mutations are present (Antinori et al, *AIDS Res Hum Retroviruses*, 2002; Lecossier et al, *J Acquir Immune Defic Syndr*, 2005). The K103N or Y188L mutation alone prevents the clinical utility of all NNRTIs currently approved by the US FDA (Antinori et al, *AIDS Res Human Retroviruses*, 2002). The V106M mutation is more common in HIV-1 subtype C than in subtype B, and confers cross-resistance to all currently approved NNRTIs (Brenner et al, *AIDS*, 2003; Cane et al, *J Clin Micro*, 2001).

13. The same mutations usually emerge whether or not PIs are boosted with low-dose ritonavir, although the relative frequency of mutations may differ. Data on the selection of mutations in antiretroviral-naïve patients in whom a boosted PI is failing are very limited. Numerous mutations are often necessary to significantly impact virologic response to a boosted PI. Although numbers vary for the different drugs, 3 or more mutations are often required.

14. Resistance mutations in the protease gene are classified as either “major” or “minor,” if data are available.

Major mutations in the protease gene are defined in general either as those selected first in the presence of the drug; or those shown at the biochemical or virologic level to lead to an alteration in drug binding or an inhibition of viral activity or viral replication. Major mutations have an effect on drug susceptibility phenotype. In general, these mutations tend to be the primary contact residues for drug binding.

Minor mutations generally emerge later than major mutations, and by themselves do not have a significant

effect on phenotype. In some cases, their effect may be to improve replicative fitness of the virus containing major mutations. However, some minor mutations are present as common polymorphic changes in HIV-1 nonsubtype B clades, such as K201/R and M36I in protease.

15. Ritonavir is not listed separately as it is currently used at therapeutic doses as a pharmacologic booster of other PIs. At higher doses tested previously in humans, ritonavir administered as monotherapy produces mutations similar to those produced by indinavir (Molla, *Nature Med*, 1996).

16. HIV-1 Gag cleavage site changes can cause PI resistance in vitro. It has been observed that mutations in the N-terminal part of *gag* (MA: E40K; L75R; K113E and CA: M200I; A224A/V), outside the cleavage site, contribute directly to PI resistance by enhancing the overall Gag processing by wild-type protease. (Nijhuis et al. *Antivir Ther*, 2006). The clinical relevance of these mutations has not been assessed.

17. In most patients in whom an atazanavir/ritonavir-containing regimen was failing virologically, accumulations of the following 13 mutations were found (L10F/I/V, G16E, L33F/I/V, M46I/L, I54L/V/M/T, D60E, I62V, A711/T/L, V82A/T, I84V, I85V, L90M, and I93L). Seven mutations were retained in an atazanavir score (L10F/I/V, G16E, L33F/I/V, M46I/L, D60E, I84V, I85V); the presence of 3 or more of these mutations predicts a reduced virologic response at 3 months, particularly when L90M was present (Vora, et al, *Antivir Ther*, 2005). A different report (Bertoli et al, *Antivir Ther*, 2006) found that the presence of 0, 1, 2, or greater than or equal to 3 of the following mutations were associated with 92%, 93%, 75%, and 0% virologic response to atazanavir/ritonavir: L10C/I/V, V32I, E34Q, M46I/L, F53L, I54A/M/V, V82A/F/I/T, I84V; presence of I15E/G/L/V, H69K/M/N/Q/R/T/Y, and I72M/T/V improved the chances of response. For unboosted atazanavir, the presence of 0, 1, 2, or greater than or equal to 3 of the following mutations was associated with 83%, 67%, 6%, and 0% response rates: G16E, V32I, K201/M/R/T/V, L33F/I/V, F53L/Y, I64L/M/V, A711/T/V, I85V, I93L/M.

18. Darunavir (formerly TMC-114), boosted with ritonavir, was approved by the US FDA in June 2006. Resistance data are therefore still preliminary and limited. HIV RNA response to boosted darunavir

correlated with baseline susceptibility and the presence of multiple specific PI mutations. Reductions in response were associated with increasing numbers of the mutations indicated in the bar. Some of these mutations appear to have a greater effect on susceptibility than others (eg, I50V versus V11I). Further study and analysis in other populations are required to refine and validate these findings.

19. In PI-experienced patients, the accumulation of 6 or more of the mutations indicated on the bar is associated with a reduced virologic response to lopinavir/ritonavir (Masquelier et al, *Antimicrob Agents Chemother*, 2002; Kempf et al, *J Virol*, 2001). The product information states that accumulation of 7 or 8 mutations confers resistance to the drug. In contrast, in those in whom lopinavir/ritonavir is their first PI used, resistance to this drug at the time of virologic rebound is rare. However, there is emerging evidence that specific mutations, most notably I47A (and possibly I47V) and V32I are associated with high-level resistance (Mo et al, *J Virol*, 2005; Friend et al, *AIDS* 2004; Kagan et al, *Protein Sci*, 2005).

20. In some nonsubtype-B HIV-1, D30N is selected less frequently than other PI mutations (Gonzalez et al, *Antivir Ther*, 2004).

21. Accumulation of more than 2 mutations at positions 33, 82, 84, and 90 correlate with reduced virologic response to tipranavir/ritonavir, although an independent role for L90M was not found. Detailed analyses of data from phase II and III trials in PI-experienced patients identified mutations associated with reduced susceptibility or virologic response. These include: L10V, I13V, K20M/R, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V. Accumulation of these mutations is associated with reduced response. Subsequent genotype-phenotype and genotype-virologic response analyses determined some mutations have a greater effect than others (eg, I84V versus I54M). Refinement and clinical validation of these findings are pending (Schapiro et al, CROI, 2005; Kohlbrenner et al, DART, 2004; Mayers et al, *Antivir Ther*, 2004; Hall et al, *Antivir Ther*, 2003; McCallister et al, *Antivir Ther*, 2003; Parkin et al, CROI, 2006; Bachelier et al, European HIV Drug Resistance Workshop, 2006).

22. Although resistance to enfuvirtide is associated primarily with mutations in the

first heptad repeat (HR1) region of the gp41 envelope gene, wild-type viruses in the depicted HR1 region vary 500-fold in susceptibility. Such pretreatment susceptibility differences were not associated with differences in clinical responses (Labrosse et al, *J Virol*, 2003). Furthermore, mutations or polymorphisms in other regions in the envelope (eg, the HR2 region or those yet to be identified) as well as coreceptor usage and density may affect susceptibility to enfuvirtide (Reeves et al, *Proc Natl Acad Sci USA*, 2002; Reeves et al, *J Virol*, 2004; Xu et al, *Antimicrob Agents Chemother*, 2005). Thus, testing to detect only the depicted HR1 mutations may not be adequate for clinical management of suspected failure (Reeves et al, *J Virol*, 2004; Menzo et al, *Antimicrob Agents Chemother*, 2004; Poveda et al, *J Med Virol*, 2004; Sista et al, *AIDS*, 2004; Su, *Antivir Ther*, 2004).

(continued from page 125)

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Financial Disclosures: The authors disclose the following affiliations with commercial organizations that may have interests related to the content of this article: Dr Brun-Vézinet has received grant support from Bayer, bioMérieux, Bristol-Myers Squibb, GlaxoSmithKline, and PE Biosystems and has served as a consultant to Abbott, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Gilead, Roche, and Tibotec; Dr Clotet has served as a consultant and received grant support from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Pfizer, and Roche; Dr Johnson has served as a consultant to GlaxoSmithKline, Bristol-Myers Squibb, Virco, and ViroLogic and as a speaker or on a speakers bureau for Abbott, Bayer, Boehringer Ingelheim/Roxanne, Bristol-Myers Squibb, Chiron, GlaxoSmithKline, Merck, Roche, Vertex, and ViroLogic, and has received grant support from Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, and Bayer; Dr Kuritzkes has served as a consultant to Abbott, Anormed, Avexa, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiron, Gilead, GlaxoSmithKline, Merck, Monogram Biosciences, Panacos, Pfizer, Roche/Trimeris, Schering-Plough, Tanox, Tibotec, and VirXsys, and has received honoraria from Abbott, Anormed, Avexa, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Human Genome Sciences,

Merck, Monogram Biosciences, Panacos, Pfizer, Roche/Trimeris, and VirXsys, and grant support from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Human Genome Sciences, Merck, Roche/Trimeris, Schering-Plough, and Tibotec; Dr Pillay has served as a consultant to and has received research grants from GlaxoSmithKline, Gilead, Bristol-Myers Squibb, Roche, and Tibotec-Virco; Dr Richman has served as a consultant to Achillion, Anadys, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Idinex, Merck, Monogram, Pfizer, Roche, and Tibotec; Dr Schapiro has served as a scientific advisor to Bayer and Roche and on the speakers bureau for Abbott, Bristol-Myers Squibb, and Roche, and has received other financial support from GlaxoSmithKline and Virology Education.

Funding/Support: This work was funded by IAS–USA. No private sector or government funding contributed to this effort. Panel members are not compensated.

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