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Special Contribution

Perspectives

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About This Issue

This issue contains 3 *Perspectives* articles and an update of drug resistance mutations in HIV from the IAS–USA Drug Resistance Mutations Group. The drug resistance mutations update includes several new mutations as well as a complete revision of the user notes and an updated reference list. The first *Perspective* article summarizes a presentation given by Judith A. Aberg, MD, at the 11th Annual Clinical Update for the Ryan White HIV/AIDS Program Clinicians held in August 2008 in Washington, DC. There, she discussed drug interactions among newer antiretroviral drugs, which can be complex and sometimes counterintuitive. A second *Perspective* article, based on a presentation by John G. Bartlett, MD, also from the August 2008 Clinical Update for the Ryan White HIV/AIDS Program Clinicians held in Washington, DC, reviews the current state of the global epidemic of methicillin-resistant *Staphylococcus aureus* infections. The final *Perspective* article is a summary of a presentation given by Michael J. Mugavero, MD, MHSc, at the same August 2008 Clinical Update Program in Washington, DC, focusing on important factors to be considered in attempts to improve engagement in HIV care.

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Special Contribution

Perspectives

Announcements

Update of the Drug Resistance Mutations in HIV-1: December 2008

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The International AIDS Society–USA (IAS–USA) Drug Resistance Mutations Group reviews new data on HIV-1 drug resistance that have been published or presented at recent scientific meetings to maintain a current list of mutations associated with antiretroviral drug resistance. This December 2008 version of the IAS–USA drug resistance mutations figures updates those published in this journal in March/April 2008 (Johnson VA, Brun-Vézinet F, Clotet B, et al, *Top HIV Med*, 2008;16:62-68). The compilation includes mutations that may contribute to a reduced virologic response to HIV-1 drugs. It should not be assumed that the list presented here is exhaustive. 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 and listed in alphabetical order by drug class. The figures are designed for practitioners to use in identifying key mutations associated with viral resistance to antiretroviral drugs and in making therapeutic decisions. Updates are posted periodically at www.iasusa.org. For more in-depth reading and an extensive reference list, see the 2008 IAS–USA panel recommendations for resistance testing (Hirsch MS, Gunthard HF, Schapiro JM, et al, *Clin Infect Dis*, 2008:47:266-285).

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 availability 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.

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 most commonly develops to lamivudine or the nonnucleoside analogue reverse transcriptase inhibitors [NNRTIs]). 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.

Current Revision

This December 2008 update includes several changes to the list of drug resistance mutations for HIV-1, as shown on the figure bars. For etravirine, 3 new mutations were added—K101H, E138A, and M230L—and the mutations at positions L100, K101, and Y181 were changed to boldface to indicate their newer categorization as more important mutations because they are sufficient on their own to confer partial

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reduction in virologic response based on weighting factors identified through correlations with phenotype (see User Note m). Changes to the figure bar for ritonavir-boosted darunavir include the removal of G73S and addition of L74P. For ritonavir-boosted tipranavir, the representations for 3 existing mutations—at positions I47, Q58, and T74—were changed to boldface. Finally, the mutations Y143R/H/C were added to the raltegravir figure bar.

The IAS–USA Drug Resistance Mutations Group also undertook a comprehensive revision of the user notes. The information in each note was reviewed and updated as necessary. The references were updated as needed; citations to full papers replaced those to abstract presentations whenever possible.

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 practitioners. As for all IAS–USA panels, a rotation procedure is in place whereby 1 or 2 panel members periodically step down from panel participation and new members join. These rotations are designed to ensure that all IAS–USA expert panels remain diverse in member affiliations and areas of expertise.

Comments

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

Please send your evidence-based comments, including relevant reference citations, to the IAS–USA at **resistance2009''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**. If you wish to reprint the mutations figures, please send your request to the IAS–USA via e-mail or fax (see above).

To ensure the integrity of the mutations figures, IAS–USA policy is to grant permission for only minor, preapproved adaptations of the figures (eg, an adjustment in size). Minimal adaptations only will be considered; no alterations of the content of the figures or user notes will be permitted. Please note that permission will be granted only for requests to reprint or adapt the most current version of the mutations figures as they are posted on the Web site (www.iasusa.org). Because scientific understanding of HIV drug resistance evolves rapidly and the goal of the Drug Resistance Mutations Group is to maintain the most up-to-date compilation of mutations for HIV clinicians and researchers, publication of out-of-date figures is counterproductive. If you have any questions about reprints or adaptations, please contact us.

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

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)[a]

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

M	A	▼	K	L	T	K
41	**62**	**69**	**70**	**210**	**215**	**219**
L	V	Insert	R	W	Y F	Q E

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

A	V	F	F	Q
62	**75**	**77**	**116**	**151**
V	I	L	Y	M

Multi-nRTI Resistance: Thymidine Analogue-associated Mutations[d,e] (TAMs; affect all nRTIs currently approved by the US FDA)

M	D	K	L	T	K
41	**67**	**70**	**210**	**215**	**219**
L	N	R	W	Y F	Q E

Abacavir[f,g]

K	L	Y	M
65	**74**	**115**	**184**
R	V	F	V

Didanosine[g,h]

K	L
65	**74**
R	V

Emtricitabine

K	M
65	**184**
R	V I

Lamivudine

K	M
65	**184**
R	V I

Stavudine[d,e,i,j]

M	D	K	L	T	K
41	**67**	**70**	**210**	**215**	**219**
L	N	R	W	Y F	Q E

Tenofovir[k]

K	K
65	**70**
R	E

Zidovudine[d,e,i,j]

M	D	K	L	T	K
41	**67**	**70**	**210**	**215**	**219**
L	N	R	W	Y F	Q E

Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)[a,l]

Efavirenz

L	K	V	V	Y	Y	G	P
100	**103**	**106**	**108**	**181**	**188**	**190**	**225**
I	N	M	I	C I	L	S A	H

Etravirine[m]

V	A	L	K	V	E	V	Y	G	M
90	98	**100**	**101**	106	138	179	**181**	190	230
I	G	I	E H P	I	A	D F T	C I V	S A	L

Nevirapine

L	K	V	V	Y	Y	G
100	**103**	**106**	**108**	**181**	**188**	**190**
I	N	A M	I	C I	C L H	A

MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS[n,o,p]

	L	G	K	L	V	L	E	M	M	G	I	F	I	D	I	I	A	G	V	I	I	N	L	I
Atazanavir +/– ritonavir[q]	10	16	20	24	32	33	34	36	46	48	**50**	53	54	60	62	64	71	73	82	**84**	85	**88**	90	93
	I F V C	E	R M I T V	I	I	I F V	Q	I L V	I L	V	L	L Y	L V M T A	E	V	L M V	V I T L	C S T A	A T F I	V	V	S	M	L M

	V	V	L	I	I	I	T	L	I	L
Darunavir/ ritonavir[r]	11	32	33	47	**50**	**54**	74	**76**	**84**	89
	I	I	F	V	V	M L	P	V	V	V

	L	V	M	I	I	I	G	L	V	I	L
Fosamprenavir/ ritonavir	10	32	46	47	**50**	54	73	76	82	**84**	90
	F I R V	I	I L	V	V	L V M	S	V	A F S T	V	M

	L	K	L	V	M	M	I	A	G	L	V	V	I	L
Indinavir/ ritonavir[s]	10	20	24	32	36	**46**	54	71	73	76	77	**82**	**84**	90
	I R V	M R	I	I	I	I L	V	V T	S A	V	I	A F T	V	M

	L	K	L	V	L	M	I	I	F	I	L	A	G	L	V	I	L
Lopinavir/ ritonavir[t]	10	20	24	**32**	33	46	**47**	50	53	54	63	71	73	76	**82**	84	90
	F I R V	M R	I	I	F	I L	V A	V	L	V L A M T S	P	V T	S	V	A F T S	V	M

	L	D	M	M	A	V	V	I	N	L
Nelfinavir[s,u]	10	**30**	36	46	71	77	82	84	88	**90**
	F I	N	I	I L	V T	I	A F T S	V	D S	M

	L	L	G	I	I	A	G	V	V	I	L
Saquinavir/ ritonavir[s]	10	24	**48**	54	62	71	73	77	82	84	**90**
	I R V	I	V	V L	V	V T	S	I	A F T S	V	M

	L	I	K	L	E	M	K	M	I	I	Q	H	T	V	N	I	L
Tipranavir/ ritonavir[v]	10	13	20	**33**	35	36	43	46	**47**	54	**58**	69	**74**	**82**	83	**84**	90
	V	V	M R	F	G	I	T	L	V	A M V	E	K	P	L T	D	V	M

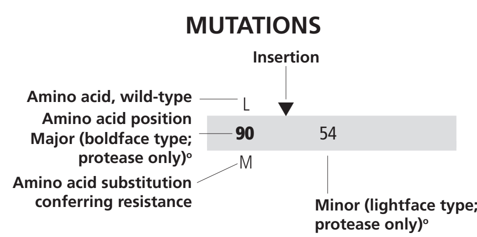
MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

	G	I	V	Q	Q	N	N
Enfuvirtide[w]	36	37	38	39	40	42	43
	D S	V	A M E	R	H	T	D

Maraviroc[x] See User Note

MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE INHIBITORS

	Y	Q	N
Raltegravir[y]	**143**	**148**	**155**
	R H C	H K R	H



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 (IAS–USA) Drug Resistance Mutations Group reviews new data on HIV-1 drug resistance that have been published or presented at recent scientific meetings to maintain a current list of mutations associated with antiretroviral drug resistance. The compilation includes mutations that may contribute to a reduced virologic response to HIV-1 drugs. It should not be assumed that the list presented here is exhaustive. Drugs that have been approved by the US Food and Drug Administration (FDA) as well as any drugs available in expanded access programs are included and listed in alphabetic order by drug class.

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 availability 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.

User Notes

a. Numerous nucleoside (or nucleotide) analogue reverse transcriptase inhibitor (nRTI) mutations, like M41L, L210W, and T215Y, may lead to viral hypersusceptibility to the nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs), including etravirine,[1] 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[2-6] or with etravirine in some 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.[7] 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.[7]

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.[8] The degree to which cross-resistance is observed depends on the specific mutations and number of mutations involved.[9-12] 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-1 drug resistance. The clinical relevance of these in vitro findings remains unclear, and there is yet no evidence that they have a substantial impact in the absence of other, established mutations. Thus, they are not depicted on the figure bars.

e. The E44D and the V118I mutations increase the level of resistance to zidovudine and stavudine in the presence of TAMs and correspondingly increase cross-resistance to other nRTIs. Their presence in the absence of other key mutations does not substantially alter resistance.[13,14] Furthermore, V118I alone does not compromise response to nRTI-containing regimens.[15]

f. The M184V mutation alone does not appear to be associated with a reduced virologic response to abacavir in vivo.[16,17] When present with 2 or 3 TAMs, M184V contributes to reduced susceptibility to abacavir and is associated with impaired virologic response in vivo.[17] The M184V mutation plus 4 or more TAMs results in no virologic response to abacavir in vivo.[17] Slightly increased treatment responses to tenofovir are observed if M184V is present.[7]

g. The K65R mutation may be selected by didanosine or abacavir and is associated with decreased susceptibility to these drugs.[16,18,19] The impact of K65R on clinical response to didanosine-containing triple-drug regimens remains unclear.

h. The presence of 3 of the following mutations—M41L, D67N, L210W, T215Y/F, K219Q/E—is associated with resistance to didanosine.[20] The presence of K70R or M184V alone does not decrease virologic response to didanosine.[21]

i. The presence of M184V appears to delay or prevent emergence of TAMs.[22] This effect may be overcome by an accumulation of TAMs or other mutations.

j. 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.[23-25] The T215Y mutant may emerge quickly from 1 of these mutations in the presence of zidovudine or stavudine.[26,27]

k. The presence of K65R is associated with a reduced virologic response to tenofovir.[7] A reduced response also occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W.[7] Slightly increased treatment responses to tenofovir are observed when M184V is present.[7]

l. The sequential use of nevirapine and efavirenz (in either order) is not recommended because of cross-resistance between these drugs.[28]

m. 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.[29-31] The single mutations Y181C/I/V, K101P, and L100I reduce but do not preclude clinical utility. The presence of K103N does not affect etravirine response.[32] Accumulation of several mutations results in greater reductions in susceptibility and virologic response than do single mutations.[33]

n. Often, numerous mutations are necessary to substantially impact virologic response to a ritonavir-boosted protease inhibitor (PI).[34] When used as unboosted

agents, atazanavir, fosamprenavir, and saquinavir generally select the same mutations as the ritonavir-boosted drug regimen, although the relative frequency of mutations may differ.

o. 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.

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

q. 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 + L76V might increase susceptibility to atazanavir.[35]

r. 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. 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[36] and is associated with a diminished virologic response.[37]

s. 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.

t. 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.[38,39] The product information states that accumulation of 7 or 8 mutations confers resistance to the drug.[40] However, there is emerging evidence that specific mutations, most notably I47A (and possibly I47V) and V32I, are associated with high-level resistance.[41-43] The addition of L76V to 3 PI resistance–associated mutations substantially increases resistance to lopinavir/ritonavir.[35]

u. In some nonsubtype-B HIV-1, D30N is selected less frequently than are other PI mutations.[44]

v. 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, V82L/T, 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.

w. 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.[45-47]

x. Maraviroc activity is limited to patients with virus that uses only the CC chemokine receptor 5 (CCR5) for entry (R5 virus); viruses that use both CCR5 and the CXC chemokine receptor 4 (CXCR4) (termed dual/mixed or D/M) or only CXCR4 (X4) do not respond to maraviroc treatment. Virologic failure with maraviroc therapy frequently is associated with outgrowth of X4 virus that preexisted as a minority population below the level of assay detection. Mutations in the HIV-1 gp120 molecule that allow the virus to bind to the maraviroc-bound form of CCR5 have been described in viruses from some patients whose virus remained R5 at the time of virologic failure. The resistance profile for maraviroc is too complex to be depicted on the figure bar. The frequency and rate at which maraviroc resistance mutations emerge are not yet known.

y. Raltegravir 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/K/R, N155H, or Y143R/H/C; and (2) 1 or more additional minor mutations. Minor mutations described in the Q148H/K/R pathway include L74M + E138A, E138K, or G140S. The most common mutational pattern in this pathway is Q148H + 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 + T97A, Y143H, G163K/R, V151I, or D232N.[48] The Y143R/H/C mutation is uncommon.[49-53]

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Perspective

Drug-Drug Interactions With Newer Antiretroviral Agents

Knowledge of drug interactions among antiretroviral agents and other drugs used by HIV-infected patients is essential to maintaining safety and efficacy of drug treatment. Often, the clinical impact of drug-drug interactions cannot be predicted on the basis of pharmacokinetic interactions alone, highlighting the need for studies and analyses that provide exposure-response data. Drug interactions in HIV-infected patients can be complex and sometimes counterintuitive, and practitioners must increasingly rely on a concerted approach to gathering information on drug interactions that goes beyond studies showing exposure changes for coadministered drugs. This article summarizes a presentation on drug-drug interactions of newer antiretroviral agents made by Judith A. Aberg, MD, at the 11th Annual Clinical Update for the Ryan White HIV/AIDS Program Clinicians held in August 2008 in Washington, DC. The original presentation is available as a Webcast at www.iasusa.org

Information on drug-drug interactions involving antiretroviral agents and other drugs used by HIV-infected patients is confusing. To understand the interactions and how they affect clinical practice, it is necessary to have a grasp of the basic concepts and terminology involved in assessing drug behavior. *Pharmacokinetics* is the mathematics of the time course of absorption, distribution, metabolism, and excretion of drugs in the body. *Pharmacodynamics* refers to relationships between the dose or concentration of a drug in the body (exposure) and the measured effects of the drug. *Pharmacogenomics* refers to the entire spectrum of genes that determine drug efficacy and safety, whereas *pharmacogenetics* concerns distinct inherited traits related to drug absorption, disposition, and response. Inducers of enzymes (or transporters) that metabolize drugs are agents that stimulate production of enzymes and thus decrease levels of the substrate; rifampin, nevirapine, and efavirenz are examples of inducers. *Inhibitors* are agents that inhibit production of enzymes (or transporters) responsible for metabolism and thus act to increase levels of substrate; ritonavir is an example of a potent inhibitor.

Much of the discussion about inducers and inhibitors concerns the interaction of drugs with cytochrome P450 (CYP) enzymes. These enzymes reside primarily in the liver and gut mucosa (and at lower levels in the lungs, kidney, and brain). Six isoenzymes account for the metabolism of nearly half of all clinically used drugs (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A3, and CYP3A4). Patients may have genetic variants of CYP enzymes that affect their metabolic activity such that the activity can be classified according to each patient's phenotype as "poor," "intermediate," "extensive," or "ultrarapid"/"ultraextensive." Drug interactions occur when the pharmacokinetics or pharmacodynamics of 1 drug is altered by another. These interactions are a source of variability in drug responses, which can differ according to concentrations of the interacting drugs, dose, and time. Pharmacokinetic interactions can affect absorption rate, availability, distribution, and hepatic or renal clearance. Pharmacodynamic interactions can be antagonistic, additive, or synergistic.

Case 1: Ineffective Pain Control

A 46-year-old African American man, doing well on antiretroviral therapy with tenofovir, emtricitabine, and ritonavir-boosted (/r) fosamprenavir, presents 1 day after falling off a motorcycle and receiving sutures for lacerations and treatment for arm and leg pain at the emergency department. He states that he is unable to sleep or concentrate at work because of the pain, which was not responsive to ibuprofen. Examination shows multiple abrasions and contusions. He is prescribed acetaminophen with codeine, after reporting a history of using codeine years before with no adverse effects. He calls the office 2 days later and states that he has been vomiting and feels "sick" all day. He denies having a fever or eating any new foods since the accident and states that the codeine did not relieve the pain.

The likely explanation for these symptoms concerns interactions with codeine, which is a prodrug and substrate of CYP2D6 that requires metabolism to its active metabolite (morphine) to provide pain relief. In an individual who has inhibited catabolism, codeine levels will accumulate, causing gastrointestinal toxicity without pain relief. The patient had no history of adverse events the last time he took codeine; however, he is now receiving ritonavir, a CYP2D6 inhibitor. The CYP2D6 inhibition reduces codeine metabolism, thereby raising codeine levels and producing codeine toxicity with no pain relief.

Drug Interactions: Not So Simple

Many of the potential drug interactions in HIV-infected patients are not as readily identified as that between ritonavir and codeine in the patient described above. Understanding drug interactions is crucial to making accurate benefit-risk assessments in HIV patients, but these interactions can be complex and, at times, counterintuitive. Drugs may serve as substrates, inducers, or inhibitors of drug-metabolizing enzymes and transporters, and the complexity of drug metabolism when several medications are prescribed makes predicting interactions nearly impossible. The clinical importance of interactions can-

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not be determined solely on the basis of the reported magnitude of changes in drug plasma concentrations.

Increasingly, practitioners must rely on a concerted approach to gathering information on drug interactions that goes beyond the studies showing changes in exposure for 2 coadministered drugs. To this end, several principles of drug-interaction studies should be observed (Huang et al, *Clin Pharmacol Ther*, 2007): (1) An in vitro and in vivo integrated approach may reduce the number of studies required to detail interactions and optimize knowledge of interactions. (2) Appropriately designed studies of interactions are crucial to reaching the clinical goal of avoiding potentially harmful interactions in patients receiving numerous drugs simultaneously. (3) The clinical importance of interactions should be based on clinical trial data and well-defined exposure-response data and analyses. (4) Classification of CYP inhibitors and substrates can aid in study design and cross-labeling. (5) Information on drug interactions should be placed appropriately in drug labeling.

Case 2: Etravirine and Darunavir

A 21-year-old man with vertically acquired HIV has resistance to several nucleoside analogue reverse transcriptase inhibitors (nRTIs), the K103N nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance mutation, and several protease inhibitor (PI) resistance mutations. Results of coreceptor tropism testing show a dual or mixed profile. Phenotypic analysis indicates that darunavir, lopinavir/r, and tipranavir should be active, with reduced activity of atazanavir and fosamprenavir. It is decided to prescribe the integrase inhibitor raltegravir, the NNRTI etravirine, and a ritonavir-boosted PI. The choice of PI from among darunavir, lopinavir, tipranavir, atazanavir, or fosamprenavir requires clinical judgment regarding which drug would provide the most potency, tolerability, and ability to be coadministered with other active agents.

A look at etravirine interactions with PIs narrows the selection. The effects of ritonavir-boosted PIs on etravirine maximum concentration (C_{max}), area under the curve (AUC), and minimum concentration (C_{min}) and the effects of etravirine on ritonavir-boosted-PI exposure are shown in Table 1. Etravirine exposure is reduced by darunavir/r but reduced more by tipranavir/r, whereas exposure is increased somewhat with lopinavir/r and increased to a greater extent with atazanavir/r. For the PIs, etravirine coadministration results in a marked decrease in atazanavir C_{min} value and a marked increase in exposure to fosamprenavir, with minimal to moderate effects on exposure to darunavir and lopinavir.

Recommendations from the etravirine package insert are summarized in Table 2. Coadministration of atazanavir/r or tipranavir/r is not recommended because of the decreased PI exposure, and use of fosamprenavir/r is not recommended because of increased fosamprenavir exposure. Although the etravirine C_{min} value is reduced by approximately 50% with darunavir/r, coadministration without dose adjustment can still be recommended on the basis of clinical findings in the DUET studies indicating reduction in plasma HIV RNA level to less than 50 copies/mL in 59% of patients receiving the 2 drugs (Lazzarin et al, *Lancet*, 2007; Madruga et al, *Lancet*, 2007).

This finding provides an example of a situation in which the clinical importance of the drug interaction does not appear to be predictable from data on the pharmacokinetic interaction alone, emphasizing the utility of clinical trial or exposure-response data in clinical decision-making. Similarly, although etravirine exposure is increased with coadministered lopinavir/r, data from a clinical trial population have suggested that coadministration is safe, with the current recommendation being that etravirine and lopinavir/r can be coadministered with caution.

Case 3: Coinfection With Tuberculosis

A 36-year-old woman who received a diagnosis of HIV 6 years ago presents

Table **1.** Etravirine and Protease Inhibitor (PI) Interactions

	Maximum Concentration	Area Under the Curve	Minimum Concentration
Effect of PI on etravirine: Ratio in presence of PI (1.00 = no effect)			
Atazanavir/r 300 mg/100 mg, daily	1.30	1.30	1.26
Darunavir/r 600 mg/100 mg, twice daily	0.68	0.63	0.51
Lopinavir/r 400 mg/100 mg, soft gel capsule, twice daily	1.15	1.17	1.23
Tipranavir/r 500 mg/200 mg, twice daily	0.29	0.24	0.18
Effect of etravirine on PI: Ratio in presence of etravirine (1.00 = no effect)			
Atazanavir/r 300 mg/100 mg, twice daily	0.97	0.86	0.62
Darunavir/r 600 mg/100 mg, twice daily	1.11	1.15	1.02
Lopinavir/r 400 mg/100 mg, soft gel capsule, twice daily	0.85	0.80	0.92
Fosamprenavir/r 700 mg/100 mg, twice daily	1.62	1.69	1.77

/r indicates ritonavir-boosted.
Adapted from etravirine package insert, 2008.

Table **2.** Recommendations for Etravirine Coadministration with Protease Inhibitors

Protease Inhibitor	Recommendation for Etravirine Coadministration
Atazanavir/ritonavir	Should NOT be coadministered; atazanavir exposure decreased by 38%
Darunavir/ritonavir	May be coadministered without dose adjustment; recommendation based on DUET study (etravirine exposure decreased by 50%, yet 59% vs 41% had plasma HIV RNA level < 50 copies/mL)
Lopinavir/ritonavir	Etravirine exposure may be increased by 85% in HIV-infected patients; may be coadministered with caution
Fosamprenavir/ritonavir	Should NOT be coadministered; fosamprenavir exposure increased by 77%
Tipranavir/ritonavir	Should NOT be coadministered; etravirine exposure decreased by 75%

Adapted from etravirine package insert, 2008.

with pulmonary tuberculosis. She has a history of nonadherence to medications. Prior genotypic testing indicated M184V, K103N in reverse transcriptase, and 2 minor PI resistance mutations. She is started on 4-drug therapy for tuberculosis with isoniazid, rifampin, pyrazinamide, and ethambutol, tolerating treatment well for 3 weeks, and agrees to start antiretroviral therapy.

What would be the best antiretroviral therapy option? Possibilities include (1) nRTI plus efavirenz and change rifampin to rifabutin 300 mg/day; (2) nRTI plus etravirine and change rifampin to rifabutin 300 mg/day; (3) nRTI plus any ritonavir-boosted PI and continue rifampin as prescribed; or (4) nRTI plus etravirine plus ritonavir-boosted PI and change rifabutin dosage to 150 mg every other day.

The best choice would be option 2. For option 1, the dose of rifabutin would have to be increased to 450 mg/day if it were used with efavirenz. Of note, in this particular case, the patient has a K103N mutation, which confers resistance to efavirenz, so efavirenz is not an option for this patient. Option 3 is not correct because rifampin cannot be used with a PI. A summary of etravirine drug interactions (Table 3) reveals that choices of ritonavir-boosted PIs that can be administered with etravirine are limited. For those that can be coadministered, use is not recommended with rifabutin because of the potential for substantial reductions in etravirine exposure; thus, option 4 is not correct. If no boosted PI is used in this patient's regimen, neither the dose of rifabutin nor that of etravirine needs to be altered.

Ritonavir-boosted darunavir is among the few PI options for coadministration with etravirine. As for other PIs, coadministration with rifabutin affects rifabutin exposure, requiring dose adjustment. However, as a caution against assuming class effects in drug interactions, note that unlike for other PIs, darunavir/r increases, rather than reduces, levels of pravastatin. Pravastatin is metabolized mainly by glucuronidation. The mechanism of the interaction of darunavir/r with pravastatin remains unclear, although it may involve effects on drug-transporter proteins. The darunavir package insert recommends starting with the lowest possible dose of pravastatin with careful monitoring when coadministered with darunavir/r or to consider an alternative statin (darunavir package insert, 2008).

Raltegravir

Raltegravir is not a CYP substrate. Based on in vitro and in vivo studies, it appears to be eliminated mainly by metabolism via a glucuronidation pathway mediated by uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1). Rifampin is a strong inducer of UGT1A1 and reduces raltegravir trough levels (concentration at 12 hours, C_{12h}) by 61%, consistent with a clinically meaningful reduction (mean AUC and C_{max} values reduced by 40% and 38%, respectively). Currently, the effect of other inducers of drug-metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Raltegravir exposure is reduced with coadministered efavirenz (AUC ratio, 0.64; C_{12h} ratio, 0.79) (Iwamoto et al, ICAAC, 2006) and tipranavir/r (AUC ratio, 0.76; C_{12h} ratio, 0.45) (Wenning et al, ICAAC, 2006) and increased with atazanavir/r (AUC ratio, 1.41; C_{12h} ratio, 1.77) (Mistry et al, CROI, 2006), but no dosing changes for any of these drugs are currently recommended with coadministration.

Despite the reduced raltegravir exposure with tipranavir/r, efficacy in approximately 100 patients receiving the 2 drugs in 2 trials (protocols 018 and 019) was similar to that in patients receiving non–tipranavir/r (Steigbigel et al, *N Engl J Med*, 2008). Although atazanavir/r is a strong inhibitor of UGT1A1 and increases raltegravir exposure, concomitant use was safe and effective in patients in 3 trials (protocols 005, 018, and 019) (Steigbigel et al, *N Engl J Med*, 2008; Grinsztejn et al, *Lancet*, 2007).

Maraviroc

The CC chemokine receptor 5 (CCR5) antagonist maraviroc is a substrate for both CYP3A isoenzymes and the P-glycoprotein transporter. A 50% dose reduction for maraviroc is recommended when it is coadministered with most PIs. Because the combined use of maraviroc and tipranavir/r is desirable in heavily treatment-experienced patients, a randomized, open-label, 2-way crossover trial in 12 healthy volunteers was performed to evaluate the pharmacokinetic interaction of maraviroc 150 mg twice daily with tipranavir/r (500/200 mg) (Abel et al, *Br J Clin Pharmacol*, 2008). Coadministration had no effect on maraviroc concentrations compared with maraviroc

Table 3. Coadministration and Dosing Considerations for Etravirine

No Dose Adjustment of Etravirine or Coadministered Drug	
Darunavir/ritonavir	Methadone
Saquinavir/ritonavir	Rifabutin (unless combined with ritonavir-boosted protease inhibitor)[b]
Tenofovir	Oral contraceptives
Didanosine	Paroxetine
Raltegravir	Clarithromycin (alternative should be considered for treatment of *Mycobacterium avium* complex)
Elvitegravir/ritonavir[a]	
Omeprazole	
Ranitidine	
Coadminister with Caution	
Lopinavir/ritonavir	
Modify Dose of Coadministered Drug	
Sildenafil (alter based on clinical effect)	Maraviroc (modify dose)
Atorvastatin (alter based on clinical effect)	
Do Not Coadminister	
Tipranavir/ritonavir	Delavirdine
Atazanavir/ritonavir	Nevirapine
Fosamprenavir/ritonavir	Efavirenz
Full-dose ritonavir	
Protease inhibitors without ritonavir	
Atazanavir	Indinavir
Fosamprenavir	Nelfinavir

[a]Ramanathan et al, ICAAC, 2007.
[b]If etravirine is *not* coadministered with a ritonvair-boosted (/r) protease inhibitor, use rifabutin at a dosage of 300 mg once daily; if etravirine is coadministered with darunavir/r or saquinavir/r, rifabutin should not be coadministered because of potential for substantial reductions in etravirine exposure.
Adapted from etravirine package insert, 2008.

plus placebo, with 5 patients having increased levels of liver enzymes.

The absence of effect on maraviroc concentrations indicates that the effects of CYP inhibition and P-glycoprotein induction balanced each other, and that the recommended maraviroc dose does not need to be altered with concomitant tipranavir/r. Available data on effects of coadministration of maraviroc with antiretroviral combinations indicate reduced maraviroc exposure with a regimen of efavirenz, zidovudine, and lamivudine (C_{max}, −33%; AUC, −53%), reduced exposure with a regimen of efavirenz, didanosine, and tenofovir (C_{max}, −24%; AUC, −52%), increased peak concentrations with a regimen of nevirapine, lamivudine, and tenofovir (C_{max}, +54%; AUC, no change), and increased exposure with a regimen of lopinavir/r, stavudine, and lamivudine (C_{max}, +180%; AUC, +265%) (Muirhead et al, CROI, 2005; Abel et al, *Br J Clin Pharmacol*, 2008).

A further example of competing interactions arises with the use of maraviroc with efavirenz and PIs that increase maraviroc exposure by inhibiting CYP3A4. Maraviroc exposure (as measured by C_{max} and AUC values) is reduced with the known CYP3A4 inducers rifampicin and efavirenz by approximately 70% and 50%, respectively. The addition of efavirenz to maraviroc-plus-PI regimens reduces the magnitude of the PI-mediated increase in maraviroc exposure (by approximately 50%), with the net effect still being CYP3A4 inhibition (Abel et al, *Br J Clin Pharmacol*, 2008). Thus, a dose reduction for maraviroc is needed in this situation.

Overall, based on data from clinical trials, exposure-response information, the drug interaction program, and population pharmacokinetics analysis in phase IIb/III trials, the recommended dosing for maraviroc is:

- 150 mg twice daily when used with PIs, excluding tipranavir/r, and delavirdine
- 300 mg twice daily when used with tipranavir/r, nRTIs, enfuvirtide, or nevirapine
- 600 mg twice daily when used with efavirenz in the absence of PIs

Additional Information Sources

Because some clinically important drug interactions are counterintuitive or seem inconsistent with assumed class effects, HIV practitioners should consult the drug interaction sections of prescribing information for antiretroviral drugs. The following are additional antiretroviral drug interaction resources:

- **www.hivinsite.com:** Updated drug interaction database with references and interactive tool to assess drug interactions.
- **www.aidsinfo.nih.gov:** US Department of Health and Human Services guidelines for use of antiretroviral agents and updated drug interaction tables.
- **www.drug-interactions.com:** Downloadable drug interaction charts; interactive tools to assess interactions; updated news on published abstracts and papers.
- **www.hivmedicationguide.com:** Interactive drug interaction database.
- **www.hivpharmacology.com:** Updated summary of drug interaction data; guidelines for therapeutic drug monitoring.
- Micromedex: Comprehensive drug database; subscription required.

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Perspective

Methicillin-Resistant *Staphylococcus aureus* Infections

Community-acquired methicillin-resistant Staphylococcus aureus *(MRSA) infection is epidemic in the community, differs from nosocomial MRSA in virulence, mechanisms, and antibiotic susceptibility, and exhibits diverse and often unique pathologic characteristics. The community-acquired MRSA USA 300 strains are transmitted largely by person-to-person contact and cause characteristic soft-tissue abscesses and, less commonly, other sometimes unusual and serious infections including a necrotizing pneumonia, and other necrotic infections such as necrotizing fasciitis, pelvic thrombophlebitis, and septic phlebitis. This MRSA 300 family remains susceptible to drugs active against nosocomial MRSA (ie, vancomycin, linezolid, daptomycin) and is often susceptible to trimethoprim-sulfamethoxazole, doxycycline, and clindamycin. Recent epidemiologic data indicate that nosocomial MRSA (eg, mainly USA 100) strains are also present in the community and that MRSA USA 300 strains are present in hospital settings, with both families found in intermediate frequency in health care–associated settings (eg, nursing homes, dialysis centers). More work is needed to identify effective barrier precautions to limit their spread. This article summarizes a presentation on MRSA made by John G. Bartlett, MD, at the 11th Annual Clinical Update for the Ryan White HIV/AIDS Program Clinicians held in August 2008 in Washington, DC. The original presentation is available as a Webcast at www.iasusa.org.*

Infection with methicillin-resistant *Staphylococcus aureus* (MRSA) has no clear specific relationship with HIV disease as yet, although higher frequencies of *S aureus* infection are observed in persons at risk of acquiring HIV, including injection drug users and, in recent studies, men who have sex with men (MSM). MRSA is a general public health problem widely encountered in health care practices, and there is now a global epidemic involving a newly emerged form referred to as the USA 300 strains. This article contains frequent references to MRSA strains such as USA 100, 200, and 300, each of which represents a family of related strains that have distinct lineage and evolution. The article's main focus is on USA 300 strains, which appear to have evolved in the 1960s from phage type 80/81.

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Background

MRSA was first identified in the 1960s, reflecting the response of *S aureus* to widespread exposure to penicillins. This includes a group of related *S aureus* strains, many of which are referred to as the USA 100 strains, that became rampant in hospital settings around 1983. A new family of strains, the USA 300 strains, emerged in the community setting around 2000 and appear related to the old phage type 80/81; they are now referred to as a "super bug."

The USA 300 strains differ from the earlier strains in several ways (Table 1), including presence of the cytotoxin Panton-Valentine leukocidin (PVL) and different methicillin resistance elements. Infections characteristically caused by the hospital-acquired USA 100 strains include wound infections, line-associated bacteremia, ventilator-associated pneumonia, and other common nosocomial infections. Infections with the community-acquired USA 300 strains include skin and soft-tissue infection, community-acquired pneumonia including a distinctive type of necrotizing pneumonia, and necrotizing fasciitis.

Active antibiotics for the nosocomial MRSA strains are usually limited to vancomycin, linezolid, and daptomycin. There is broader susceptibility with the USA 300 strains that often includes trimethoprim-sulfamethoxazole (TMP-

Table **1.** Characteristics of Methicillin-Resistant *Staphylococcus aureus* USA 100 and USA 300 Strains and Infections

	USA 100	**USA 300**
Where originated	Hospital	Community
When	~1983	~2000
Panton-Valentine leukocidin	Absent	Present
Methicillin resistance elements	Mec I-III	Mec IV
Active antibiotics	Vancomycin, linezolid, daptomycin	PLUS trimethoprim-sulfamethoxazole, doxycycline, clindamycin
Infections	Wound, ventilator-associated pneumonia, line infections, other plastic- or metal-associated infections	Skin and soft tissue, community-acquired necrotizing pneumonia, necrotizing fasciitis

SMX), minocycline, and clindamycin. The USA 300 strains continue to dominate the community-acquired forms of *S aureus* infections but now are being found with increasing frequency in hospital settings and are increasingly resistant to antibiotics including tetracycline and clindamycin.

Initial Reports of Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Infections

A widely publicized story of a MRSA epidemic in the St. Louis Rams football team and transmission through physical contact with another team raised awareness in 2000 of the importance of the USA 300 strains in the community. The hospital strains such as USA 100 or 200 have considerable heterogeneity of types, whereas isolates of the USA 300 strain are remarkably similar. Initial pulsed-field gel electropheresis (PFGE) studies in outbreaks showed that USA 300 strains were present not only in the professional football team but in college football teams, fencers, children, prison inmates, and MSM from various locations across the country. The classic MRSA lesion in these outbreaks is known as the "spider bite" abscess (Figure 1). An outbreak in a Los Angeles jail before wide recognition of the prevalence of this problem prompted authorities to call in an exterminating company, which informed them, after inspection, that spiders were not among the many problems present.

Moran and colleagues shed light on the magnitude of the problem with community-acquired MRSA (Moran et al, *N Engl J Med,* 2006). Isolates were analyzed from 422 cases of soft-tissue infection at 11 emergency departments in the United States. Lesions consisted of abscess in 81% of cases, wounds in 11%, and cellulitis with exudate in 8%. MRSA was found in 60% (n = 249) of cases and was the most common organism in 10 of 11 centers. Methicillin-susceptible *S aureus* (MSSA) accounted for 17% of cases (n = 71), and *Streptococcus* species for 8% (n = 30); lesions were sterile in 9% of cases (n = 38). Virtually all of the MRSA isolates (99%) were identified as USA 300, and most were strain type 0114. More than 98% had the Mec IV resistance mechanism and *pvl* genes. Antibiotic susceptibilities showed 100% were sensitive to TMP-SMX, 100% to rifampin, 95% to clindamycin, 92% to tetracycline, 60% to quinolones, and 6% to macrolides.

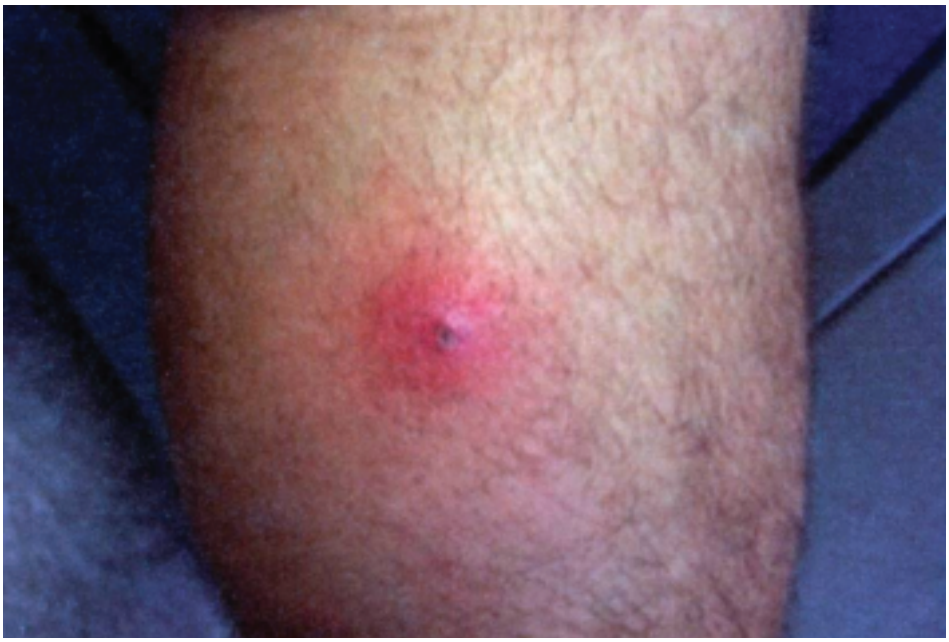

Figure **1.** Classic "spider bite" abscess caused by methicillin-resistant *Staphylococcus aureus* USA 300.

A major message from this study is that MRSA has supplanted MSSA as the dominant *S aureus* in community-acquired infections. Treatment consisted of incision and drainage plus antibiotic treatment in 60% of cases and incision and drainage alone in 19%. A beta-lactam antibiotic was used in 64% of cases in which antibiotic therapy was used, including 57% of MRSA cases treated with an antibiotic. Assessment of outcome at 15 days to 21 days by telephone showed resolution of infection in 96% of cases, with no correlation of outcome according to treatment with an antibiotic, an inactive antibiotic, or no antibiotic. There is widespread agreement that the cutaneous abscess needs drainage, but indications for antibiotics to supplement drainage are unclear. A prospective study sponsored by the National Institutes of Health is currently evaluating the issue of use of antibiotics in MRSA cutaneous abscesses.

The necrotizing infections associated with the USA 300 MRSA strains are often remarkable and devastating. Although health care practitioners have had experience with necrotizing fasciitis for decades, most of these infections have been caused by group A streptococci or anaerobic bacteria. Staphylococci were not previously among likely pathogens, but they are now the major cause. With regard to necrotizing pneumonia, the author's own experience with 4 young, previously healthy adult patients at The Johns Hopkins Hospital 4 years ago shows how devastating this community-acquired disease can be: 2 young, previously healthy women underwent amputations of both legs as a result of septic shock, 1 man died, and the fourth survived but only after 103 days in the intensive care unit.

An initial Centers for Disease Control and Prevention (CDC) report on community-acquired pneumonia caused by MRSA presented details on 10 cases in Louisiana and Georgia during the influenza season of 2006 and 2007 (*MMWR Morb Mortal Wkly Rep,* 2007). The infection was lethal in 6 of 10 patients at an average of 3.5 days after onset of symptoms. In addition to these new staphylococcal syndromes, communi-

ty-acquired MRSA has been associated with septic thrombophlebitis and pediatric "pelvic syndromes" (eg, septic arthritis of the hips, pelvic abscess).

The particular virulence factors underlying the types of infections caused by these strains remain disputed. Although the presence of *pvl* genes in the USA 300 strains suggest that PVL could be a virulence factor, debate remains over whether it is the major determinant of the greater virulence of these strains. For example, 2 experienced research groups performed well-designed studies that were published in 2 highly reputable scientific journals and came to very different conclusions. One group stated that PVL is a key virulence factor in pulmonary infections, as supported by showing that a nasal challenge of just PVL in mice causes lethal pneumonia (Labandeira-Rey et al, *Science,* 2007). However, the second group repeated this experiment and concluded that although PVL may be a marker for community-acquired MRSA, it is not an important virulence determinant and might even be protective (Voyich et al, *J Infect Dis,* 2006).

Staphylococcus aureus is an organism with more than 60 virulence factors including cytotoxic peptides thought to be important by some. Identifying individual factors that account for the changing behavior of the diverse pathogenic processes attributed to MRSA may be impossible. By comparison, group A streptococci also can cause severe infections but remain relatively simple in both virulence factors and antibiotic sensitivities. For example, *S pyogenes* remains sensitive to penicillin despite having been exposed extensively to the drug for more than 5 decades.

Current Epidemiology

A large-scale CDC surveillance study described the incidence and burden of invasive MRSA in the United States (Klevens et al, *JAMA,* 2007). The study was hospital-based and involved sentinel laboratories covering approximately 16.5 million patients, approximately 5.6% of the US population. MRSA was isolated from blood or other normally sterile site from 8987 cases with community onset. The site of disease acquisition was classified as community onset in 28%, whereas 58% were health care–associated onset, and 14% were nosocomial onset. Bacteremia accounted for 75% of infections and pneumonia for 13%. Mortality was 13%. PFGE typing showed USA 300 strains accounted for 16% of hospital-acquired cases, 22% of health care–associated cases, and 67% of community-acquired cases. Note the "health care–associated" category is a relatively new, hybrid form of epidemiologic classification representing patients recently discharged from the hospital (within 30 days), patients admitted from chronic care facilities, and those who are part of the hospital network, for example, outpatients of dialysis centers.

These data indicate the lack of restrictions on where the older versus newer MRSA strains are to be found. The USA 100 strains can be found in community-acquired infections, and the USA 300 strains are now found in nosocomial infections, and both strains are found at intermediate frequencies in health care–associated sites. On the basis of this report, an estimated 94,360 invasive MRSA infections occur each year, with 18,650 associated deaths. The incidence was estimated at 32 cases per 100,000 population, with geographic variation including rates of 20 per 100,000 population in Portland and 118 per 100,000 in Baltimore.

Treatment

Vancomycin remains the standard treatment for serious MRSA infections. It is the second most commonly used antibiotic in hospitals, and approximately 16 tons of the drug are used every year. In 50 years of use, only 6 clinical MRSA strains with vancomycin resistance have been identified. However, recent reports provide cause for concern. Tenover and Moellering (*Clin Infect Dis,* 2007) showed several concerns about vancomycin: 1) heteroresistance in MRSA, in which small numbers of organisms with high vancomycin minimal inhibitory concentrations (MICs) are present within large populations of organisms that show vancomycin resistance despite resistance of a subpopulation; 2) "MIC creep," in which an increase has occurred in recent years in numbers of both MRSA and MSSA clinical isolates with vancomycin MICs of 2 µg/mL or greater (strains now considered only intermediately sensitive to vancomycin) (Wang et al, *J Clin Microbiol,* 2006); and 3) prolonged MRSA bacteremia in many patients despite adequate vancomycin treatment as indicated by trough levels of 15 mcg/mL to 20 mcg/mL.

The standard regimen of intravenous vancomycin is 1 g every 12 hours or, preferably, 15 mg/kg to 22 mg/kg every 12 hours. Although this regimen may suffice for many staphylococcal infections, drug levels should be considered and monitored in serious staphylococcal infections with a goal of reaching trough levels of 15 µg/mL to 20 µg/mL in pneumonia, 20 µg/mL in central nervous system infection, 10 µg/mL to 20 µg/mL in endocarditis, and 10 µg/mL to 15 µg/mL in bacteremia. In cases of vancomycin failure, options are linezolid (600 mg every 12 hours), daptomycin (6-8 mg/kg/day), clindamycin (600 mg every 8 hours), or TMP-SMX (10/50 mg/kg/day). A new drug was just recommended for approval by the US Food and Drug Administration Advisory Panel (November 20, 2008). This may provide another option.

For USA 100 strains, use of linezolid or daptomycin is likely to be required in vancomycin failures; linezolid is the only available oral agent for these infections and is preferred for pneumonia (see below). For USA 300 strains, sensitivity testing should be performed to determine that a tetracycline (preferably minocycline), clindamycin, or TMP-SMX can be used. However, more recent experience suggests the USA 300 strains are becoming more resistant to tetracycline and clindamycin.

For pulmonary infections involving USA 300 strains linezolid is usually preferred because of its superior lung penetration and better 28-day survival in MRSA nosocomial pneumonia compared with vancomycin (Wunderink et al, *Chest,* 2003). A highly controversial area is that of indications for antibiotics for the common cutaneous abscess. There is widespread agreement that in-

cision and drainage are key in most such infections, but there is no consensus on indications for antibiotics or on the drug to use, except that cephalexin and dicloxacillin (once the favored agents) are now considered "wrong" choices unless the strain is known to be MSSA.

Important factors to consider with vancomycin include the potential for nephrotoxicity and the need to monitor drug levels with treatment of serious infections. Linezolid occasionally causes marrow toxicity and serious optic toxicity. Daptomycin has been associated with elevated levels of creatine kinase, although the clinical consequences of this seem rare. The optimal dosing of daptomycin is still not clear, and it should not be used in pneumonia because of poor lung penetration. TMP-SMX is associated with rash, and its use may be problematic because of a potential for severe reactions. Clindamycin is associated with *Clostridium difficile* colitis and presents potential problems with resistance.

Control Efforts

All cutaneous abscesses should be covered. Colonization sites for staphylococci are the nose, skin, intestines, genital tract, and objects. The nose harbors MSSA in approximately 30% of individuals and MRSA in approximately 2% to 5%. Fomites such as towels were implicated in the MRSA USA 300 epidemic in the St. Louis Rams players. Studies in MSM have indicated a genital or perirectal source; in a survey in San Francisco hospitals, MSM had a relative risk for MRSA infection of 13.2 that was unrelated to HIV infection; affected sites included buttocks, genitals, and perineum (Diep et al, *Ann Intern Med,* 2008).

Given the potential sources of infection, it is reasonable to attempt barrier precautions in the health care setting, including use of mupirocin for the nose and chlorhexidine soap and hexachlorophene cleanser for the body. The effects of a strategy of universal screening for MRSA and barrier precautions were assessed in a recent study in surgical wards in a Swiss teaching hospital (Harbarth et al, *JAMA,* 2008). Surgical patients underwent randomization to rapid screening (polymerase chain reaction testing) for the presence of MRSA in the nose. The intervention for MRSA carriers found through screening included contact isolation, adjusted antibiotic prophylaxis, a computerized MRSA alert, and use of mupirocin ointment and chlorhexidine body wash. The investigators found no differences in rates of MRSA surgical site infection or nosocomial acquisition with the screening and intervention.

On the other hand, a study of screening and barrier precautions in 3 affiliated hospitals in Chicago did show benefit (Robicsek et al, *Ann Intern Med,* 2008). In this study, patients underwent surveillance for MRSA using polymerase chain reaction testing, with isolation and barrier precautions used for MRSA carriers and decolonization attempted using mupirocin and chlorhexidine wash. The strategy of universal screening and infection control in those colonized was studied in sequence with no intervention, followed by intervention restricted to the intensive care unit, and then universal screening.

Compared with a control period during which the rate of MRSA infection was 8.9 per 10,000 patient-days, the infection rate was similar (7.4) with the intensive care unit–based strategy and statistically significantly reduced (3.9) with the universal strategy. The aggregate MRSA disease prevalence density was reduced by greater than 70% with universal screening. The point to emphasize is that screening, covering lesions, and decontamination with mupirocin and chlorhexidine all make sense, but evidence that they work is limited in number and variable in results. We now have universal screening for MRSA in Veterans Administration hospitals and in some states with a legislated requirement, but we do not know what strategies are effective in controlling this organism in health care settings, and these mandated and unfunded policies represent extensive resources.

Conclusion

Staphylococcus aureus features incredibly diverse pathogenic and resistance mechanisms, and MRSA has emerged as the major bacterial pathogen of the 21st century to date. The primary mode of transmission of community-acquired MRSA is human-to-human contact. Management of the infections includes drainage of abscesses, but the criteria for antibiotics are often unclear. Many strains of the USA 300 family are sensitive to TMP-SMX, clindamycin, and/or minocycline. Serious infections and most nosocomial MRSA strains are best treated with vancomycin, aiming for trough levels of 15 mcg/mL to 20 mcg/mL in serious infections. Screening for nasal carriage combined with use of barrier techniques is often employed to contain spread of the organism, but there is no consensus on the utility of this intervention. The history of MRSA strongly indicates that even if the organism is controlled, the victory will be temporary.

Presented by Dr Bartlett in August 2008. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Bartlett in November 2008.

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Perspective

Improving Engagement in HIV Care: What Can We Do?

Engagement in HIV care needs to be improved. Important factors to be considered in attempts to improve engagement in care include the following: (1) initial linkage and subsequent retention are distinct processes; (2) engagement in care is vital for HIV treatment success at both the individual and population levels; (3) missed clinic visits can identify patients at high risk for poor health outcomes; (4) engagement in care is worse in groups bearing a disproportionate burden of the domestic HIV epidemic; and (5) ancillary services play a crucial role in improving linkage to and retention in care. This article summarizes a presentation on engagement in HIV care made by Michael J. Mugavero, MD, MHSc, at the 11th Annual Clinical Update for the Ryan White HIV/AIDS Program Clinicians held in August 2008 in Washington, DC. The original presentation is available as a Webcast at www.iasusa.org.

The "blueprint" for HIV treatment success includes making the diagnosis of HIV infection, linking infected individuals to outpatient care, and retaining patients in care. There is considerable need for improvement in each of these areas (Figure 1). Substantial benefits come by increasing engagement in HIV care. A useful way of conceptualizing engagement as put forth by the US Health Resources and Services Administration (HRSA) is as a continuum from HIV-seropositive people unaware they are infected to patients who are fully engaged in HIV care, with gradations in between of categories including patients who are aware of their HIV status and not receiving any medical care, are receiving medical care but not HIV care, have entered HIV care but dropped out, or are in and out of HIV care or infrequent users of care (Cheever, *Clin Infect Dis*, 2007). For patients anywhere along the continuum, there is an opportunity to move them forward with appropriate interventions.

The design and implementation of effective interventions, however, require taking many factors into account. Using a behavioral model of health services utilization, these factors can be organized into environmental and patient characteristics to better understand their interplay and their relationship with health behaviors such as engagement in care and adherence to antiretroviral medications that influence health outcomes. This conceptual framework allows for identification of modifiable factors that may serve as targets to affect these behaviors and ultimately improve outcomes (Figure 2).

Improved engagement in HIV care carries the promise of substantially improved outcomes at both the individual and population levels. At the individual level, better engagement is associated with better antiretroviral therapy receipt and adherence, immunologic and virologic outcomes, and survival (Keruly et al, *Am J Public Health,* 2002; Robbins et al, *JAIDS*, 2007; Giordano et al, *Clin Infect Dis,* 2007; Park et al, *J Intern Med,* 2007). At the population level, improved engagement may help address observed racial and socioeconomic disparities in HIV outcomes (Mugavero et al, *JAIDS*, 2008). Further, it can have a substantial role in reducing transmission of disease because improved engagement has been associated with reduced risk behaviors and improved receipt of and adherence to antiretroviral therapy (Marks et al, *AIDS,* 2006; Metsch et al, *Clin Infect Dis,* 2006; Giordano et al, *Clin Infect Dis,* 2007; Quinn et al, *N Engl J Med,* 2000; Cohen et al, *Ann Intern Med,* 2007).

Although they share many barriers and facilitating factors, linkage to care and retention in care are distinct processes. Characteristics of these processes and elements of strategies to improve engagement are discussed herein.

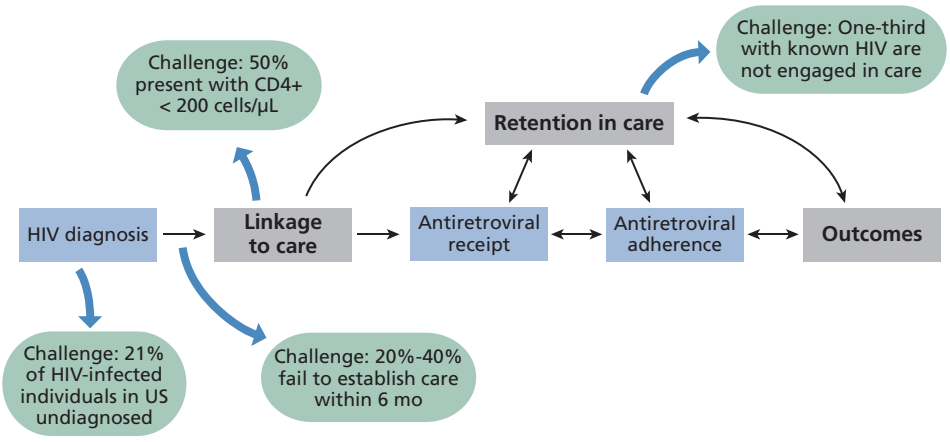

Figure **1.** Blueprint for HIV treatment success, indicating the population-level challenges currently faced in the United States (Glynn and Rhodes, NHIVPC, 2005, Gardner et al, *AIDS*, 2005; Mugavero et al, *Clin Infect Dis*, 2007; Gay et al, *AIDS*, 2006; Mugavero et al, *Am J Med*, 2007; Fleming et al, CROI, 2002). Adapted with permission from Ulett et al, *AIDS Patient Care STDs*, 2008.

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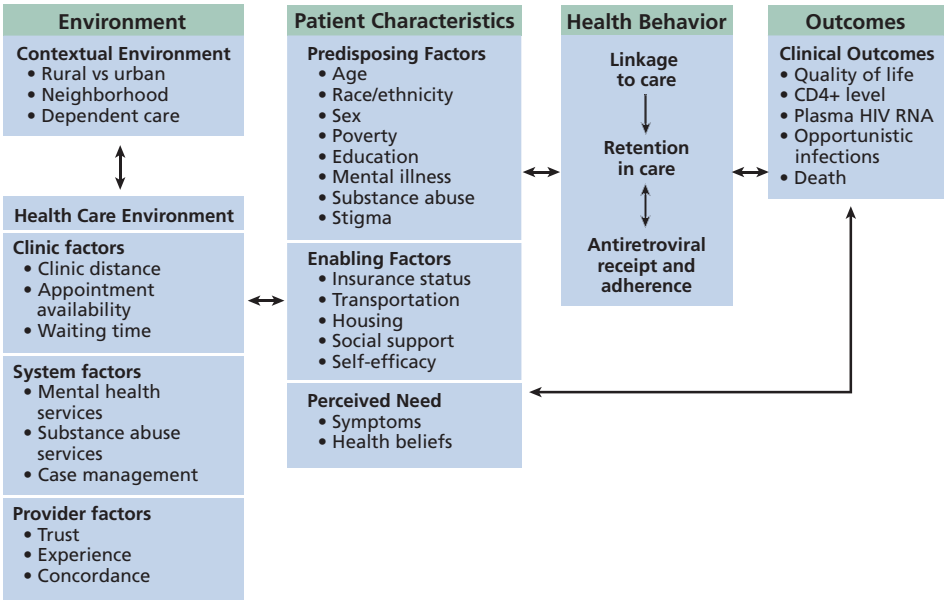

Figure **2.** Interplay of environmental factors and patient characteristics with HIV care behaviors and outcomes. Adapted with permission from Ulett et al, *AIDS Patient Care STDs*, 2008, and Andersen RM, *J Health Soc Behav*, 1995.

Linkage to Care

In September 2006, the US Centers for Disease Control and Prevention (CDC) issued revised HIV testing recommendations advocating routine opt-out testing for adults in all health care settings. An estimated 25% to 50% increase in patients needing outpatient HIV care is anticipated from implementation of these recommendations. The CDC guidelines further highlight the importance of linkage to medical services at the time of diagnosis because newly diagnosed patients frequently delay or fail to establish outpatient HIV care (CDC, *MMWR Recomm Rep*, 2006; Mugavero and Saag, *MedGenMed*, 2007; Samet et al, *AIDS*, 2001; del Rio et al, CROI, 2001).

In the only randomized controlled trial reported to date of an intervention to improve linkage to care, the CDC examined the potential role of a strength-based case-management strategy in the Antiretroviral Treatment Access Study (ARTAS). The intervention was based on promotion of empowerment and self-efficacy. Case managers asked clients to identify internal strengths and assets to foster linkage to care, and up to 5 case manager contacts were allowed within the first 90 days of enrollment (Gardner et al, *AIDS*, 2005). A primary HIV care provider visit was attended within 6 months by 78% of patients in the case-management group versus 60% of patients in the standard-of-care group ($P < .01$), and a second visit occurred within the first 12 months for 64% versus 49%, respectively ($P < .01$) (Gardner et al, *AIDS*, 2005).

On the assumption that a case manager carries a load of 120 clients per year, the cost of the program was estimated at $599 per client, with a cost of $3993 per additional client linked to care above and beyond the standard-of-care group. These findings indicate that the intervention is efficacious in terms of both cost and linkage of care. However, the fact that only two-thirds of patients in the case-management group and less than half in the standard-of-care group remained in care after the first year indicates substantial room for improvement.

In a study at the University of Alabama at Birmingham (UAB) 1917 Clinic among patients calling to establish HIV care during 2004 to 2006, 31% (160/522) failed to attend a clinic visit within 6 months of the initial call (Mugavero et al, *Clin Infect Dis*, 2007). Minority men and women and white women were statistically significantly more likely to be "no shows" compared with white men, as were patients with public health insurance and those without insurance compared with patients with private insurance (Table 1). A longer delay from the time of the initial call to the scheduled appointment was also associated with greater likelihood of not showing for a clinic visit.

To reduce the no-show rate, a program, Client-Oriented New Patient Navigation to Encourage Connection to Treatment (Project CONNECT), was developed and launched on January 1, 2007. In the program, new patients have a scheduled orientation visit within 5 days of their initial call to the clinic. When a prospective client calls, he or she speaks to a team member, who says, in essence, "I'd like you to come over in the next few days–when are you available? I'd like to meet you personally, talk with you, show you around the clinic." At this visit, the patient has a semistructured interview, completes a psychosocial questionnaire, and undergoes baseline laboratory testing. Uninsured patients also meet with a clinic social worker at this initial orientation visit.

The orientation visit has proved to be very advantageous in facilitating rapid institution of prophylactic medications when necessary. For example, patients coming in with CD4+ counts less than 200 cells/μL are often started on *Pneumocystis jiroveci* pneumonia (PCP; formerly *Pneumocystis carinii* pneumonia) prophylaxis even before their primary provider visit. It has also allowed for prompt referral for substance abuse and mental health services when necessary through problems identified on the psychosocial questionnaire. Although the Project CONNECT questionnaire contains 7 domains, it is administered fairly rapidly because the validated screening instrument for each domain contains few questions. The domains and instruments are medication adherence (ACTU-4), depression (Patient Health Questionnaire, PHQ), anxiety (PHQ), alcohol use (Alcohol Use Disorders Identification Test–Consumption, AUDIT-C),

Table **1**. Risk of Being a "No Show" at First Scheduled Visit After Initial Call to University of Alabama at Birmingham 1917 Clinic

Characteristic	"Show" Group (n = 362)	"No Show" Group (n = 160)	Odds Ratio (95% confidence interval)
Age in years, mean (SD)	39.3 (9.6)	37.1 (9.5)	0.84 (0.68-1.04)[a]
Race, sex, no. (%)			
White men	125 (34.5)	32 (20.0)	1.0 (Reference)
Minority men	154 (42.5)	76 (47.5)	1.75 (1.05-2.91)
White women	31 (8.6)	20 (12.5)	2.72 (1.30-5.68)
Minority women	52 (14.4)	32 (20.0)	2.39 (1.27-4.52)
Insurance, no. (%)			
Private	127 (35.1)	26 (16.2)	1.0 (Reference)
Public	77 (21.3)	34 (21.3)	1.91 (1.03-3.54)
Uninsured	158 (43.6)	100 (62.5)	2.62 (1.56-4.39)
Days from call to appointment, mean (SD)	25.6 (13.8)	30.2 (13.4)	1.32 (1.14-1.53)[a]

SD indicates standard deviation.
[a]Odds ratio per every 10 years of age, or odds ratio per every 10 days between call and appointment.
Adapted from Mugavero et al, *Clin Infect Dis*, 2007.

substance abuse (Alcohol, Smoking and Substance Involvement Screening Test, ASSIST), health-related quality of life (EuroQOL-5D), and symptoms (HIV Symptom Index). The questionnaire is subsequently repeated every 6 months to identify new needs or barriers that need to be addressed to keep the patient engaged in care.

The preliminary results in improving linkage to HIV care at the UAB 1917 Clinic have been encouraging. For patients scheduling an orientation visit during the 2007 calendar year (with follow-up through June 30, 2008, to allow patients 6 months to attend a primary HIV provider visit), 81% (296/364) attended a primary HIV provider visit. The no-show rate of 19% is statistically significantly lower than the 31% rate identified in 2004 to 2006 ($P < .01$). Cost for the program was estimated at $200 per client and $1628 per additional client linked to care through Project CONNECT, indicating a reasonable cost of the intervention. Reimbursement has been set up partially through Ryan White HIV/AIDS Program Part B by working with the local Ryan White HIV/AIDS Program grantee in Alabama. Although these results are encouraging and provide a foundation for continued efforts, more work remains to be done to improve linkage to HIV care.

Retention in Care

Missed visits are common after establishment of outpatient care and are associated with delayed receipt of antiretroviral therapy, emergence of antiretroviral resistance, and virologic failure (Ulett et al, *AIDS Patient Care STDs*, 2008; Giordano et al, *JAIDS*, 2003; Lucas et al, *Ann Intern Med*, 1999; Sethi et al, *Clin Infect Dis*, 2003; Robbins et al, *JAIDS*, 2007). However, few studies have examined the relationship between missed visits and mortality after initial linkage to outpatient care. Thus, this relationship was examined in a retrospective study of 543 newly diagnosed patients with no prior outpatient care who initiated treatment at the UAB 1917 Clinic between 2000 and 2005 (Mugavero et al, *Clin Infect Dis*, 2008). Approximately 60% of patients missed visits during the first year after initial linkage to outpatient care. Younger patients, African American patients, and patients with public health insurance were more likely than other groups to have a missed visit. Missed visits were associated with increased risk of mortality. Mortality rates were 2.3 versus 1.0 per 100 patient-years of follow-up in the missed-visit versus no-missed-visit groups, respectively ($P = .02$).

Although further work is needed to better understand this relationship, these findings should serve to heighten clinician awareness of missed visits among new patients. A missed visit early in care may identify patients at risk of poor long-term outcome and may serve as a marker for providers to identify patients at heightened risk who may require specific attention to retention in care, adherence to medications, and assessment of other factors in their lives that may contribute to the higher observed mortality in this study.

To improve the understanding and assessment of the effects of variation in retention in care, a methodology that allows engagement to be evaluated using multiple measures has been devised. Appointment adherence is measured as the overall proportion of scheduled visits that are attended over a given time period. This measure allows gradations of adherence among patients to be identified, rather than treating it as a dichotomous variable (eg, assigning adherence versus nonadherence on the basis of a missed visit).

Persistence is measured as the proportion of 3- or 6-month intervals during which at least 1 visit was attended over a period of time. A gap in care occurs when a patient goes without a visit for a predefined interval such as 6 months or 12 months.

Appointment adherence was assessed over a 2.5-year period in 1221 patients attending the UAB 1917 Clinic. Figure 3 shows the distribution of appointment adherence rates and the percentage of patients achieving plas-

ma HIV RNA levels of less than 50 copies/mL according to adherence rate. The relationship between appointment adherence and virologic response is similar to the dose-response relationship observed with adherence to antiretroviral therapy. Achievement of plasma HIV RNA levels below 50 copies/mL occurs in approximately one-third of patients with appointment adherence of less than 60% and in approximately three-fourths of those with 100% appointment adherence. Analysis of risk factors for virologic failure, defined as plasma HIV RNA level greater than 50 copies/mL, showed that appointment nonadherence was a statistically significant predictor with roughly twice the odds of virologic failure per additional 25% nonadherence, along with younger age and public health insurance (Table 2) (Mugavero et al, *JAIDS*, 2008).

In a study of US veterans with HIV starting antiretroviral therapy, Giordano and colleagues assessed treatment outcomes by clinic visit persistence, defined as the number of quarters (3-month periods) with attendance at a scheduled visit during the first year of antiretroviral therapy (Giordano et al, *Clin Infect Dis*, 2007; Cheever, *Clin Infect Dis*, 2007). Visit persistence was associated with 1-year CD4+ cell count and plasma HIV RNA level outcomes, antiretroviral therapy adherence, and long-term survival. Analysis of survival showed increasing risk of mortality with increasing number of quarters with no attended clinic visit. Compared with the 1685 patients (64%) with an attended visit in each quarter, the hazard ratio (95% confidence interval) for survival was 1.41 (1.10-1.82) among 479 patients (18%) who attended in 3 of 4 quarters, 1.68 (1.24-2.26) among 286 patients (11%) who attended in 2 of 4 quarters, and 1.94 (1.36-2.76) among 169 patients (7%) who attended in 1 of 4 quarters (Giordano et al, *Clin Infect Dis*, 2007).

Studies sponsored by HRSA of the US Department of Health and Human Services have indicated that retention in HIV care is associated with use of ancillary services including case management, transportation, housing, substance abuse, and mental health services (*AIDS Care*, 2002). HRSA-sponsored Special Projects of National Significance initiatives involving peer navigators and other types of patient outreach have also proven effective in promoting retention in care (Tobias, *AIDS Patient Care STDs*, 2007). Currently, the CDC and HRSA are sponsoring a randomized controlled trial to develop and test an intervention to improve retention in HIV care, although results of this study will not be available for several years as it has only recently been launched.

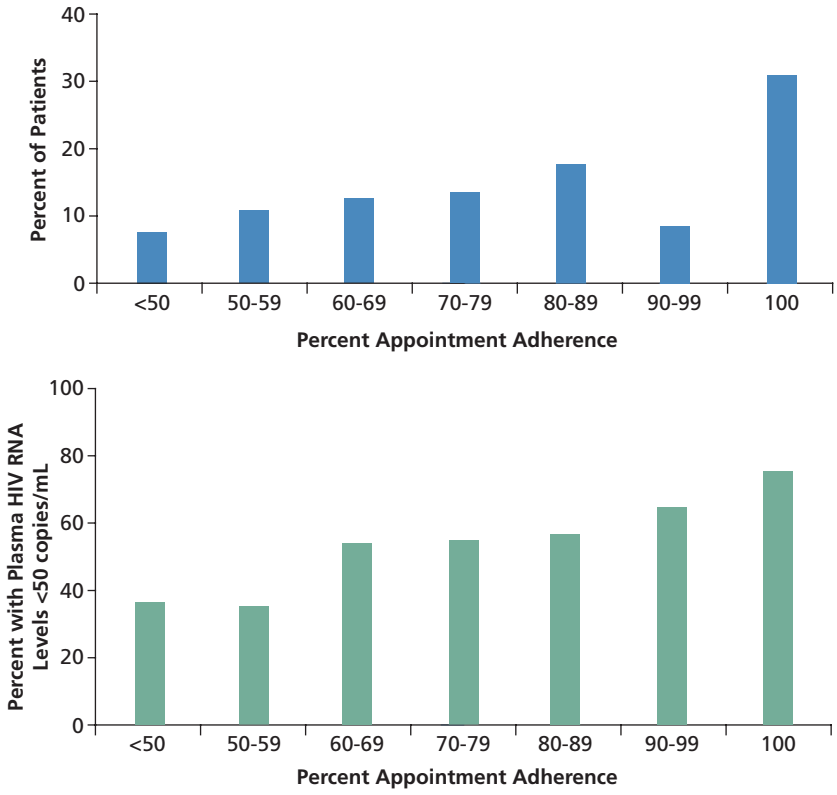

Figure **3.** Appointment adherence (top) and virologic response (plasma HIV RNA level < 50 copies/mL) according to adherence rate (bottom) in patients at the University of Alabama at Birmingham 1917 Clinic (adapted from Mugavero et al, *JAIDS*, 2008).

What Can We Do?

Important messages to be gleaned from our current experience with linkage to and retention in care are as follows:

- Linkage and retention are distinct processes
- Engagement in care is vital for HIV treatment success at the individual and population levels
- Early missed visits can identify patients at high risk of poor health outcomes
- Engagement in care is worse in groups bearing a disproportionate burden of the HIV epidemic in this country
- Ancillary services have a crucial role in improving linkage to and retention in care

Several initiatives for improving linkage and retention can be implemented relatively promptly. Partnerships can be established among local Ryan White HIV/AIDS Programs, public health departments, community-based organizations, and hospital emergency departments in implementing HIV testing coupled with the ARTAS case-management program to improve linkage to care. Clinics can evaluate their own no-show profiles and consider revising their new patient orientation processes; implement routine psychosocial screening to identify barriers to engagement in care (eg, substance

Table **2**. Odds Ratio (OR) for Virologic Failure (Plasma HIV RNA Level < 50 Copies/mL) According to Characteristics in Patients at University of Alabama at Birmingham 1917 Clinic

Characteristic (n = 1088)	Odds Ratio (95% confidence interval)
Age, per 10 years	**0.78 (0.68-0.91)**
Female	0.82 (0.59-1.13)
African American	1.30 (0.98-1.72)
Public health insurance	**1.62 (1.20-2.20)**
Uninsured	1.21 (0.86-1.72)
Affective mental health disorder	1.18 (0.90-1.54)
Alcohol abuse	1.00 (0.66-1.51)
Substance abuse	1.27 (0.90-1.80)
Appointment nonadherence (per 25% nonadherence)	**1.78 (1.48-2.13)**

Adapted from Mugavero et al, *JAIDS*, 2008.

abuse); and attempt to strengthen social-worker and case-manager, mental health, and substance-abuse programs as resources allow. Clinics can also develop partnerships to implement and strengthen patient-outreach and peer-navigation programs with existing community organizations currently providing these services. Discussion with patients about their need to adhere to antiretroviral therapy is commonplace in the clinic. Similarly, patients need to be informed that adherence to visits is also associated with improved outcomes–that patients who remain engaged in care do better.

Presented by Dr Mugavero in August 2008. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Mugavero in November 2008.

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Management of Cryptococcal Meningitis in the Antiretroviral Therapy Era: More than Just Antifungals

by Henry Masur, MD, and Anuradha Ganesan, MD

In many urban areas, one-third of patients presenting with an initial HIV diagnosis have CD4+ counts below 200 cells/µL, and many present with opportunistic infections. This activity reviews the presentation and management of cryptococcal infections in HIV-infected patients. Learners will review cryptococcal treatment strategies, the management of complications such as intracranial hypertension, the indicators of poor prognosis for cryptococcosis, and the risk factors for cryptococcal-related immune reconstitution inflammatory syndrome (IRIS).

Immune Reconstitution Inflammatory Syndrome in HIV-Infected Patients: Diagnostic and Management Challenges

by Jaime C. Robertson, MD, and Carl J. Fichtenbaum, MD

IRIS, as it pertains to HIV-infected patients, is a deterioration of the patient's condition due to the restored ability to mount an inflammatory response to a specific pathogen, or the occurrence of an inflammatory condition not known to be due to a specific pathogen, as the result of antiretroviral therapy. This activity identifies the clinical criteria for the diagnosis of IRIS, reviews considerations for starting antiretroviral therapy in patients with opportunistic infections, and presents approaches to the management of patients with IRIS.

HIV-Associated Cognitive Impairment

by Miguel G. Madariaga, MD, and Susan Swindells, MBBS

HIV-associated cognitive impairment remains a difficult diagnosis that requires the exclusion of several other conditions including psychiatric illness, substance use, opportunistic infection, neoplasia, and other causes of dementia. This case will help learners distinguish between the clinical manifestations of HIV-associated cognitive impairment and those of conditions with a similar presentation. Learners will also consider the selection of appropriate diagnostic tests and the clinical management of an HIV-infected patient with this condition.

Issues in the Care of HIV and Hepatitis C Virus–Coinfected Patients: Antiretroviral Pharmacokinetics, Drug Interactions, and Liver Transplantation

by David L. Wyles, MD

An understanding of the sequelae of chronic hepatitis C virus (HCV) coinfection, such as antiretroviral drug intolerance and decompensated liver disease, is vital to the optimal management of coinfected patients. This presentation explains the impact of hepatic dysfunction on antiretroviral pharmacokinetics and the effect of antiretroviral therapy on the natural history of HCV infection. Learners will also identify unique issues in liver transplantation for end-stage liver disease resulting from HCV coinfection.

Treatment of Hepatitis C Virus and HIV Coinfection: Selecting Candidates for HCV Therapy and Managing Side Effects of Treatment

by Melissa K. Osborn, MD

Treatment of hepatitis C virus (HCV) is crucial in HIV-coinfected patients to slow progression to cirrhosis and end-stage liver disease. This state-of-the art activity describes the differences in the response to HCV therapy in HIV-coinfected patients compared with HCV-monoinfected patients. Learners will identify candidates for HCV therapy, management of the adverse effects of therapy, and treatment options for those who do not respond to peginterferon alfa and ribavirin therapy or who experience recurrence of active infection.

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The following guidelines describe the types of articles and contributions published in the journal, outline its policies, and provide instructions for authors. For further information, contact *Topics in HIV Medicine* at topics2009"at"iasusa.org.

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1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2007. Available at http://www.icmje.org. Accessed January 17, 2008.

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