Special Contribution

Update of the Drug Resistance Mutations in HIV-1: December 2009
International AIDS Society–USA Drug Resistance Mutations Group

Perspectives

Antiretroviral Therapy: New Drugs, Formulations, Ideas, and Strategies
Joseph J. Eron, Jr. MD
Strategies in Treatment-Naive Patients • Alternatives to Nucleoside Analogue Reverse Transcriptase Inhibitors • Switching Therapy in Suppressed Patients • Three-Active-Drug Postfailure Regimens

Review

HIV-Associated Resources on the Internet
Wendy S. Armstrong, MD, and Carlos del Rio, MD
Search Methods • Results • Web Sites With Images and Case Studies • HIV-Related Journals • HIV-Related Research Web Sites • Web Sites for Patient Information and Advocacy • Epidemiology and Policy Web Sites • Web Sites of US and International Societies for HIV Practitioners
About This Issue

This issue features an update of drug resistance mutations in HIV from the IAS–USA Drug Resistance Mutations Group, 1 Perspective article, and 1 Review article. The drug resistance mutations update includes 3 new mutations and a change in designation to 3 mutations as well as revisions to the user notes and additions to the reference list. The Perspective article is based on a presentation by Joseph J. Eron, Jr, MD, at the IAS–USA continuing medical education program held in Chicago in May 2009. There, he discussed advances in treatment expected to come from strategies using new or available drugs in different classes. The Review article, by Wendy S. Armstrong, MD, and Carlos del Rio, MD, describes the myriad of HIV-related resources currently available on the Internet and provides a comprehensive listing of many useful Web sites. We close our issue with grateful acknowledgment of those who have contributed to our programs in 2009.

Topics in HIV Medicine

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Special Contribution

Update of the Drug Resistance Mutations in HIV-1: December 2009

Victoria A. Johnson, MD, Françoise Brun-Vézinet, MD, PhD, Bonaventura Clotet, MD, PhD, Huldrych F. Günthard, MD, Daniel R. Kuritzkes, MD, Deenan Pillay, MD, PhD, Jonathan M. Schapiro, MD, and Douglas D. Richman, MD

This December 2009 version of the International AIDS Society–USA (IAS–USA) drug resistance mutations list updates the figures last published in December 2008 (Johnson VA et al, Top HIV Med, 2008;16:138-145). This update includes 3 new mutations—K65R for stavudine (Hawkins CA et al, JAIDS, 2009;52:228-234 and Wallis C et al, JAIDS, October 2009; Epub ahead of print) and K101P for efavirenz and nevirapine (Parkin NT et al, Antimicrob Agents Chemother, 2006;50:351-354; Rhee SY et al, Antimicrob Agents Chemother, 2004;48:3122-3126; and Rhee SY et al, Proc Natl Acad Sci USA, 2006;46:17355-17360). In addition, the darunavir I47V mutation and the lopinavir/ritonavir L76V mutation designations were changed to boldface to indicate their recognition as major rather than minor mutations. One mutation, L33F for tipranavir/ritonavir, was changed from a major mutation to that of a minor to reflect recent information. Also, many of the user notes were substantially revised.

Methods

Mutations Panel

The authors comprise the IAS–USA Drug Resistance Mutations Group, an independent, volunteer panel of experts charged with the goal of delivering accurate, unbiased, and evidence-based information on these mutations to HIV clinical practitioners. The group reviews new data on HIV drug resistance 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.

In addition, the group reviews only 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 (US FDA) as well as any drugs available in expanded access programs 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.

Identification of Mutations

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) nucleotide 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 a drug.

The development of more recently approved drugs that cannot be tested as monotherapy precludes assessment of the impact of resistance on antiretroviral activity that is not seriously confounded by activity of other drug components in the background regimen. Readers are encouraged to consult the literature and experts in the field for clarification or more information about specific mutations and their clinical impact. Polymorphisms associated with impaired treatment responses that occur in wild-type viruses should not be used in epidemiologic analyses to identify transmitted HIV-1 drug resistance.

Clinical Context

The figures are designed for practitioners to use in identifying key mutations associated with viral resistance to antiretroviral drugs and in making therapeutic decisions. In the context of making clinical decisions regarding antiretroviral therapy, evaluating the results of HIV-1 genotypic testing includes: (1) assessing whether the pattern or absence of a pattern in the mutations is consistent with the patient’s antiretroviral therapy 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 develops most commonly to lamivudine or the nonnucleoside analogue reverse transcriptase inhibitors [NNRTIs]).

Author Affiliations: Dr Johnson (Group Chair), Birmingham Veterans Affairs Medical Center and the University of Alabama at Birmingham School of Medicine, Birmingham, AL; Dr Brun-Vézinet, University Paris 7 and Bichat-Claude Bernard, Paris, France; Dr Clotet, HIV Unit, Hospital Universitari Germans Trias i Pujol and Fundacio irsiCAIXA, Barcelona, Spain; Dr Günthard, University Hospital and University of Zurich, Zurich, Switzerland; Dr Kuritzkes, Harvard Medical School and Brigham and Women’s Hospital, Boston, MA; Dr Pillay, Department of Infection, University College London, and Centre for Infections, Health Protection Agency, United Kingdom; Dr Schapiro, Sheba Medical Center, Tel Aviv, Israel; Dr Richman (Group Vice Chair), Veterans Affairs San Diego Healthcare System and the University of California San Diego, San Diego, CA.
The absence of detectable viral resistance after treatment failure may result from any combination of the following factors: the presence of drug-resistant minority viral populations, nonadherence to medications, laboratory error, lack of current knowledge of the association of certain mutations with drug resistance, the occurrence of relevant mutations outside the regions targeted by routine resistance assays, 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.

For more in-depth reading and an extensive reference list, see the 2008 IAS–USA panel recommendations for resistance testing (Hirsch MS et al, Clin Infect Dis, 2008;47:266-285). Updates are posted periodically at www.iasusa.org.

**Comments**

Please send your evidence-based comments, including relevant reference citations, to the IAS–USA at resistance2010“at”iasusa.org or by fax at 415-544-9401. Please include your name and institution.

**Reprint Requests**

The Drug Resistance Mutations Group welcomes interest in the mutations figures as an educational resource for practitioners and encourages dissemination of the material to as broad an audience as possible. However, permission is required to reprint the figures and no alterations in the content can be made.

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The authors are grateful to Ann McGuire for editorial support in convening the panel and assistance in preparing the manuscript.
### Mutations in the Reverse Transcriptase Gene Associated with Resistance to Reverse Transcriptase Inhibitors

#### Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)

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

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

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- **Multi-nRTI Resistance:** Thymidine Analogue-Associated Mutations (TAMs; affect all nRTIs currently approved by the US FDA)

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- Lamivudine

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- Stavudine

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- Zidovudine

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#### Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)

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MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE INHIBITORS

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<td>46 48 50 53 54 60 62 64 71 73 81 84 85 88 90 93</td>
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MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

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<td>42 43</td>
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| Maraviroc* | See User Note |

MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE INHIBITORS

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<th>Raltegravir**</th>
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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.
International AIDS Society–USA

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User Notes

a. Some nucleoside (or nucleotide) analogue reverse transcriptase inhibitor (nRTI) mutations, like T215Y and H208Y,1 may lead to viral hypersusceptibility to the non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), including etravirine,2 in nRTI-treated individuals. The presence of these mutations may improve subsequent virologic response to NNRTI-containing regimens (nevirapine or efavirenz) in NNRTI-naive individuals.3,12 although no clinical data exist for improved response to etravirine in NNRTI-experienced individuals.

b. 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 215.4 Some other amino acid changes from the wild-type T at codon 69 without the insertion may be associated with broad nRTI resistance.

c. Tenofovir retains activity against the Q151M complex of mutations.

d. Mutations known to be selected by thymidine analogues (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E, termed TAMs) also confer reduced susceptibility to all approved nRTIs.9 The degree to which cross-resistance is observed depends on the specific mutations and number of mutations involved.11-13 Mutations in the C-terminal reverse transcriptase domains, including RNase H, outside of the regions depicted in the figure may prove to be important for HIV-1 drug resistance.14 The clinical relevance of these in vitro findings remains unclear. Recent analyses showed no clear effect on phenotypic susceptibility to efavirenz or nevirapine in already NNRTI-resistant clinical isolates.15 Moreover, connection domain mutations were not clearly associated with reduced phenotypic susceptibility or virologic response to etravirine in the DUET trials.16 Thus, they are not depicted on the figure bars.

e. Although reverse transcriptase changes associated with the E44D and V118I mutations may have an accessory role in increased resistance to nRTIs in the presence of TAMs, their clinical relevance is very limited.17-19

f. The M184V mutation alone does not appear to be associated with a reduced virologic response to abacavir in vivo.20,21 When associated with TAMs, M184V increases abacavir resistance.20,21

g. As with tenofovir, the K65R mutation may be selected by didanosine, abacavir, or stavudine (particularly in patients with nonsubtype-B clades) and is associated with decreased viral susceptibility to these drugs.22,23 Data are lacking on the potential negative impact of K65R on clinical response to didanosine.

h. The presence of 3 of the following mutations—M41L, D67N, L210W, T215Y/F, K219Q/E—is associated with resistance to didanosine.24 The presence of K70R or M184V alone does not decrease virologic response to didanosine.25

i. K65R is selected frequently (4%-11%) in patients with nonsubtype-B clades for whom stavudine-containing regimens are failing in the absence of tenofovir.26,27

j. The presence of M184V appears to delay or prevent emergence of TAMs.28 This effect may be overcome by an accumulation of TAMs or other mutations.

k. The T215A/C/D/E/G/H/I/L/N/S/V substitutions are revertant mutations at codon 215 that confer increased risk of virologic failure of zidovudine or stavudine in antiretroviral-naive patients.29-31 The T215Y mutant may emerge quickly from 1 of these mutations in the presence of zidovudine or stavudine.32,33

l. The presence of K65R is associated with a reduced virologic response to tenofovir.34 A reduced response also occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W.35 The presence of TAMs or combined treatment with zidovudine prevents the emergence of K65R in the presence of tenofovir.34,35

m. The sequential use of nevirapine and efavirenz (in either order) is not recommended because of cross-resistance between these drugs.36

n. Resistance to etravirine has been extensively studied only in the context of coadministration with darunavir/ritonavir. In this context, mutations associated with virologic outcome have been assessed and their relative weights (or magnitudes of impact) assigned. In addition, phenotypic cutoff values have been calculated, and assessment of genotype-phenotype correlations from a large clinical database have determined relative importance of the various mutations. These 2 approaches are in agreement for many, but not all, mutations and weights.37-40 The single mutations Y181C/I/V, K101P, and L100I reduce but do not preclude clinical utility. The presence of K103N alone does not affect etravirine response.41 Accumulation of several mutations results in greater reductions in susceptibility and virologic response than do single mutations.42,43

o. Often, numerous mutations are necessary to substantially impact virologic response to a ritonavir-boosted protease inhibitor (PI).44 In some specific circumstances, atazanavir might be used unboosted. In such cases, the mutations that are selected are the same as with ritonavir-boosted atazanavir, but the relative frequency of mutations may differ.

p. Resistance mutations in the protease gene are classified as “major” or “minor.” Major mutations in the protease gene are defined as those selected first in the presence of the drug or those substantially reducing drug susceptibility. 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 substantial effect on phenotype. They may improve replication of viruses containing major mutations. Some minor mutations are present as common polymorphic changes in HIV-1 nonsubtype-B clades.

q. Ritonavir is not listed separately, as it is currently used only at low dose as a pharmacologic booster of other PIs.

r. Many mutations are associated with atazanavir resistance. Their impacts differ, with I50L, I84V, and N88S having the greatest effect. Higher atazanavir levels obtained with ritonavir boosting increase the number of mutations required for loss of activity. The presence of M46I plus L76V might increase susceptibility to atazanavir.45

s. HIV-1 RNA response to ritonavir-boosted darunavir correlates with baseline susceptibility and the presence of several specific PI mutations. Reductions in response are associated with increasing numbers of the mutations indicated in the figure bar. The negative impact of the protease mutations I47V, I54M, T74F, and I84V and the positive impact of the protease mutation V82A on virologic response to darunavir/ritonavir were shown in...
2 data sets independently. Some of these mutations appear to have a greater effect on susceptibility than others (eg, I50V vs V11I). A median darunavir phenotypic fold-change greater than 10 (low clinical cutoff) occurs with 3 or more of the 2007 IAS–USA mutations listed for darunavir and is associated with a diminished virologic response.

The mutations depicted on the figure bar cannot be considered comprehensive because little relevant research has been reported in recent years to update the resistance and cross-resistance patterns for this drug.

In PI-experienced patients, the accumulation of 6 or more of the mutations indicated on the figure bar is associated with a reduced virologic response to lopinavir/ritonavir. The product information states that accumulation of 7 or 8 mutations confers resistance to the drug. However, there is emerging evidence that specific mutations, most notably I47A (and possibly I47V) and V32I, are associated with high-level resistance. The addition of L76V to PI resistance–associated mutations substantially increases resistance to lopinavir/ritonavir.

In some nonsubtype-B HIV-1, D30N is selected less frequently than are other PI mutations.

Clinical correlates of resistance to tipranavir are limited by the paucity of clinical trials and observational studies of the drug. Lists of mutations associated with accumulating resistance have been presented, with some conflicting results. In vitro studies and initial analysis of clinical data show mutations L33F, V82I, and I84V as having substantial contributions. Confirmatory studies are pending. A number of mutations (L24I, I50L/V, I54L, and L76V) are associated with decreased resistance in vitro and improved short-term virologic response if 2 or more are present.

Resistance to enfuvirtide is associated primarily with mutations in the first heptad repeat (HR1) region of the gp41 envelope gene. However, mutations or polymorphisms in other regions of the envelope (eg, the HR2 region or those yet to be identified) as well as coreceptor usage and density may affect susceptibility to enfuvirtide.

The activity of CC chemokine receptor 5 (CCR5) antagonists is limited to patients with virus that uses only CCR5 for entry (R5 virus). Viruses that use both CCR5 and CXCR4 chemokine receptor 4 (CXCR4; termed dual/mixed (D/M) or only CXCR4 (X4 virus) do not respond to treatment with CCR5 antagonists.

Virologic failure of these drugs frequently is associated with outgrowth of D/M or X4 virus from a preexisting minority population present at levels below the limit of assay detection. Mutations in HIV-1 gp120 that allow the virus to bind to the drug-bound form of CCR5 have been described in viruses from some patients whose virus remained R5 after virologic failure of a CCR5 antagonist. Most of these mutations are found in the V3 loop, the major determinant of viral tropism. There is as yet no consensus on specific signature mutations for CCR5 antagonist resistance, so they are not depicted in the figure. Some CCR5 antagonist-resistant viruses selected in vitro have shown mutations in gp41 without mutations in V3, the clinical significance of such mutations is not yet known.

Railegravir failure is associated with integrase mutations in at least 3 distinct genetic pathways defined by 2 or more mutations including (1) a signature (major) mutation at Q148H/R/K, N155H, or Y143R/H/C; and (2) 1 or more additional minor mutations. Minor mutations described in the Q148H/K/R pathway include L74M plus E138A, E138K, or G140S. The most common mutualional pattern in this pathway is Q148H plus G140S, which also confers the greatest loss of drug susceptibility. Mutations described in the N155H pathway include this major mutation plus either L74M, E92Q, T97A, E92Q plus T97A, Y143H, G163K/R, V151I, or D232N. The Y143R/H/C mutation is uncommon.

The mutations depicted on the figure bar are present.

References to the User Notes


50. Masquelier B,Breilh D, Neau D, et al. Human immunodeficiency virus type 1 geno- typic and pharmacokinetic determinants of


**Perspective**

**Antiretroviral Therapy: New Drugs, Formulations, Ideas, and Strategies**

There is a continuing need for new antiretroviral drugs and formulations and updated strategies for using new and established drugs. Strategies being investigated for expanding initial treatment options include use of rilpivirine, raltegravir, or maraviroc as an alternative to efavirenz, use of pharmacokinetics enhancers without anti-HIV activity as an alternative to ritonavir as a boosting agent, and use of regimens sparing nucleoside analogue reverse transcriptase inhibitors, including ritonavir-boosted (r) lopinavir plus raltegravir; darunavir/r plus raltegravir; vicriviroc plus atazanavir/r; and unboosted atazanavir plus raltegravir. For patients receiving fully suppressive regimens, strategies such as switching from lopinavir/r to raltegravir and from enfuvirtide to raltegravir have been examined. In highly treatment-experienced patients, use of 3 new active drugs has been found to be successful in suppressing virus. This article summarizes a presentation made by Joseph J. Eron, Jr, MD, at the International AIDS Society–USA continuing medical education program in Chicago in May 2009. The original presentation is available as a Webcast at www.iasusa.org.

New antiretroviral drugs and formulations and new strategies for using available drugs are continually needed. Because no new drugs are expected to be available in the near future from new classes of antiretroviral drugs, advances in treatment will come from strategies using new or available drugs in established classes. For treatment-naive patients, the need is for well-tolerated, highly active, and convenient antiretroviral therapy for all individuals requiring treatment, including women of child-bearing potential, individuals with tuberculosis or other complex medical or psychiatric conditions, and patients with transmitted drug-resistant virus, among others. Expanded treatment options will also become increasingly important as more is learned about long-term toxic effects of existing drugs and regimens. For treatment-experienced patients, new drugs and strategies are needed to expand treatment choices, avoid complex regimens and drugs with substantial toxic effects, and improve the ability to achieve full suppression of HIV replication in highly treatment-experienced patients and others with drug-resistant virus.

**Strategies in Treatment-Naive Patients**

For initial treatment, options may be expanded by identifying alternatives to the fixed-dose combination of efavirenz/tenofovir/emtricitabine, to the use of ritonavir to boost protease inhibitors (PIs), and to the use of nucleoside analogue reverse transcriptase inhibitors (nRTIs). Among drugs used in initial or second-line treatment, ritonavir and efavirenz are 2 sources of difficulty in terms of tolerability, drug-drug interactions or limitations in certain patient groups (eg, for efavirenz, women of child-bearing potential who are considering pregnancy). The nRTIs remain a mainstay in initial regimens, but options have dwindled as the long-term toxic effects of these drugs have become more apparent.

**Alternatives to Efavirenz**

**Rilpivirine.** A recent phase IIb trial compared the second-generation investigational nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) rilpivirine (TMC278) with efavirenz, each plus 2 nRTIs in treatment-naive patients with plasma HIV RNA levels of at least 5000 copies/mL (Santoscoy et al, IAC, 2008). At 96 weeks, rates of virologic response (plasma HIV RNA level < 50 copies/mL) were 71% to 76% with rilpivirine 25 mg daily (n = 93), 75 mg daily (n = 95), or 150 mg daily (n = 91) and 71% with efavirenz (n = 89).

The overall incidence of adverse events was similar in the rilpivirine and efavirenz groups, with efavirenz associated with a higher incidence of rash (21% vs 9%, respectively; P < .01), nervous system disorders (48% vs 31%; P < .01), and neuropsychiatric disorders (21% vs 16%). The corrected QT interval (QTc) increased in all study groups through week 48 and then plateaued. QTc prolongation was smallest with the rilpivirine 25 mg daily dose, the dose selected for study in phase III trials. NNRTI resistance-associated mutations emerged at similar rates with rilpivirine and efavirenz, though the most common resistance mutations that emerge during rilpivirine therapy have not yet been described.

Rilpivirine 25 mg daily is being evaluated in 2 parallel, 48-week phase III trials: the ECHO (Efficacy Comparison in Treatment-Naive HIV-Infected Subjects of TMC278 and Efavirenz) trial, comparing rilpivirine versus efavirenz with tenofovir/emtricitabine; and the THRIVE (TMC278 Against HIV, in a Once-Daily Regimen Versus Efavirenz) trial, comparing rilpivirine versus efavirenz with investigator-chosen tenofovir/emtricitabine, abacavir/lamivudine, or zidovudine/lamivudine. Both trials have a target population of 680 patients and are fully enrolled.

**Raltegravir.** In the STARTMRK trial comparing the integrase inhibitor raltegravir with efavirenz, each plus tenofovir/emtricitabine, virologic response...
...suggesting there were no substantial concerns in this lead cohort.

**Maraviroc.** Patients are more likely to have CC chemokine receptor 5 (CCR5)-tropic virus in early infection. The MERIT (Maraviroc Versus Efavirenz Regimens as Initial Therapy) trial compared the CCR5 inhibitor maraviroc with efavirenz, each with 24 weeks of tenofovir/efavirenz. Maraviroc twice daily was associated with a poorer virologic response rate than efavirenz. At the time of the trial, minority variants in patients’ viral population could be detected only down to a threshold of approximately 10%. A new phenotypic tropism assay now permits detection of CXCR4-CXC che-

Figure 1. Proportions of patients achieving plasma HIV RNA level below 50 copies/mL in STARTMRK trial comparing raltegravir twice daily versus efavirenz plus tenofovir/emtricitabine. Adapted from Lennox et al, *Lancet*, 2009.

2 arms in the subgroups with baseline HIV RNA level of 100,000 copies/mL or below and with baseline HIV RNA level above 100,000 copies/mL (Saag et al, ICAAC/IDSA, 2008). Another comparative trial using the enhanced tropism assay may be needed to clarify the efficacy of maraviroc versus efavirenz in this setting.

**Alternatives to Ritonavir**

Pharmacokinetic enhancers without anti-HIV activity. Several drugs that can enhance the pharmacokinetics of antiretroviral drugs without exerting anti-HIV effects are currently being developed. As noted, ritonavir use as a PI booster is associated with poor tolerability in some patients, extensive drug-drug interactions, and substantial effects on lipid metabolism. Ritonavir has been used primarily to boost other PIs, but it can also boost drugs in other classes such as the investigational agents elvitegravir (an integrase inhibitor) and vicriviroc (a CCR5 inhibitor). In clinical studies other than short-term proof-of-principle studies, regulatory agencies have preferred that low-dose ritonavir be used in regimens that contain a PI even if elvitegravir, for example, is also being used and boosted. The logic behind this preference is to avoid low-dose PI exposure (with ritonavir) in a non-PI-based regimen. Further, although ritonavir exerts its boosting activity by inhibiting the cytochrome P450 (CYP) 3A4 enzyme, it also inhibits other CYP isoenzymes and is an inducer of several liver enzymes, yielding complicated pharmacokinetic interactions with other drugs.

Among the pharmacokinetic enhancers currently under development is GS-9350, a drug with no anti-HIV activity that is being investigated in combination with the integrase inhibitor elvitegravir and with the PI atazanavir. GS-9350 exhibits potent inhibition of CYP3A similar in magnitude to that observed with ritonavir, has minimal inductive effects on CYP3A, and has less effect on other CYP enzymes than ritonavir. It also appears to have a lower potential for causing lipid abnor-
Adapted from data presented by Mathias et al, CROI, 2009.

AUC<sub>tau</sub> indicates area under concentration curve at end of dosing interval (1 dose in 24 h); given at 25 mg, 50 mg, or 200 mg in-concept study showed that SPI-452 anti-HIV activity. A proof-of-clinical-concept from pretreatment of 92% at 50 mg and 95% at 200 mg, compared with 95% with ritonavir; Mathias et al, CROI, 2009). Assessment of fixed-dose combinations of 100 mg and 150 mg GS-9350 with elvitegravir showed boosting of elvitegravir similar to that with ritonavir 100 mg (Table 1). The 150-mg GS-9350 dose resulted in higher trough concentrations of elvitegravir (11-fold higher than the protein-binding adjusted elvitegravir 95% inhibitory concentration), with low within-subject variability (15% coefficient of variation). A phase II study called the Quad study currently is evaluating a fixed-dose combination of GS-9350-boosted elvitegravir/tenofovir/emtricitabine compared with fixed-dose efavirenz/tenofovir/emtricitabine, and studies comparing ritonavir-boosted atazanavir with GS-9350-boosted atazanavir are ongoing.

SPI-452 is another investigational pharmacokinetic enhancer without anti-HIV activity. A proof-of-clinical-concept study showed that SPI-452 given at 25 mg, 50 mg, or 200 mg increased exposure to darunavir and to atazanavir after 2 weeks of coadministration (Gulnik et al, CROI, 2009).

### Alternatives to Nucleoside Analogue Reverse Transcriptase Inhibitors

A number of alternatives to nRTIs in initial regimens are being examined. An open-label study comparing lopinavir/r plus ritonavir versus lopinavir/r plus tenofovir/emtricitabine is under way. The combination of darunavir/r plus ritonavir as an alternative to nRTI-containing regimens for initial therapy is being examined in an ACTG (AIDS Clinical Trials Group) single-arm pilot study and a small comparative trial; a large-scale study is being planned in Europe. The combination of the CCR5 inhibitor vicriviroc 30 mg daily plus atazanavir/r 500 mg/100 mg daily is being compared with atazanavir/r plus tenofovir/emtricitabine in a phase II randomized, open-label trial in treatment-naive patients with CCR5-tropic virus and a CD4+ count of at least 200 cells/µL.

Other studies are examining use of twice-daily, unboosted atazanavir plus ritonavir. In a pharmacokinetic study in healthy volunteers, coadministration of atazanavir 500 mg twice daily and ritonavir 400 mg given twice daily increased atazanavir exposure and increased ritonavir exposure (Zhu et al, CROI, 2009). For atazanavir (based on geometric mean values), maximum concentration (C<sub>max</sub>) was reduced by 11%, area under the concentration-time curve for 48 hours to 12 hours (AUC<sub>0-12h</sub>) was reduced by 17%, and minimum concentration (C<sub>min</sub>) was reduced by 29%. For ritonavir, increases were 59% for C<sub>max</sub>, 54% for AUC<sub>0-12h</sub>, and 48% for C<sub>min</sub> (Zhu et al, CROI, 2009). The atazanavir C<sub>min</sub> value (817 ng/mL) with twice-daily dosing of the combination was similar to the trough atazanavir concentration observed with atazanavir/r (300 mg/100 mg) once daily in HIV patients (although healthy volunteers do achieve higher atazanavir levels than HIV patients). The combination of atazanavir 300 mg plus ritonavir 400 mg, given twice daily, currently is being compared with atazanavir/r plus tenofovir/emtricitabine in a phase II randomized, open-label study in treatment-naive patients.

### Switching Therapy in Suppressed Patients

Goals for switching therapy in patients with viral suppression include simplifying regimens, reducing toxic effects, and improving tolerability; reducing cost would be good, too.

### Switching from Lopinavir/Ritonavir to Raltegravir

The SWITCHMRK 1 (protocol 032) and 2 (protocol 033) studies were identical randomized, double-blind studies, conducted in different areas of the world (patients from North America and Australia were included in both studies). These studies examined the lipid effects, virologic effects, and safety and tolerability profiles associated with switching from lopinavir/r to raltegravir in patients on stable treatment with a lopinavir/r twice-daily regimen plus at least 2 nRTIs and no additional PIs for at least 3 months. In both trials, patients were randomly assigned to switch to raltegravir (n = 174 in protocol 032; n = 176 in protocol 033) or continue treatment with lopinavir/r (n = 174 in protocol 032; n = 178 in protocol 033) while maintaining background therapy. Patients were required to have had a plasma HIV RNA level below 50 copies/mL by polymerase chain reaction assay or 75 copies/mL by branch DNA assay and no lipid-lowering therapy for at least 12 weeks before study entry.

<table>
<thead>
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<th>Variable (units)</th>
<th>Mean Elvitegravir Exposure With:</th>
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<tr>
<td></td>
<td>GS-9350, 100 mg</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;tau&lt;/sub&gt; (ng·h/mL)</td>
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<tr>
<td>C&lt;sub&gt;tau&lt;/sub&gt; (ng/mL)</td>
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</tr>
</tbody>
</table>

Adapted from data presented by Mathias et al, CROI, 2009.

AUC<sub>tau</sub> indicates area under concentration curve at end of dosing interval (1 dose in 24 h); C<sub>max</sub>, maximum concentration; C<sub>tau</sub>, minimum concentration after 24h.
Study participants were not required to be intolerant of lopinavir/r; those with prior virologic failure with other antiretroviral regimens were not excluded; and there was no limit on the number of prior regimens (Eron et al, CROI, 2009).

Primary endpoints included changes in lipid levels at 12 weeks and proportions of patients with a viral load below 50 copies/mL at 24 weeks. More than 80% of patients in each group in both studies had been taking lopinavir/r for more than 1 year. The median durations of prior antiretroviral therapy were 3.3 years to 4.6 years across the 4 treatment groups. Minimum durations of treatment ranged from 0.3 years to 0.6 years and maximum from 16.3 years to 22.3 years; median numbers of prior antiretroviral drugs taken were 5 or 6, with maximum numbers of 13 to 16. This wide heterogeneity in prior exposure to treatment makes findings on the virologic effect of switching to raltegravir from stable lopinavir/r somewhat difficult to interpret.

As shown in Figure 2, switching to raltegravir was associated with a pronounced reduction in triglyceride levels (median, 41% to 43% reduction from baseline) at 12 weeks, along with statistically significant reductions in levels of total cholesterol and non-high-density lipoprotein cholesterol compared with continued treatment with lopinavir/r. At 24 weeks, however, virologic response rates (noncompleter = failure analysis) were lower in the raltegravir groups in both protocol 032 (81% vs 87%, respectively) and protocol 033 (88% vs 94%, respectively). Confirmed virologic failure (requiring confirmation of viral rebound by measurements taken at least 1 week apart, with plasma HIV RNA level above 400 copies/mL) occurred in 3 raltegravir patients versus 2 lopinavir/r patients in protocol 032 and in 9 versus 2 patients, respectively, in protocol 033, with failure at greater than 50 copies/mL occurring in 13 versus 10 patients, respectively, and 19 versus 7 patients, respectively.

A post hoc analysis showed that the regimen at entry to the study was not the first antiretroviral regimen in 27 (84%) of the 32 raltegravir patients with virologic failure; among these 27 patients, 18 (66%) reported a history of virologic failure with a prior regimen. Study of resistance mutations in 9 raltegravir patients with virologic failure to greater than 400 copies/mL in protocol 033 showed raltegravir resistance mutations in 7. Analysis of the findings in the SWITCHMRK studies is ongoing; despite the lipid benefits observed with the switch, there is clearly concern over the loss of virologic control in a substantial subgroup of patients switched to raltegravir and the emergence of resistance mutations in cases of virologic failure.

**Switching from Enfuvirtide to Raltegravir**

Use of the fusion inhibitor enfuvirtide requires twice-daily subcutaneous injection. The EASIER (Efficacy and Tolerance of the Switch From Enfuvirtide to Raltegravir in Antiretroviral Therapy Regimen in Patients With Undetectable Viral Load; ANRS 138) trial compared the substitution of raltegravir (n = 85) with remaining on enfuvirtide (n = 85) in patients with triple-class-resistant virus or enfuvirtide intolerance who had a plasma HIV RNA level below 400 copies/mL for at least 3 months on a stable enfuvirtide-containing regimen. After the primary analysis at week 24, patients in the enfuvirtide group were switched to raltegravir for the remainder of the 48-week study. The mean duration of enfuvirtide use was 2.3 years.

The findings at 24 weeks indicate that switching does not result in loss of virologic control. At baseline, HIV RNA level was less than 50 copies/mL in 88% of the enfuvirtide group and 85% of the raltegravir group; at week 24, suppression to less than 50 copies/mL was achieved in 89% and 88%, respec-
Three-Active-Drug Postfailure Regimens

The phase II TRIO (Efficacy of Darunavir/Ritonavir, Etravirine, and Raltegravir in HIV Patients With Resistance Viruses; ANRS 139) study provided evidence that a regimen of 3 active drugs could suppress virus in highly treatment-experienced patients. The combination of darunavir/r, etravirine, and raltegravir was given to 103 patients with 3 or fewer darunavir resistance-associated mutations and 3 or fewer etravirine resistance-associated mutations; 59% of patients had no active drugs in optimized background therapy on genotypic analysis. Enfuvirtide or NRTIs could be used at physician discretion. At week 24, 90% of patients (95% confidence interval, 85% to 96%) had HIV RNA levels below 50 copies/mL, and the median increase in CD4+ cell count was 99/µL (interquartile range, 32 to 147/µL) (Yazdanpanah et al, IAC, 2008). Of 10 patients with detectable virus at week 24, only 3 had HIV RNA levels above 400 copies/mL. Two possibly drug-related grade 4 adverse events were reported, with 1 leading to treatment discontinuation.

Suggested Reading


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Review

HIV–Associated Resources on the Internet

Wendy S. Armstrong, MD, and Carlos del Río, MD

The Internet provides easy, widespread access to new developments in the field of medicine. The pace of HIV-related research is rapid and has global relevance, making the Internet a particularly well-suited technology for dissemination of information. The number of sites offering HIV-related information is vast, and the quality is variable. Nevertheless, access to reliable information can be a highly efficient method to acquire up-to-date knowledge about advances in HIV investigation. This review summarizes high-quality HIV-related Web sites, including sites that provide access to HIV-related guidelines, conferences with Web content, images, case studies, and clinical and scientific databases. Also included are HIV-related reference sites, Web sites for journals that publish regularly on HIV- and AIDS-related advances and epidemiology, and policy-oriented sites. In addition, Web sites with materials for patient information and advocacy and specialty societies for HIV practitioners are listed.

In the 25 years since the first descriptions of AIDS, there has been an explosion of scientific discovery; clinical, social, and behavioral research; epidemiologic investigation; and community organization associated with the HIV infection. The pace of discovery and number of ongoing projects and clinical trials exceed the capacity of the HIV practitioner to remain current in all aspects of HIV investigation. Parallel with the HIV epidemic has been the emergence of the Internet and the World Wide Web as crucial resources to help manage and access information for researchers, clinicians, epidemiologists, members of the allied health services, patients, and others.

The total number of Web sites dedicated to HIV-related issues is staggering. In 2000, Shafer and Deresinski1 published an early guide to Internet resources for HIV disease. Almost a decade later, some of the sites they mentioned remain highly relevant, and new ones have been developed. Sheer numbers prevent listing all high-quality HIV-associated Web sites, but this article describes some of the most utilized sites across a variety of related subject areas. Although several important international sites are included, the focus is on those in English.

Search Methods

A search using 2 standard Internet search engines (Google, Yahoo) yielded 65.6 × 10^6 and 279 × 10^6 visits, respectively, for the search term “HIV” and 122 × 10^6 and 501 × 10^6 visits, respectively, for the search term “AIDS.” Of these, Web sites included in this compilation were identified from (1) personal knowledge or experience, (2) personal communication with experts in various aspects of HIV disease or AIDS, (3) Web links from other recognized Internet sites, and (4) articles identified after a MEDLINE search for “Internet” and “HIV” or “AIDS.” Web sites were assessed for ease of use, presence of up-to-date information (unless otherwise noted), and quality of overall content.

In addition, the quality criteria set forth by Silberg and colleagues2 were assessed. These criteria describe standards to be applied to Web sites and include (1) identification of authors and their affiliations and credentials, (2) a listing of content sources with copyright information, (3) identification of dates content was posted, and (4) disclosure of Web site ownership, sponsorship, advertising, underwriting or commercial funding arrangements. Most sites included are affiliated with an academic institution, governmental organization, nonprofit organization, or commercial entity, and the majority focus exclusively on HIV- and AIDS-related issues.

Results

Web Sites for HIV-Related Guidelines

Table 1 lists Web sites with the most commonly referenced guidelines for testing and treatment of HIV infection and AIDS. The AIDSinfo Web site is sponsored by the US Department of Health and Human Services (DHHS). On the site, the current treatment guidelines developed by working groups convened by the US Office of AIDS Research Advisory Council are posted in Portable Document Format (PDF) and Personal Digital Assistant (PDA) versions. The most recent revisions of these documents are readily available. These include the (1) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, (2) Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, and (3) Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.

In addition, guidelines are available for management of occupational and nonoccupational exposure to HIV and...
recommendations for postexposure prophylaxis, as are guidelines for counseling, testing, and referral and for the prevention and treatment of opportunistic infections. Many of these were originally published in journals or the Morbidity and Mortality Weekly Report (MMWR). The site also includes links to fact sheets on other aspects of HIV disease, drug information, and listings of clinical trials including those pertinent to research on HIV vaccines.

Treatment and resistance testing guidelines developed by the International AIDS Society–USA (IAS–USA) are available on the IAS–USA Web site, along with additional content described below. The British HIV Association, the European AIDS Clinical Society, and the World Health Organization (WHO) also have guidelines available at the corresponding Web sites for these organizations.

A variety of other management guidelines for HIV-associated conditions are also available online. For example, the Infectious Diseases Society of America (IDSA) has published recommendations for primary care of HIV-infected patients and the management of chronic kidney disease and dyslipidemia. The British HIV Association has guidelines that address transplantation in patients with HIV disease, HIV and tuberculosis coinfection, and other conditions, and the European AIDS Clinical Society also publishes guidelines regarding hepatitis B virus and hepatitis C virus coinfections and metabolic diseases associated with HIV infection. Many of these documents are available in languages other than English.

**Web Sites Providing HIV-Related References**

Electronic media provide a convenient method of maintaining up-to-date reference material, which is particularly important in specialties for which the pace of new investigation is rapid such as in the HIV medicine field. Table 2 lists Web sites with reference material related to HIV and AIDS in general and to specific HIV-associated issues. The HIV InSite Web site, sponsored by the University of California San Francisco, offers a wide array of reference material, in addition to the HIV InSite Knowledge Base. The Knowledge Base is a comprehensive online textbook on HIV disease posted as a series of more than 100 chapters written by content experts and individually updated periodically. The topics are broad

### Table 1. Selected Web Sites Providing HIV-Related Clinical Guidelines

<table>
<thead>
<tr>
<th>Title of Web Site, in Alphabetical Order</th>
<th>Uniform Resource Locator</th>
<th>Source or Sponsor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guidelines Published in the United States</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDSinfo</td>
<td><a href="http://www.aidsinfo.nih.gov">http://www.aidsinfo.nih.gov</a></td>
<td>US Department of Health and Human Services (DHHS)</td>
<td>Links to guidelines, including treatment (adult, pediatric, perinatal), postexposure prophylaxis, opportunistic infections, testing</td>
</tr>
<tr>
<td>US Health Resources and Services Administration</td>
<td><a href="http://hab.hrsa.gov/publications.htm">http://hab.hrsa.gov/publications.htm</a></td>
<td>DHHS</td>
<td>Guidelines and protocols for HIV primary care, hepatitis C virus and HIV coinfection, others</td>
</tr>
<tr>
<td><strong>Guidelines Published Outside the United States</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>British HIV Association</td>
<td><a href="http://www.bhiva.org">http://www.bhiva.org</a> <a href="http://www.bhiva.org/cms1191540.asp">http://www.bhiva.org/cms1191540.asp</a></td>
<td>British HIV Association</td>
<td>Links to several guidelines for treatment, opportunistic infections, transplantation, others</td>
</tr>
</tbody>
</table>
and include sections on HIV pathogenesis, diagnosis, clinical management, opportunistic infections, transmission, prevention, and policy. Although many chapters are currently in need of updating, the Knowledge Base remains a valuable and high-quality source of information. HIV InSite also lists news developments and links to sites with clinical tools or additional information on treatment, prevention, and policy.

The Johns Hopkins (University) HIV Point-of-Care Information Technology (POC-IT) Center is home to the HIV Guide, which offers short bullets on a broad array of issues in HIV care. The manual Medical Management of HIV Infection by Bartlett and Gallant can be purchased as of December 2009 at this site (http://www.hopkins-aids.edu/publications/main/medical_management_of_hiv_infection/medical_management_of_hiv_infection.html?contentInstanceId=50315&siteId=). The Centers for Disease Control and Prevention (CDC) Web site has many links to guidelines and information for HIV care practitioners. It also offers access to the MMWR and the MMWR Recommendations and Reports.

Medscape HIV/AIDS, Clinical Care Options (CCO)-HIV, and The Body Pro are commercial Web sites supported by advertising fees and grants from commercial pharmaceutical and laboratory testing companies. The sites provide conference summaries and access to current published data along with expert commentary. CCO also provides sum-

<table>
<thead>
<tr>
<th>Table 2. Selected Web Sites Providing HIV-Related Literature Citations and Other Educational Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title of Web Site, in Alphabetical Order</strong></td>
</tr>
<tr>
<td><strong>General Sites</strong></td>
</tr>
<tr>
<td>Centers for Disease Control and Prevention HIV/AIDS</td>
</tr>
<tr>
<td>Clinical Care Options HIV</td>
</tr>
<tr>
<td>HIV InSite</td>
</tr>
<tr>
<td>HIV Medicine</td>
</tr>
<tr>
<td>Johns Hopkins Point-of-Care Information Technology (POC-IT) Center</td>
</tr>
<tr>
<td>Medical Matrix</td>
</tr>
<tr>
<td>Medscape HIV/AIDS</td>
</tr>
<tr>
<td>Pathology of AIDS</td>
</tr>
<tr>
<td>The Body Pro</td>
</tr>
</tbody>
</table>

(Continued on next page)
marieties of recent abstracts and selected studies and an annual HIV update.

Additional general references available online include 2 HIV textbooks reproduced in full (Pathology of AIDS and HIV Medicine). Training and education materials can be found at the AIDS Education and Training Centers (AETCs) Web site. The AETCs are regional organizations funded by the Health Resources and Services Administration (HRSA, part of the US DHHS), dedicated to providing multidisciplinary educational programs to train HIV care practitioners.

Several reference Web sites focus on specialized aspects of HIV and AIDS care. The Stanford University HIV Drug Resistance Database is an up-to-date, high-quality Web site that serves as a valuable resource for information on HIV drug resistance. The site is extensively referenced and has an easy-to-use interface permitting entry of individual resistance profiles for interpretation. Additional Web-based resources for resistance interpretation are well reviewed by Liu and Shafer and include the resistance algorithms developed by the French National Agency for Research on AIDS and Viral Hepatitis (ANRS).

Sponsored by the University of Liverpool, the HIV Drug Interactions Web site is also a key resource for the HIV practitioner. Practitioners can request individualized interaction data between antiretroviral drugs and other medications, including other antiretroviral drugs. The resultant reports give extensive information about the importance of the specific interaction(s) and any necessary dose adjustments. In addition, interaction charts for each antiretroviral drug class are available for downloading. Specific information on drugs can always be found at the manufacturer’s site as well as at aidsinfo.nih.gov.

The Web site HIVandHepatitis.com focuses on new developments in patients infected with HIV, hepatitis B virus, or hepatitis C virus, particularly, in those with hepatitis and HIV coinfection. Management guidelines and conference coverage are available in addition to continuing medical education (CME) programs.

The Solid Organ Transplantation in HIV multicenter study funded by the National Institute of Allergy and Infectious Diseases (NIAID) maintains a Web site accessible to patients and practitioners. The study protocol is available on the site, as is a listing of NIAID-participating study centers and links to publications from the study. Finally, the federally funded National HIV/AIDS Clinicians’ Consultation Center (NCCC), sponsored by the Universi-
### Table 3. Selected Web Sites of HIV-Related Scientific Conferences

<table>
<thead>
<tr>
<th>Title of Conference Web Site, in Alphabetical Order</th>
<th>Uniform Resource Locator</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conference on Retroviruses and Opportunistic Infections (annual)</td>
<td><a href="http://www.retroconference.org">http://www.retroconference.org</a></td>
<td>Free access to Webcasts, posters, searchable abstracts; links to previous conferences</td>
</tr>
<tr>
<td>International AIDS Conference (even years)</td>
<td><a href="http://www.aids2010.org/">http://www.aids2010.org/</a></td>
<td>Free abstracts; some Webcasts and Podcasts of presentations</td>
</tr>
<tr>
<td>International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (odd years)</td>
<td><a href="http://www.ias2009.org/">http://www.ias2009.org/</a></td>
<td>Free Webcasts, abstracts</td>
</tr>
<tr>
<td>Interscience Conference on Antimicrobial Agents and Chemotherapy (annual)</td>
<td><a href="http://www.icaac.org/">http://www.icaac.org/</a></td>
<td>Sponsored by American Society for Microbiology; digital recordings available for purchase, free searchable posters for attendees</td>
</tr>
</tbody>
</table>

Web Sites for HIV-Related Conferences

Worldwide, many conferences are dedicated to research in HIV medicine (Table 3). Several sites provide conference material electronically. The Conference on Retroviruses and Opportunistic Infections (CROI) has been held annually since 1994. Nearly the entire oral content and all of the abstracts are available almost immediately on the CROI Web site and have been for several years. The International AIDS Conference first convened in 1985 and has been held biennially in even years since 1994. In recent years, much of the content of the conference, including Webcasts and abstracts, is available online. In addition, the biennial International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment, and Prevention (held in odd years beginning in 2001), the International HIV Drug Resistance Workshop, and the International Workshop on Adverse Drug Reactions and Co-Morbidities in HIV provide substantial amounts of conference material online.

**Web Sites With Images and Case Studies**

Several Web sites have an array of images available to upload for teaching purposes (Table 4). Among the best is the AIDS Images Library sponsored by Geneva University Hospital and maintained by HIV expert Bernard Hirschel. With more than 1000 images of manifestations of HIV-associated comorbidities, the site is an outstanding resource, and the images can be uploaded into a PowerPoint presentation. Registration is required, but access to all material is free. The CDC-funded Public Health Image Library and the VA Image Library also have good collections. The Web site AIDS Imaging has not been updated in many years, but the images remain relevant. Finally, several dozen histopathologic images can be found on the Internet Pathology Library Webpath site highlighting common opportunistic infections.

Several Web sites have an extensive selection of case studies with interactive components. The University of Washington and the Northwest AETC have teamed together to produce more than 65 Web-based case studies addressing issues in HIV care including antiretroviral therapy, dermatologic and oral manifestations of HIV infection, opportunistic infections, and issues in special populations. The IAS–USA provides an interactive *Cases on the Web* series on its Web site, with a growing library of cases that provide CME credit. Clinical Care Options also has cases for study, all with interactive components and links to relevant studies in the discussion. New cases are added to each of these sites regularly.

**HIV-Related Journals**

Original HIV-related research is published in a broad array of journals. Although listing all of these journals and
their Web sites is beyond the scope of this article, several journals that specialize in HIV-related original research plus other important high-impact general medical journals that include original HIV and AIDS research are listed in Table 5. All except AIDS Research and Therapy require a subscription for full access to all content. Other journals that publish predominantly review articles include AIDS Clinical Care, which compiles short reviews with commentary on current research and Current Opinion in HIV and AIDS, a commercial venture that publishes review articles on current topics and controversies by experts and requires a subscription for access. The IAS–USA publishes Topics in HIV Medicine, which is available free on the IAS–USA Web site and includes an annual CROI review issue written by experts, summaries of expert presentations made at IAS–USA education courses, as well as guidelines articles and drug resistance mutations updates by IAS–USA panels.

HIV-Related Research Web Sites

Clinical Trials and Trial Networks. In the United States, the National Institutes of Health (NIH) sponsors a registry (ClinicalTrials.gov) that is a searchable, useful resource for clinical trials information. Online information regarding the 5 US HIV-related clinical trials networks funded by the NIAID through the Division of AIDS (DAIDS) is also available. A Web site serves each of these networks: the AIDS Clinical Trials Group (ACTG), the HIV Prevention Trials Network (HPTN), the HIV Vaccine Trials Network (HVTN), the Microbicide Trials Network (MTN), and the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) (Table 6). The sites provide information about ongoing trials, and the amount of password-restricted content varies by site. There are 20 NIH-funded Centers for AIDS Research (CFAR) throughout the United States dedicated to supporting multidisciplinary research efforts in HIV prevention, detection, and treatment. The core Web site has links to the institutional sites, which list affiliated investigators and describe supports available at each site. The American Foundation for AIDS Research (amfAR) is a not-for-profit organization dedicated to supporting HIV research and policy efforts. Its Web site has links to funding opportunities through the foundation.
Web sites for a few prominent internationally based clinical trials networks are also listed in Table 6. EuroSIDA, a prospective cohort of more than 16,000 patients, is among the largest cohorts in the world. EuroCoord coordinates cohorts across Europe including EuroSIDA. Sites for the British-based Medical Research Council, the Canadian HIV Trials Network, and the International AIDS Vaccine Initiative are also listed.

**Table 6. Selected Web Sites of Major Journals Specializing in or Including HIV-Related Content**

<table>
<thead>
<tr>
<th>Journal Title, in Alphabetical Order</th>
<th>Uniform Resource Locator</th>
<th>Publisher, Access</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV and Infectious Diseases Specialty Journals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td><a href="http://journals.lww.com/aidsonline/pages/default.aspx">http://journals.lww.com/aidsonline/pages/default.aspx</a></td>
<td>Lippincott Williams &amp; Wilkins; requires subscription for full access</td>
</tr>
<tr>
<td>AIDS Clinical Care</td>
<td><a href="http://aids-clinical-care.jwatch.org/">http://aids-clinical-care.jwatch.org/</a></td>
<td>Massachusetts Medical Society; requires subscription for full access</td>
</tr>
<tr>
<td>AIDS Research and Human Retroviruses</td>
<td><a href="http://www.liebertonline.com/loi/aid">http://www.liebertonline.com/loi/aid</a></td>
<td>Mary Ann Liebert, Inc; requires subscription for full access</td>
</tr>
<tr>
<td>AIDS Research and Therapy</td>
<td><a href="http://www.aidsrestherapy.com/">http://www.aidsrestherapy.com/</a></td>
<td>BioMed Central; open access</td>
</tr>
<tr>
<td>Antiviral Therapy</td>
<td><a href="http://www.intmedpress.com/index.cfm?pid=12">http://www.intmedpress.com/index.cfm?pid=12</a></td>
<td>International Medical Press; requires subscription for full access</td>
</tr>
<tr>
<td>Clinical Infectious Diseases</td>
<td><a href="http://www.journals.uchicago.edu/toc/cid/current">http://www.journals.uchicago.edu/toc/cid/current</a></td>
<td>University of Chicago Press; requires subscription for full access</td>
</tr>
<tr>
<td>Current Opinion in HIV and AIDS</td>
<td><a href="http://journals.lww.com/co-hivandaids/pages/default.aspx">http://journals.lww.com/co-hivandaids/pages/default.aspx</a></td>
<td>Lippincott Williams &amp; Wilkins; requires subscription for full access</td>
</tr>
<tr>
<td>Journal of Acquired Immune Deficiency Syndromes</td>
<td><a href="http://journals.lww.com/aids/pages/default.aspx">http://journals.lww.com/aids/pages/default.aspx</a></td>
<td>Lippincott Williams &amp; Wilkins; requires subscription for full access</td>
</tr>
<tr>
<td>Journal of Infectious Diseases</td>
<td><a href="http://www.journals.uchicago.edu/toc/jid/current">http://www.journals.uchicago.edu/toc/jid/current</a></td>
<td>University of Chicago Press; requires subscription for full access</td>
</tr>
<tr>
<td>Topics in HIV Medicine</td>
<td><a href="http://www.iasusa.org/pub/">http://www.iasusa.org/pub/</a></td>
<td>International AIDS Society–USA; open access</td>
</tr>
<tr>
<td><strong>General Medical Journals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annals of Internal Medicine</td>
<td><a href="http://www.annals.org/">http://www.annals.org/</a></td>
<td>American College of Physicians; requires subscription for full access</td>
</tr>
<tr>
<td>Journal of the American Medical Association</td>
<td><a href="http://jama.ama-assn.org/">http://jama.ama-assn.org/</a></td>
<td>American Medical Association; requires subscription for full access</td>
</tr>
<tr>
<td>Nature</td>
<td><a href="http://www.nature.com/">http://www.nature.com/</a></td>
<td>Nature Publishing Group; requires subscription for full access</td>
</tr>
<tr>
<td>New England Journal of Medicine</td>
<td><a href="http://content.nejm.org/">http://content.nejm.org/</a></td>
<td>Massachusetts Medical Society; requires subscription for full access</td>
</tr>
<tr>
<td>Science</td>
<td><a href="http://www.sciencemag.org">http://www.sciencemag.org</a></td>
<td>American Association for the Advancement of Science; requires subscription for full access</td>
</tr>
<tr>
<td>The Lancet</td>
<td><a href="http://www.thelancet.com/">http://www.thelancet.com/</a></td>
<td>Elsevier; requires subscription for full access</td>
</tr>
</tbody>
</table>

**Scientific Databases.** Several of the clinical trials network Web sites offer access to research databases generated from the clinical cohorts, including EuroSIDA and EuroCoord. In addition, several others offer access to information
Table 6. Selected Web Sites and Organizations Providing HIV-Related Clinical and Scientific Databases

<table>
<thead>
<tr>
<th>Title of Web Site, in Alphabetical Order</th>
<th>Uniform Resource Locator</th>
<th>Sponsor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Trials and Trial Networks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>United States–Based Sites</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS Clinical Trials Group (ACTG)</td>
<td><a href="http://www.aactg.org">http://www.aactg.org</a></td>
<td>National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), Department of Health and Human Services</td>
<td>ACTG information site, link to member site requires password to access information</td>
</tr>
<tr>
<td>Centers for AIDS Research (CFAR)</td>
<td><a href="http://www3.niaid.nih.gov/LabsAndResources/resources/cfar/">http://www3.niaid.nih.gov/LabsAndResources/resources/cfar/</a></td>
<td>NIH, NIAID</td>
<td>CFAR information site, with links to individual center’s Web sites</td>
</tr>
<tr>
<td>ClinicalTrials.gov</td>
<td><a href="http://www.clinicaltrials.gov">http://www.clinicaltrials.gov</a></td>
<td>NIH</td>
<td>Registry of federally funded and privately supported clinical trials</td>
</tr>
<tr>
<td>HIV Prevention Trials Network (HPTN)</td>
<td><a href="http://www.hptn.org/">http://www.hptn.org/</a></td>
<td>NIH, NIAID</td>
<td>HPTN information site</td>
</tr>
<tr>
<td>HIV Vaccine Trials Network (HVTN)</td>
<td><a href="http://www.hvtn.org/">http://www.hvtn.org/</a></td>
<td>NIH, NIAID</td>
<td>HVTN information site; access to trials data requires password</td>
</tr>
<tr>
<td>International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Group</td>
<td><a href="http://www.impaaactgroup.org/">http://www.impaaactgroup.org/</a></td>
<td>NIH, NIAID</td>
<td>Cooperative group focusing on advances in therapy for infants, children, adolescents, and pregnant women; portions of site password protected</td>
</tr>
<tr>
<td>International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)</td>
<td><a href="http://insight.ccbr.umn.edu/">http://insight.ccbr.umn.edu/</a></td>
<td>NIH, NIAID</td>
<td>INSIGHT information site for trials network organized to optimize treatment and prevention strategies globally; portions password protected</td>
</tr>
<tr>
<td>Microbicide Trials Network (MTN)</td>
<td><a href="http://www.mtnstopshiv.org/">http://www.mtnstopshiv.org/</a></td>
<td>NIH, NIAID</td>
<td>MTN site for trials to reduce sexual transmission of HIV with topical or oral agents; some portions of site password protected</td>
</tr>
<tr>
<td><strong>International-Based Sites</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canadian Institutes of Health Research Canadian HIV Trials Network</td>
<td><a href="http://www.hivnet.ubc.ca/e/home/">http://www.hivnet.ubc.ca/e/home/</a></td>
<td>Canadian Institutes of Health Research</td>
<td>Canadian HIV research network site, link to Canadian HIV Trials Database</td>
</tr>
<tr>
<td>EuroCoord</td>
<td><a href="http://www.eurocoord.net/">http://www.eurocoord.net/</a></td>
<td>European Coordinating Committee for the Integration of Ongoing Coordination Actions Related to Clinical and Epidemiological HIV Research</td>
<td>Integrates projects across partners including cohorts from EuroSIDA, Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE), Collaboration of Observational Epidemiological Research Europe (COHERE), and Paediatric European Network for Treatment of AIDS (PENTA), requires password for some portions</td>
</tr>
</tbody>
</table>

(Continued on next page)
Table 6. Selected Web Sites and Organizations Providing HIV-Related Clinical and Scientific Databases (cont’d)

<table>
<thead>
<tr>
<th>Title of Web Site, in Alphabetical Order</th>
<th>Uniform Resource Locator</th>
<th>Sponsor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EuroSIDA</td>
<td><a href="http://www.eurosida.org">http://www.eurosida.org</a></td>
<td>Copenhagen HIV Programme</td>
<td>Web site includes EuroSIDA prospective cohort of &gt; 16,000 patients in Europe, Israel, and Argentina</td>
</tr>
<tr>
<td>International AIDS Vaccine Initiative</td>
<td><a href="http://www.iavi.org/">http://www.iavi.org/</a></td>
<td>Various governmental grants, foundation grants, and corporate support</td>
<td>International consortium focused on scientific discovery, vaccine design, and clinical trials work</td>
</tr>
<tr>
<td>Medical Research Council of United Kingdom Clinical Trials Unit</td>
<td><a href="http://www.ctu.mrc.ac.uk/research_areas/hiv.aspx">http://www.ctu.mrc.ac.uk/research_areas/hiv.aspx</a></td>
<td>Medical Research Council</td>
<td>United Kingdom Clinical Trials Unit</td>
</tr>
<tr>
<td><strong>Scientific Database Sites</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV Databases</td>
<td><a href="http://www.hiv.lanl.gov/context/index">http://www.hiv.lanl.gov/context/index</a></td>
<td>Los Alamos National Laboratory</td>
<td>Sequence, Resistance, Immunology, Vaccine trials databases</td>
</tr>
<tr>
<td>HIV Structural Database and Chem-BLAST</td>
<td><a href="http://xpdb.nist.gov/hivsdb/hivsdb.html">http://xpdb.nist.gov/hivsdb/hivsdb.html</a></td>
<td>National Institute of Standards and Technology (NIST)</td>
<td>Chemical taxonomy-based search engine for HIV-related compounds, specifically designed to provide structure-based data</td>
</tr>
<tr>
<td>• Chem-BLAST tree</td>
<td><a href="http://bioinfo.nist.gov/SemanticWeb_pr3d/chemblast.do">http://bioinfo.nist.gov/SemanticWeb_pr3d/chemblast.do</a></td>
<td>National Institute of Standards and Technology (NIST)</td>
<td>See above</td>
</tr>
<tr>
<td>mation (NCBI)</td>
<td><a href="http://www.ncbi.nlm.nih.gov/sites/gquery">http://www.ncbi.nlm.nih.gov/sites/gquery</a> (Entrez page)</td>
<td></td>
<td>• Entrez is a cross-database search engine</td>
</tr>
<tr>
<td>NIAID Division of AIDS Resources for Re-</td>
<td><a href="http://www3.niaid.nih.gov/LabsAndResources/resources/default.htm">http://www3.niaid.nih.gov/LabsAndResources/resources/default.htm</a></td>
<td>NIAID</td>
<td>Link to numerous resources, tools, and databases for researchers, including following 3:</td>
</tr>
<tr>
<td>searchers</td>
<td><a href="http://chemdb2.niaid.nih.gov/struct_search/default.asp">http://chemdb2.niaid.nih.gov/struct_search/default.asp</a></td>
<td>NIAID, DAIDS</td>
<td>• Chemical, biological, and bibliographic database of compounds tested against HIV or opportunistic pathogens including TB</td>
</tr>
<tr>
<td>sis Database HIV-1</td>
<td><a href="http://www3.niaid.nih.gov/LabsAndResources/resources/reposit/">http://www3.niaid.nih.gov/LabsAndResources/resources/reposit/</a></td>
<td>NIAID</td>
<td>• Links to clinical trials networks and long-term epidemiologic studies with available specimens for further study including Multicenter AIDS Cohort Study (MACS), Women’s Interagency HIV Study (WIHS), others</td>
</tr>
</tbody>
</table>

at a molecular level (Table 6). The National Center for Biotechnology Information (NCBI), established in 1988 as a division of the National Library of Medicine (NLM), acts as a national and international resource for molecular biology and other information. Resources include the literature databases (PubMed and the linked databases AIDSLINE, AIDSDRUGS, and AIDSTRIALS), nucleotide databases (including GenBank and many others), protein sequence databases (including the Protein Data Bank and others), genome-specific resources, tools for data mining, sequence analysis and 3-dimensional structure display (including BLAST searching). The search engine Entrez provides cross-referencing among the numerous available databases.

Los Alamos National Laboratory (LANL) maintains the HIV Sequence Database, the HIV Molecular Immunology Database, the HIV Vaccine Trials Database, and the HIV Drug Resistance Database. The LANL’s HIV Sequence Database includes all HIV and sim-
ian immunodeficiency virus (SIV) sequences since 1987. This content can be accessed easily along with software for analysis. Annually, the LANL produces an HIV Sequence Compendium in printed form. The HIV Molecular Immunology Database of the LANL contains a searchable database of HIV-1 cytotoxic and helper T cell epitopes and antibody binding sites. Each of these databases can be accessed fully and freely through the LANL Web site.

The Stanford HIV Drug Resistance Database (Table 2) also maintains a database of HIV sequences linked to clinical and resistance data. At present, sequence data from close to 100,000 isolates are available, with more than 40,000 associated phenotypes. Another Web site, Resources for the Researcher, can be accessed through the NIAID Web site. This important source provides links to numerous resources such as the DAIDS Database for Anti-HIV Compounds (including chemical structure and biologic data), the DAIDS HIV/AIDS Specimen Repository, the DAIDS HIV/OI/TB (opportunistic infection/tuberculosis) Therapeutics Database and the NIAID HIV-1 Human Protein Interaction Database. This last database provides a summary of known interactions of HIV proteins with host cell proteins, other HIV proteins, and proteins from disease organisms associated with HIV and AIDS. Finally, the National Institute of Standards and Technology maintains a database of HIV-related compounds specifically with structure-based data and biologic data of interest for drug-design efforts. Data can be retrieved in several ways including through use of a taxonomic tree to assess related inhibitory compounds.

**Web Sites for Patient Information and Advocacy**

Hundreds of Web sites provide information directed toward individuals living with HIV infection. The accuracy of this information is highly variable. Table 7 lists a selection of sites with reputable, carefully presented information, often with commentaries by recognized HIV researchers. The information on the sites varies from relatively basic content about the virus and transmission to more detailed summaries of ongoing research. Many sites have information in languages other than English. In addition, information pages are available for clinicians.

<p>| Table 7. Selected Web Sites With Patient Information and Advocacy Content |</p>
<table>
<thead>
<tr>
<th>&gt;Title of Web Site, in Alphabetical Order</th>
<th>Uniform Resource Locator</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS.gov</td>
<td><a href="http://www.aids.gov/">http://www.aids.gov/</a></td>
<td>US government site coordinated by the Department of Health and Human Services; HIV/AIDS information and resources</td>
</tr>
<tr>
<td>AIDS InfoNet</td>
<td><a href="http://www.aidsinfo.net">http://www.aidsinfo.net</a></td>
<td>Sponsored by the New Mexico AIDS Education and Training Center. HIV/AIDS resource for patients and practitioners, including information and fact sheets in Spanish, Russian, Bulgarian, Indonesian, and Nepali</td>
</tr>
<tr>
<td>Aidsmap</td>
<td><a href="http://www.aidsmap.com/">http://www.aidsmap.com/</a></td>
<td>Based in London with information in English, Spanish, Portuguese, French, and Russian. Sponsored by NAM, a nonprofit organization providing HIV/AIDS information</td>
</tr>
<tr>
<td>AVERT</td>
<td><a href="http://www.avert.org">http://www.avert.org</a></td>
<td>Sponsored by AVERT, an international AIDS charity based in the United Kingdom. Provides patient information on a variety of topics; includes Spanish section</td>
</tr>
<tr>
<td>Canadian AIDS Treatment Information Exchange</td>
<td><a href="http://www.catie.ca/eng/Home.shtml">http://www.catie.ca/eng/Home.shtml</a></td>
<td>Canadian HIV/AIDS resource for patients; in English and French</td>
</tr>
<tr>
<td>Centers for Disease Control and Prevention: HIV/AIDS</td>
<td><a href="http://www.cdc.gov/hiv/">http://www.cdc.gov/hiv/</a></td>
<td>Links to information for the public on HIV/AIDS</td>
</tr>
<tr>
<td>POZ</td>
<td><a href="http://www.poz.com/">http://www.poz.com/</a></td>
<td>Commercial patient information site, including link to POZ magazine; portion of site in Spanish</td>
</tr>
<tr>
<td>The Body</td>
<td><a href="http://www.thebody.com/">http://www.thebody.com/</a></td>
<td>Commercial HIV/AIDS resource for patients; portion of site in Spanish</td>
</tr>
</tbody>
</table>
to print and distribute to patients.

Particularly noteworthy are the AIDS InfoNet Web site, developed by the New Mexico AETC, and the aidsmap and AVERT sites, both run by not-for-profit organizations. These sites are committed to providing high-quality educational material. The Body and POZ are excellent commercial resources with reliable content that are updated regularly to include reports of recent studies and findings at scientific meetings. Their content is supported through advertisement and pharmaceutical sponsorship. The Canadian AIDS Treatment Information Exchange (CATIE) contains informational sections on preventing, living with, and treating HIV in addition to links to other sites.

Both AIDS.gov and CDC.gov are federally funded Web sites that maintain reliable educational information for persons living with and caring for those with HIV and AIDS. AEGiS, a site sponsored by the NLM, is easy to navigate and allows access to the vast resources available through the NLM. The site has links to daily news updates, articles on many different aspects of HIV and AIDS, conference sites, and other sites of interest to patients and the public.

**Epidemiology and Policy Web Sites**

Several government- or organization-sponsored sites are excellent sources of epidemiologic and policy information (Table 8). For current, accurate US data, the CDC posts updates on its Web site on the US epidemic including rates in different risk groups, sex-specific data, and data by race, in addition to many other detailed analyses. Much of this information is also available as downloadable slide sets. The Kaiser Family Foundation site also provides a link to another site, statehealthfacts.org, which details HIV- and AIDS-related statistics by state. This information is also available at many of the individual state health department Web sites that are not listed separately in the table but can be found using any major search engine. The newly developed HIV/AIDS Atlas Web site shows epidemiologic data graphically and at the county level.

Data detailing the international HIV epidemic can be found on the Joint United Nations Programme on HIV/AIDS (UNAIDS) and WHO Web sites. The annual report on the global AIDS epidemic can be downloaded from the UNAIDS site, which provides detailed information by region and by country throughout the world. Slide sets are also available from most of these sites.

Several Web sites outline current policy and maintain current data regarding policy changes. HRSA administers the Ryan White HIV/AIDS Program and its Web site, which has detailed information regarding the current status of this important resource. The President's Emergency Plan for AIDS Relief (PEPFAR) and the US Agency for International Development (USAID) are US programs tasked with fighting HIV and AIDS in the global arena. Their Web sites detail these programs and include recent updates of new initiatives and policy changes. Web sites for NIAID and DAIDS link to research and clinical resources in addition to funding sources for research and training programs. Finally, the US Food and Drug Administration Web site has data regarding approval and package insert updates for antiretroviral drugs and other relevant medications. Interested practitioners can subscribe to the site's HIV/AIDS listserv to receive e-mail notification of updates to medication indications and approvals.

**Web Sites of US and International Societies for HIV Practitioners**

Table 9 lists major US-based and international societies serving HIV care practitioners. In the United States, the IDSA, its subgroup, the HIV Medical Association (HIVMA), and the American Academy of HIV Medicine (AAHIVM) advocate...
The IAS–USA (which is not affiliated with IAS) has an important educational mission for HIV practitioners. The group sponsors CME update courses throughout the United States, is contracted by HRSA to sponsor the Annual CME Conference for Ryan White HIV/AIDS Program clinicians, develops treatment guidelines by panels of HIV experts, and publishes educational material and programs on its Web site and in print, as noted above. It also maintains and updates a list of drug resistance mutations in HIV-1, which are available as downloadable slides on the Web site.

Many other international organizations exist; notable examples include the International Association of Physicians in AIDS Care (IAPAC), the European AIDS Clinical Society (EACS), the AIDS Society of Asia and the Pacific, and the Society for AIDS in Africa.

Conclusions

An enormous amount of information is available on the World Wide Web pertaining to HIV and AIDS. Available Web sites provide current information on the status of the epidemic, prevention and treatment trials, molecular and research data, policy data, and educational content. Maintaining current knowledge in all of these areas is important to provide the best care for patients affected by the disease and to promote national and international collaborations to combat HIV and AIDS. Furthermore, patients access the Internet regularly, and health care practitioners must be able to direct patients and their family members to reliable sites. Readers need to be discriminatory when using the Internet as an information resource. Whereas a lot of useful information can be found online, there is also the danger that inaccurate information can be obtained as well. Knowing who is responsible for a given site is a good starting point in deciding how reliable and current the information presented by that site really is. The World Wide Web allows all of us to be members of the global community addressing the epidemic in myriad ways.

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References


Cases on the Web

www.iasusa.org/cow

Cases on the Web (COW) is a series of case-driven continuing medical education activities sponsored by the IAS–USA. The COW program was created to offer physicians convenient online access to top-quality education in the field of HIV medicine.

Human Papillomavirus-Related Anal Squamous Cell Dysplasia and Carcinoma in HIV Infection
John Koepppe, MD, and Steven C. Johnson, MD
Level: All

Human papillomavirus (HPV) infection of the anus and HPV-related anal dysplasia are prevalent among HIV-infected persons. This COW activity discusses the risk of anal squamous cell carcinoma (SCC) in HIV-infected persons with anal dysplasia that is detected on cytologic screening. The use and limitations of digital rectal examination and anal Papanicolaou testing for screening of anal dysplasia and anal SCC are considered, and available treatment options for anal dysplasia are compared. The activity also discusses the use of condoms, HPV vaccines, and antiretroviral therapy to prevent anal dysplasia and anal SCC.

Common Drug Interactions in Patients Receiving Antiretroviral Therapy
John J. Faragon, PharmD, BCPS, David Condoluci, DO, and Cindy M. Hou, DO, MBA
Level: Basic

Drug interactions are an increasing challenge for practitioners who treat HIV-infected patients. To the typical 3-drug antiretroviral regimen may be added drugs for comorbid conditions and prophylaxis for opportunistic infections. Treatment is further complicated in patients in whom numerous antiretroviral regimens have failed, because such patients often require the use of more complex regimens to suppress HIV. This activity describes the effects of antiretroviral drugs and other drugs on the cytochrome P450 enzyme system and presents strategies for preventing interactions between antiretroviral drugs and selected coadministered drugs used in primary care settings.

Non–AIDS-Defining Cancers in Patients with HIV Infection
Roger J. Bedimo, MD, MS
Level: Advanced

Despite a substantial decline in the incidence of AIDS-defining cancers that has occurred with the use of antiretroviral therapy, the incidence of malignancies not known to be associated with immunosuppression, the non–AIDS-defining cancers, has increased. This presentation discusses changes in the spectrum of cancers among HIV-infected patients, the role immunodeficiency plays in the incidence of non–AIDS-defining cancers, and the management and prognosis of selected non–AIDS-defining cancers.

Management of an HIV-Infected Patient After Initial Antiretroviral Regimen Failure
Warangkana Sangchan, MD, and Lisa M. Chirch, MD
Level: Basic

Although the management of HIV has undergone dramatic improvement in recent years, failure of an initial antiretroviral regimen remains a common clinical challenge. In this activity, learners will identify the clinical and laboratory characteristics of an initial antiretroviral regimen failure and the possible causes of such failure. The presentation discusses management strategies for patients with first-regimen failure and appropriate antiretroviral regimens for treatment-experienced patients.

The Use of Chemokine Receptor Antagonists in Antiretroviral Treatment Failure
David M. Margolis, MD, and Gretchen Shaughnessy Arnoczky, MD
Level: Advanced

HIV engages in complex interactions with host cell-surface receptors to gain cellular entry and begin viral replication. The use of entry inhibitors such as chemokine receptor antagonists offers the potential for achieving virologic suppression in highly drug-experienced patients in whom this state was previously difficult to attain. This activity discusses the interpretation and the significance of HIV tropism assay results and the implementation of a chemokine receptor antagonist in a treatment-experienced patient with numerous treatment failures.

End-Stage Renal Disease in the HIV-Infected Patient
Christina M. Wyatt, MD
Level: Advanced

HIV-infected patients are at heightened risk of kidney disease related to HIV and coinfections and to the direct toxicity of antiretroviral therapy and concomitant medications. This expertly developed activity discusses current recommendations for the screening and management of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in HIV-infected patients. Issues unique to the diagnosis and management of CKD in the HIV-infected are discussed as are criteria for identifying HIV-infected patients with ESRD who may be eligible for kidney transplantation.

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Look for these new Cases on the Web activities in coming months:
- HIV and IRIS – Level: Advanced
- Use of Buprenorphine in HIV-Infected Patients – Level: Advanced

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Acknowledgments

The International AIDS Society–USA (IAS–USA) gratefully acknowledges our audience, faculty members, funders, staff, consultants, and other contributors for their substantial contributions to IAS–USA programs in 2009. This support makes our programs possible.

HIV/AIDS Practitioners

We thank our audience—the participants in our continuing medical education (CME) courses and our readers—for actively participating in our programs and providing feedback on how we can continually improve the quality and relevance of our activities. In 2009, more than 2700 practitioners attended our live full-day, half-day, or multi-day CME courses, almost 1200 attended our interactive sessions at scientific conferences, and more than 12,000 received each issue of Topics in HIV Medicine.

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For support of the 2009 live CME series Improving the Management of HIV Disease:® HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management, the 2009 volume of Topics in HIV Medicine, or the CME Cases on the Web program, we gratefully acknowledge:

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On behalf of the Chikumbuso Project, we thank the individual donors from our CME courses whose purchases of colorful, hand-crocheted tote bags and cash contributions raised more than $8200 for the project in 2009. We now conclude our charitable partnership with the Chikumbuso Project, in which a total of more than $27,000 was raised over the past 2 years. The contributions went directly toward helping widows, orphans, and grandmothers in Ng’ombe Township, Lusaka, Zambia, whose lives have been affected by HIV and AIDS.

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The Drug Resistance Mutations Group was convened in 2000 to maintain an ongoing, up-to-date list of HIV drug resistance mutations. Each year, the group convenes during scientific conferences to review recent data and prepare updates to its list of mutations, the most recent of which appears in this December 2009 issue of *Topics in HIV Medicine*. Periodic updates can also be found at www.iasusa.org/resistance_mutations.

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Monday, March 22, 2010
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