

Topics in HIV Medicine®

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Perspectives

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The International AIDS Society–USA

About This Issue

This issue contains 3 *Perspectives* articles based on recent presentations at CME activities and conferences. At the 8th annual Ryan White CARE Act (RWCA) Clinical Conference in New Orleans in June 2005, Joel E. Gallant, MD, MPH, spoke about managing antiretroviral drug resistance. He detailed resistance profiles of specific antiretroviral drugs and drug classes, explained how to use these resistance profiles to select drug regimens, and discussed when and how to use genotypic and phenotypic testing in making clinical decisions. Also at the RWCA Clinical Conference, David A. Reznik, DDS, presented information on diagnosing and treating oral manifestations of HIV. His talk outlined symptoms, causes, and treatment. At the same conference, Toby A. Maurer, MD, discussed dermatologic manifestations of HIV and appropriate treatment options.

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Perspective

Antiretroviral Drug Resistance and Resistance Testing

Antiretroviral resistance testing should be performed in newly diagnosed patients with acute or recent HIV infection and at the time of treatment failure, and there is growing support for testing in newly diagnosed, treatment-naive patients with chronic infection as well. Genotypic testing is preferred for baseline screening, because it is more sensitive than phenotypic testing for the presence of mixed populations of drug-susceptible and -resistant virus and because it is less expensive. Phenotypic testing provides quantitative information on the degree of resistance and is also able to assess interactions among mutations. As a result, it can be particularly useful in determining treatment options for treatment-experienced patients with multi-drug resistant virus. In many cases, there may be advantages to the use of both tests. This article summarizes a presentation on antiretroviral resistance and resistance testing by Joel E. Gallant, MD, MPH, at the 8th Annual Clinical Conference for Ryan White CARE Act clinicians in New Orleans in June 2005.

Resistance Testing in Treatment-naive Patients

The International AIDS Society–USA, the US Department of Health and Human Services, and European guidelines recommend antiretroviral resistance testing for primary HIV infection and in cases of treatment failure. These guidelines also recommend or encourage consideration of testing in chronic infection of less than 2 years' duration.

US surveillance data indicate that transmission of resistant virus is a substantial and growing problem. Data gathered in 2003 and 2004 from 787 newly diagnosed antiretroviral therapy-naive subjects from 89 sites in 6 states indicate the presence of resistance to at least 1 antiretroviral drug class in 14.5% of cases, including resistance to nucleoside analogue reverse transcriptase inhibitors (nRTIs) in 7.1%, nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs) in 8.4%, protease inhibitors (PIs) in 2.8%, and 2 or more

classes in 3.1% (Bennet, CROI, 2005). Although it was once believed that acquired resistant strains would be quickly replaced by wild-type virus, it has become clear that resistant virus persists for prolonged periods. This phenomenon probably reflects the fact that only the resistant strain is transmitted, so that reversion to wild-type virus requires “back mutation,” a more time-consuming process than the selection of pre-existing wild-type strains that occurs in treatment-experienced patients. In one recent study, the average time to reversion to wild-type virus after identification of resistant strains among newly infected patients was 375 days for NNRTI-resistant virus and 362 days for nRTI-resistant virus; no reversion was seen with up to 2 years of follow-up for PI-resistant virus (Little, CROI, 2004). For this reason, there is growing support for resistance testing in chronically infected, treatment-naive patients. However, despite the persistence of mutant virus after infection, the diagnostic yield of resistance testing is highest with earlier testing. It is therefore recommended that resistance testing be performed at the time of HIV diagnosis, regardless of the current need for therapy; it can be assumed that transmitted resistance mutations will still

be present, even if not detected in the circulation, when therapy is eventually initiated. Genotypic analysis is preferred over phenotypic testing in this setting, primarily because it is more sensitive for the detection of mixtures of susceptible and resistant virus, which would be expected if reversion to wild-type had begun to occur at the time of testing. Genotyping is also faster and less expensive.

Resistance to nRTIs

Resistance patterns after initial failure of commonly used nRTI backbones and the resistance map for the individual nRTIs are shown in Figure 1. In patients in whom a combination that includes lamivudine plus either zidovudine or stavudine is failing, the M184V mutation is always the first to appear. It is eventually followed by cumulative acquisition of thymidine analogue-associated mutations (TAMs) if treatment with the nonsuppressive regimen is continued. It should be noted that TAMs are completely preventable mutations; they should become less common in the future, since patients with suppressive options should not be left on a failing thymidine analogue-based regimen. There are 6 TAMs: M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/N/R; the presence of these mutations confers cross-resistance to all nRTIs, with the degree of nRTI cross-resistance increasing as the number of TAMs increases (Johnson et al, *Top HIV Med*, 2005). The acquisition of TAMs is slowed by the presence of the M184V mutation, which also serves to partially counter the effects of TAMs on susceptibility to zidovudine, tenofovir, and stavudine. Figure 2 shows the fold change in drug susceptibility as a function of the number of TAMs with or without the presence of the M184V resistance mutation.

There are different pathways to

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Abacavir	K65R; L74V; Y115F; M184V
Didanosine	K65R; L74V
Emtricitabine	K65R; M184V/I
Lamivudine	K65R; M184V/I
Stavudine	M41L; E44D; K65R; D67N; K70R; V118I; L210W; T215Y/F; K219Q/E
Tenofovir	K65R
Zidovudine	M41L; E44D; D67N; K70R; V118I; L210W; T215Y/F; K219Q/E

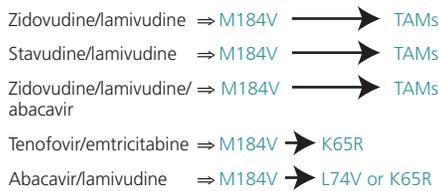


Figure 1. Top: Mutations that affect susceptibility to nucleoside (or nucleotide) analogue reverse transcriptase inhibitors (nRTIs). Adapted with permission from the International AIDS Society–USA (Johnson et al, *Top HIV Med*, 2005). For user notes and updated figures, visit www.iasusa.org. Bottom: Resistance patterns after initial failure of commonly used nRTI backbones. The longer arrow indicates the delay in emergence of thymidine analogue-associated mutations (TAMs) caused by M184V, which does not occur with K65R or L74V, for which the arrow is shorter.

resistance for nRTIs. In the case of zidovudine or stavudine therapy, as yet unidentified factors can result in acquisition of either the M41L, L210W, and T215Y TAMs or the D67N, K70R, and K219Q/E/N/R mutations. The former pathway is associated with higher-level zidovudine resistance, greater nRTI cross-resistance, and a smaller decrease in resistance in the presence of the M184V mutation. The D67N, K70R, and K219Q pathway is associated with a lower level of zidovudine resistance, less nRTI cross-resistance, and a greater decrease in resistance when M184V is present. Unfortunately, it appears to be the less common pathway. When abacavir, tenofovir, or didanosine are used with lamivudine or emtricitabine in the absence of thymidine analogues, the likely mutations are M184V, K65R, and L74V, which result in variable decreases in susceptibility to abacavir, tenofovir,

and didanosine but maintained susceptibility to thymidine analogues. K65R is the signature mutation of tenofovir; it can also emerge with abacavir, though L74V is more common. In the presence of zidovudine (and, to a lesser extent, stavudine), the pathway involves the acquisition of the M184V mutation and TAMs, resulting, as already noted, in resistance to both thymidine analogues and other nRTIs.

A brief profile of nRTI resistance mutations and their effects is shown in Table 1, and some sequencing options in cases of specific mutations are shown in Table 2. Options in the presence of TAMs depend on whether M184V is present and on the particular resistance pathway exhibited. Phenotypic testing may be useful when multiple TAMs are present.

Resistance to NNRTIs

Resistance mutations selected by NNRTIs are shown in Figure 3. NNRTI-associated resistance mutations, the most common of which is K103N, are common at the time of virologic failure and may occur as the first resistance mutations, even preceding the detection of M184V. Most NNRTI resistance is associated with high-level cross-resistance to other drugs in the

class. There are limited prospects for sequential use of currently available NNRTIs following virologic failure with resistance. It had been proposed that efavirenz would be active in cases of nevirapine failure due to the Y181C mutation, but poor results were observed with clinical sequencing, possibly because of the presence of low levels of K103N not detected by commercial assays. Mutations at codons 190 and 225 are associated with delavirdine hypersusceptibility, but there are no clinical data to support delavirdine use in this setting. There are some investigational second-generation NNRTIs that are promising with regard to potential sequential use, such as TMC-125 and TMC-278, and it is hoped that such drugs will remain active in the presence of the K103N and other mutations. However, it is currently advisable to use NNRTIs only in fully virologically suppressed patients. NNRTI resistance mutations do not reduce replicative fitness of the virus as do some resistance mutations to nRTIs or PIs. In addition, continued use of an NNRTI in a non-suppressive regimen allows accumulation of additional NNRTI resistance mutations that may jeopardize the future use of the second-generation NNRTIs now in development.

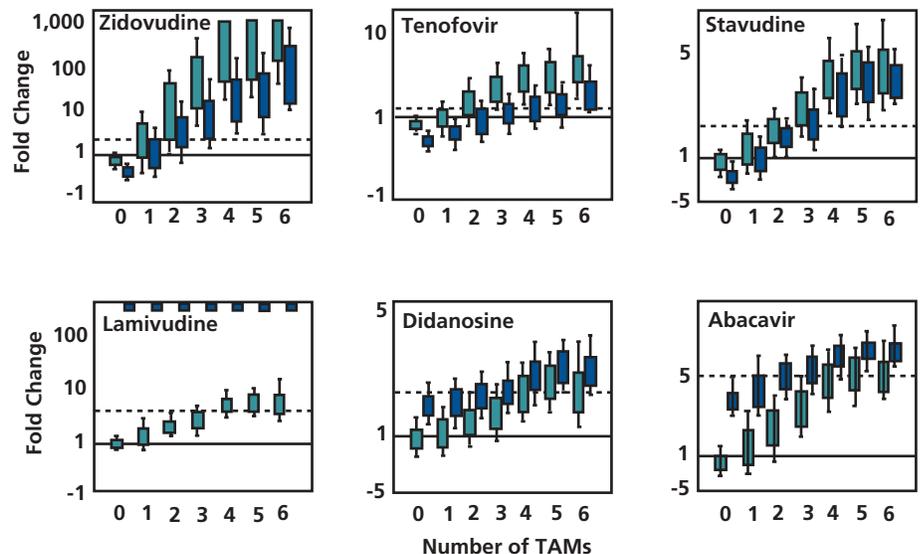


Figure 2. Change in susceptibility as a function of the number of thymidine analogue-associated mutations (TAMs) and the presence of the M184V mutation. Green indicates presence of wild-type M184; blue indicates presence of mutant M184V. Adapted with permission from Whitcomb et al, *J Infect Dis*, 2003.

Table 1. Selected Important Information on Nucleoside (and Nucleotide) Analogue Reverse Transcriptase Inhibitor Resistance

Mutation(s)	Selected by	Effects on other Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)
M184V	Lamivudine, emtricitabine	<ul style="list-style-type: none"> Loss of susceptibility to lamivudine, emtricitabine ↓ Susceptibility to abacavir, didanosine (clinically insignificant) Delayed TAMs and ↑ susceptibility to zidovudine, stavudine, tenofovir
TAMs	Zidovudine, stavudine	<ul style="list-style-type: none"> ↓ Susceptibility to all nRTIs based on number of TAMs Greatest loss of susceptibility with the M41L/L210W/T215Y pathway
Q151M complex, T69 insertion	Zidovudine/didanosine, didanosine/stavudine	<ul style="list-style-type: none"> Q151M complex: resistance to all nRTIs except tenofovir T69 insertion: resistance to all nRTIs
K65R	Tenofovir, abacavir, didanosine	<ul style="list-style-type: none"> Variable ↓ susceptibility to tenofovir, abacavir, didanosine (and lamivudine, emtricitabine) ↑ Susceptibility to zidovudine
L74V	Abacavir, didanosine	<ul style="list-style-type: none"> ↓ Susceptibility to abacavir, didanosine ↑ Susceptibility to zidovudine, tenofovir
E44D, V118I	Zidovudine, stavudine	<ul style="list-style-type: none"> Increased nRTI resistance (with M41L/L210W/T215Y pathway)

TAMs indicates thymidine analogue-associated mutations; nRTIs, nucleoside (and nucleotide) analogue reverse transcriptase inhibitors.

Resistance to PIs

PI resistance mutations and resistance patterns after initial failure of commonly used PIs are shown in Figure 4, and the major mutations for each agent are highlighted in bold. Some major mutations are not associated with PI cross-resistance, notably the D30N nelfinavir resistance mutation and the I50L atazanavir resistance mutation. However, many other major PI mutations, such as mutations at codons 82, 84, and 90, are associated with significant cross-resistance. Accumulation of minor mutations, which by themselves do not cause resistance, can increase cross-resistance in the presence of major mutations. It is notable with regard to PIs that HIV does not always seem to “know the rules” regarding resistance, making sequencing after failure problematic. For example, although it has been argued that nelfinavir failure is

not associated with cross-resistance to other PIs because of the emergence of the unique D30N mutation, it is now known that it is not uncommon for L90M to emerge instead of D30N. Finally, PI resistance mutations are emerging less frequently today because of the widespread use of ritonavir-boosted regimens. Data from previously PI-naïve patients show that failure with several of the ritonavir-boosted PIs is not associated with PI resistance. Furthermore, since the accumulation of PI mutations is gradual and sequential, like that of TAMs, it can be prevented by responding promptly to early virologic failure rather than allowing continued therapy with a nonsuppressive PI-based regimen.

Resistance to Enfuvirtide

As with NNRTIs, there appears to be a low genetic barrier to resistance to the

fusion inhibitor enfuvirtide. Resistance to this agent has been observed at early virologic failure, and failure often is associated with rapid viral rebound to baseline HIV RNA level. In one study, enfuvirtide was stopped in 22 patients with detectable viremia while on enfuvirtide, and only a small viral rebound was observed when the drug was discontinued. Phenotypic susceptibility to the drug reemerged by week 16 in most of these patients, and although there was increased replicative fitness of the virus as resistance faded, there was very little change in plasma viral load. Such findings suggest that there is no benefit to continuing enfuvirtide once resistance has emerged and underscore the importance of using enfuvirtide in combination with other active agents.

Phenotypic Testing

Advantages of phenotypic testing for resistance include relatively easy interpretation, the ability to provide quantitative information on the degree of resistance, the ability to assess interactions among resistance mutations on overall resistance and susceptibility, and the fact that it does not require an understanding of genotypic corre-

Table 2. Some Nucleoside (or Nucleotide) Analogue Reverse Transcriptase Inhibitor Sequencing Options for Specific Genotypic Resistance Patterns

Mutation(s)	Sequencing Options
K65R	Zidovudine > stavudine, with or without abacavir
K65R with M184V	Zidovudine > stavudine, with or without tenofovir
L74V with or without M184V	Zidovudine, tenofovir > stavudine
M184V	Zidovudine, stavudine, tenofovir > abacavir, didanosine
TAMs with or without M184V	Depends on the number of TAMs and the TAM pathway

TAMs indicates thymidine analogue-associated mutations.

Delavirdine	K103N; V106M; Y181C; Y188L; P236L
Efavirenz	L100I; K103N; V106M; V108I; Y181C/I; Y188L; G190S/A; P225H
Nevirapine	L100I; K103N; V106A/M; V108I; Y181C/I; Y188C/L/H; G190A
Multi-NNRTI Resistance	K103N; V106M; Y188L
Multi-NNRTI Resistance: Accumulation of Mutations	L100I; V106A; V181C/I; G190S/A; M230L

Figure 3. Mutations selected by nonnucleoside reverse transcriptase inhibitors. Adapted with permission from the International AIDS Society–USA (Johnson et al, *Top HIV Med*, 2005). For user notes and updated figures, visit www.iasusa.org.

lates of resistance. Phenotypic analysis determines the degree to which a drug inhibits replication of the patient’s virus, with the results showing the fold change in 50% inhibitory concentration (IC₅₀) compared with a wild-type reference HIV. Interpreting the results is not as straightforward as it may appear, however, since it may be unclear what fold-change cutoff should be used to indicate decreased susceptibility. The likelihood of response to a drug decreases gradually with increasing fold change, as in the example shown in Figure 5, so that the cutoff used on a phenotypic report turns quantitative data into a qualitative determination of resistance versus susceptibility. Studies with tenofovir showed that the best virologic response was achieved in patients whose fold change was less than 1.4, partially reduced when at 1.4 to 4, and that the drug was virtually inactive in the setting of greater than 4-fold resistance (Figure 5; Miller et al, *J Infect Dis*, 2004). Knowledge of such gradations in response are helpful for treatment-experienced patients with limited options, for whom it may be necessary to use drugs with partial susceptibility. Phenotypic reports also indicate whether cutoffs are derived from clinical data or simply from in vitro testing; more confidence can be placed in

clinical cutoffs than biologic ones.

Phenotyping should be considered after multiple regimen failures when mutation patterns and their interpretation are likely to be complex, or when there may be limited treatment options making even partial activity desirable. The presence of multiple TAMs or PI mutations can be especially difficult to interpret genotypically. Phenotyping can also be used to evaluate viral susceptibility to newer drugs, or for patients infected with nonsubtype-B HIV, since in both cases genotypic correlates of resistance may not be well-established. Finally, phenotypic testing may prove useful in correlating resistance with blood drug levels (ie, in determining inhibitory quotient) or viral fitness (replication capacity).

Other Approaches to Genotypic Testing

One form of genotypic testing uses a database to predict phenotype, as opposed to the standard algorithmic approach to interpretation. In this

case, the genotype is used to provide an estimated, or “virtual,” phenotype based on comparison with a large database of paired genotypic and phenotypic test results. The cost of the test is slightly more than that of genotyping alone.

Combined Resistance Testing

Another popular, though expensive, approach is combination genotypic-and-phenotypic testing, which offers the advantages of both tests and is particularly useful when mixtures of virus are present (eg, when there is low-level emerging or reverting resistance). In addition to indicating the results of both tests, the report provides a net assessment of viral susceptibility to each drug, which is useful in cases of discordance between genotypic and phenotypic results. In general, if phenotypic test results indicate resistance and genotypic test results indicate susceptibility, it is assumed that the phenotype is a more accurate measure of susceptibility. The same is true when phenotyping suggests sus-

Atazanavir	L10I/F/V; G16E; K20R/M/I; L24I; V32I; L33I/F/V; M36I/L/V; M46I/L; G48V; I50L ; I54L/V/M/T; D60E; I62V; A71V/I/T/L; G73C/S/T/A; V82A/T; I84V ; I85V; N88S ; L90M; I93L
Fosamprenavir	L10F/I/R/V; V32I; M46I/L; I47V; I50V ; I54L/V/M; G73S; V82A/F/T/S; I84V ; L90M
Indinavir	L10I/R/V; K20M/R; L24I; V32I; M36I; M46I/L ; I54V; A71V/T; G73S/A; V77I; V82A/F/T ; I84V ; L90M
Lopinavir/ritonavir	L10F/I/R/V; K20M/R; L24I; V32I ; L33F; M46I/L; I47V/A ; I50V; F53L; I54V/L/A/M/T/S; L63P; A71V/T; G73S; V82A/F/T/S ; I84V; L90M
Nelfinavir	L10F/I; D30N ; M36I; M46I/L; A71V/T; V77I; V82A/F/T/S; I84V; N88D/S; L90M
Ritonavir	L10F/I/R/V; K20M/R; V32I; L33F; M36I; M46I/L; I50V; I54V/L; A71V/T; V77I; V82A/F/T/S ; I84V ; L90M
Saquinavir	L10I/R/V; G48V ; I54V/L; A71V/T; G73S; V77I; V82A; I84V; L90M
Tipranavir/ritonavir	L10V; I13V; K20M/R; L33F ; E35G; M36I; K43T; M46L; I47V; I54A/M/V; Q58E; H69K; T74P; V82L/T ; N83D; I84V ; L90M

Atazanavir	→	I50L
Atazanavir/r	→	?
Fosamprenavir	→	154L/M, V32I + 147V
Fosamprenavir/r	→	None
Lopinavir/r	→	None
Nelfinavir	→	D30N > L90M

Figure 4. Top: Mutations selected by protease inhibitors. Major mutations are highlighted in bold. Adapted with permission from the International AIDS Society–USA (Johnson et al, *Top HIV Med*, 2005). For user notes and updated figures, visit www.iasusa.org. Bottom: Resistance patterns after initial failure of commonly used protease inhibitors. /r indicates ritonavir-boosted.

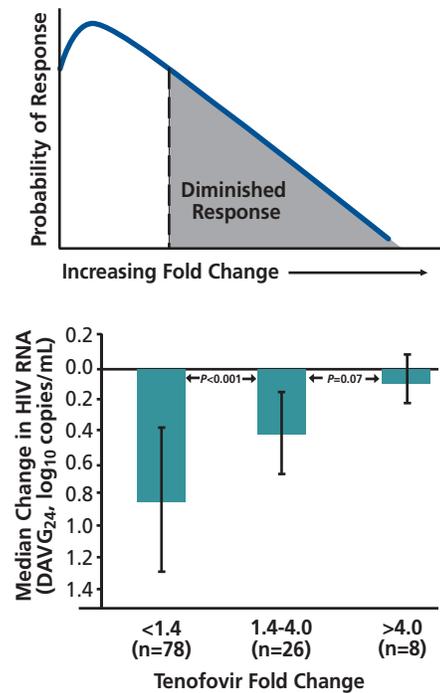


Figure 5. Top: Probability of virologic response to a drug according to fold increase in resistance; the dotted line marks the clinical cutoff (the fold change at which the virologic response begins to decline below wild-type susceptibility). Bottom: Reduction in viral load with tenofovir treatment according to baseline susceptibility of virus (tenofovir fold change). DAVG₂₄ indicates difference in average HIV RNA level between baseline and week 24. Adapted from data in Miller et al, *J Infect Dis*, 2004.

ceptibility and genotyping indicates resistance, unless mixtures of wild-type and mutant virus are present on the genotype, in which case the phenotype may underestimate the degree of resistance. The detection of mixtures by the genotype indicates the presence at low levels of mutants that may be emerging or that could become predominant with selective pressure. Some practitioners rarely order phenotyping without genotyping because of the concern about missing mixtures. Other reasons for discordance between the phenotypic and genotypic test results include interactions among mutations, as in the case of “resensitizing” mutations, or incomplete genotypic algorithms.

For example, there may be novel resistance mutations whose effects on viral susceptibility are not yet defined, and specific mutations may be under-weighted or over-weighted because their effect on susceptibility is not fully understood. Also, since most of the data on genotypic resistance comes from patients infected with subtype-B virus, interpretation of genotypes in patients infected with other subtypes may be difficult.

Limitations of Resistance Tests

All currently available forms of resistance testing have limitations. They cannot detect minority populations of virus in a mixture (eg, those accounting for less than about 20% of the sample) and they cannot detect resistant virus archived in viral reservoirs. Because of the ability of wild-type virus to replace mutant virus when selective drug pressure is withdrawn, resistance tests are most reliable at predicting activity of drugs or drug classes that the patient is currently taking. For example, a patient with a distant history of NNRTI failure may no longer demonstrate the presence of the K103N mutation on a genotype, but its presence can and should be inferred, as it would emerge rapidly if NNRTI treatment were to be reinstated. It is crucial to remember that the patient’s viral resistance should be assessed based on the results of the current resistance test plus any and all prior resistance tests, or, when prior tests are not available, based on assumptions made about resistance based on a review of the treatment history. Finally, resistance testing requires a minimum viral load (around 500 to 1000 plasma HIV RNA copies/mL). This can be a problem in patients with early virologic failure, since waiting until the viral load is high enough for resistance testing may sometimes guarantee the emergence of additional resistance mutations.

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Suggested Reading

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Perspective

Oral Manifestations of HIV Disease

HIV-related oral conditions occur in a large proportion of patients, and frequently are misdiagnosed or inadequately treated. Dental expertise is necessary for appropriate management of oral manifestations of HIV infection or AIDS, but many patients do not receive adequate dental care. Common or notable HIV-related oral conditions include xerostomia, candidiasis, oral hairy leukoplakia, periodontal diseases such as linear gingival erythema and necrotizing ulcerative periodontitis, Kaposi's sarcoma, human papilloma virus-associated warts, and ulcerative conditions including herpes simplex virus lesions, recurrent aphthous ulcers, and neutropenic ulcers. This article summarizes a presentation on oral manifestations of HIV disease made by David A. Reznik, DDS, at the 8th Annual Clinical Conference for Ryan White CARE Act Clinicians in New Orleans in June 2005.

In 2000, US Surgeon General David Satcher stated, "Those who suffer the worst oral health include poor Americans. Members of racial and ethnic groups also experience a disproportionate level of oral health problems. And people with disabilities and complex health conditions are at greater risk for oral diseases that, in turn, further complicate their health."

Dental expertise is necessary for proper management of oral complications in HIV infection or AIDS. Medical clinicians should be able to recognize HIV-associated oral disease and to provide appropriate care and referral. Factors that predispose to HIV-related oral conditions include CD4+ cell count of less than 200/ μ L, plasma HIV-RNA levels greater than 3000 copies/mL, xerostomia, poor oral hygiene, and smoking. For individuals with unknown HIV status, oral manifestations may suggest possible HIV infection, although they are not diagnostic of infection. For persons living with HIV disease who are not yet on therapy, the presence of certain oral manifestations may signal progression of HIV disease. For patients on antiretroviral therapy, the presence of certain oral manifestations may signal an increase in the plasma HIV-1 RNA level.

HIV-related oral abnormalities are present in 30% to 80% of HIV-infected individuals, and these abnormalities are often inaccurately described in medical care. Rates of treatment for oral conditions are also very low; findings in 1424 adults in the AIDS Cost and Utilization Study indicated that only 9.1% received treatment for oral manifestations of HIV disease (Mascarenhas, *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 1999). Factors predictive of receiving oral care included education beyond a high school level, participation in clinical trials, and utilization of support services such as medical social workers. African-Americans and Hispanic-Americans were significantly less likely to receive treatment than were white patients. The overall prevalence of oral manifestations of HIV disease has changed since the advent of potent antiretroviral therapy. One study by Patton and colleagues noted a reduction of oral lesions from 47.6% pre-potent antiretroviral therapy to 37.5% during the potent antiretroviral therapy era (*Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 2000). Overall, there appears to be a reduced incidence of candidiasis, Kaposi's sarcoma, oral hairy leukoplakia, and necrotizing ulcerative periodontitis; an increased incidence of salivary gland disease, oral warts, and dental caries in the form of "brittle teeth syndrome;" and a relatively unchanged

incidence of oral ulcers.

Some of the oral conditions encountered in HIV-infected individuals are discussed below. A good resource for information on these and other conditions is www.hivdent.org.

Xerostomia

Xerostomia is a major contributing factor in dental decay in HIV-infected individuals. More than 400 medications lead to symptoms of xerostomia. Approximately 30% to 40% of HIV-infected individuals experience moderate to severe xerostomia in association with the effects of medications (eg, didanosine) or the proliferation of CD8+ cells in the major salivary glands. Changes in the quantity and quality of saliva, including diminished antimicrobial properties, lead to rapidly advancing dental decay and periodontal disease (Figure 1).

Use of crystal methamphetamine is associated with increased risk of HIV acquisition, and its use by infected individuals can be associated with rapid dental decay known as "meth mouth" (Figure 2). The primary factor in this condition is probably xerostomia, with contributions from bruxism, poor diet, sugar cravings, and the corrosive constituents of crystal methamphetamine—ie, lithium, muriatic and sulfuric acids, and lye.

Candidiasis

The 3 common presentations of oral candidiasis are angular cheilitis, erythematous candidiasis, and pseudomembranous candidiasis.

Angular cheilitis presents as erythema or fissuring of the corners of the mouth (Figure 3). It can occur with or without erythematous or pseudomembranous candidiasis, and can persist for an extensive period of time if left untreated. Treatment involves the use of a topical antifungal cream

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applied directly to the affected areas 4 times a day for the 2-week treatment period.

Erythematous candidiasis may be the most underdiagnosed and misdiagnosed oral manifestation of HIV disease. The condition presents as a red, flat, subtle lesion on the dorsal surface of the tongue or on the hard or soft palates (Figure 4). It may present as a “kissing” lesion—if a lesion is present on the tongue, the palate should be examined for a matching lesion, and vice versa. The condition tends to be symptomatic, with patients complaining of oral burning, most frequently while eating salty or spicy foods or drinking acidic beverages. Clinical diagnosis is based on appearance, as well as on the patient’s medical history and virologic status. The presence of fungal hyphae or, more likely, blastospores can be confirmed by performing a potassium hydroxide (KOH) preparation.

Pseudomembranous candidiasis (or thrush) appears as creamy, white, curd-like plaques on the buccal mucosa, tongue, and other oral mucosal surfaces. The plaques can be wiped away, typically leaving a red or bleeding underlying surface. The most common organism involved is *Candida albicans*; however, there are increasing reports of involvement of non-*albicans* species. As with erythematous candidiasis, diagnosis is based on appearance. Figure 5A shows a mild to moderate case; Figure 5B shows more severe disease.

Topical treatments for mild to moderate cases of both erythematous and pseudomembranous candidiasis include clotrimazole troches, nystatin oral suspension, and nystatin pastilles (Table 1). It should be noted that the common nystatin oral suspension contains 50% sucrose, which is cariogenic; this is less of a potential problem if fluoride is prescribed along with the nystatin. The clotrimazole oral treatment is formulated with fructose, which is less cariogenic. Systemic agents for moderate to severe disease consist of fluconazole, the most widely used drug; itraconazole; and voriconazole, the latter of which should be reserved for cases

Table 1. Topical and Systemic Agents for Oral Candidiasis

Topical agents (mild to moderate oral candidiasis)	
Clotrimazole troches	10 mg: Dispense 70, dissolve 1 troche in mouth 5 times a day for 14 days
Nystatin oral suspension	500,000 units: Swish 5 mL in mouth as long as possible then swallow (optional), 4 times a day for 14 days
Nystatin pastilles	100,000 units: Dispense 56, dissolve 1 in mouth 4 times a day for 14 days
Systemic agents	
Fluconazole	100 mg: Dispense 15 tablets, take 2 tablets on day 1, followed by 1 tablet a day for the remainder of the 14-day treatment period
Itraconazole oral suspension	10 mg/10 mL: Dispense 140 mL, swish and swallow 10 mL per day for 7 to 14 days. Take medication without food
Voriconazole	200 mg: Dispense 14 tablets, take 1 tablet twice daily for 2 weeks or at least 7 days following resolution of symptoms
Drug interactions	
Contraindications: rifampin, rifabutin, ritonavir, and efavirenz (all are potent CYP450 inducers). Drug interactions are most significant with voriconazole and present with itraconazole oral suspension, but less critical with fluconazole	

of fluconazole resistance (Table 1). Figure 6A shows disease with fluconazole-resistant *Candida albicans*; its attachment to tissue is stronger, and it is more difficult to wipe away than azole-susceptible candidiasis. Figure 6B shows disease due to *Candida glabrata*, which is intrinsically azole-resistant. Factors associated with azole-resistant disease include prior exposure to azoles, low CD4+ cell count, and presence of non-*albicans* species.

The primary lesson to be learned in the treatment of any candidiasis—whether it be with a topical agent for mild to moderate disease or a systemic agent for more severe disease—is that treatment must be continued for at least 2 weeks in order to reduce organism colony-forming units to levels low enough to prevent recurrence.

Oral Hairy Leukoplakia

Oral hairy leukoplakia, which is caused by Epstein-Barr virus, presents as a white, corrugated lesion

on the lateral borders of the tongue; the lesion cannot be wiped away (Figure 7). There has been a marked decrease in the incidence of oral hairy leukoplakia in the potent antiretroviral era. This condition is normally asymptomatic and does not require therapy unless there are cosmetic concerns. However, it is important to note that the condition is observed with immune deterioration and that patients presenting with it while on antiretroviral therapy may thus be experiencing failure of their current regimen.

Periodontal Disease

Linear gingival erythema

Linear gingival erythema, or “red band gingivitis,” presents as a red band along the gingival margin and may or may not be accompanied by occasional bleeding and discomfort (Figure 8). It is seen most frequently in association with anterior teeth, but

commonly extends to the posterior teeth. It can also present on attached and non-attached gingiva as petechial-like patches. Some data indicate a relationship between sub-gingival colonization of *Candida* species and HIV-related periodontal conditions including linear gingival erythema. The most recent American Academy of Periodontology classification of periodontal diseases groups linear gingival erythema under “gingival disease of fungal origin.” However, antifungals typically are not needed for treatment. Treatment includes debridement by a dental professional, twice-daily rinses with a 0.12% chlorhexidine gluconate suspension for 2 weeks, and improved home oral hygiene.

Necrotizing Ulcerative Periodontitis

Although necrotizing gingivitis and necrotizing periodontitis may reflect the same disease entity, they are differentiated by the rapid destruction of soft tissue in the former condition and hard tissue in the latter. Necrotizing ulcerative periodontitis is a marker of severe immune suppression. The condition is characterized by severe pain, loosening of teeth, bleeding, fetid odor, ulcerated gingival papillae, and rapid loss of bone and soft tissue (Figure 9). Patients often refer to the pain as “deep jaw pain.” Treatment includes removal of dental plaque, calculus, and necrotic soft tissues utilizing a 0.12% chlorhexidine gluconate or 10% povidone-iodine lavage, and institution of antibiotic therapy (Table 2). Pain management is crucial, as is attention to nutrition in these patients. Timely referral to primary care is indicated to rule out other systemic opportunistic infections.

Kaposi’s Sarcoma

Kaposi’s sarcoma is still the most frequent HIV-associated oral malignancy, although its incidence has dramatically decreased in the potent antiretroviral therapy era. Kaposi’s sarcoma-associated herpesvirus (KSHV) has been identified as the etiologic agent.

Table 2. Management of Necrotizing Ulcerative Periodontitis

Initial visit

- Prescribe narrow spectrum antibiotics such as metronidazole 500 mg, dispense 14 to 20 tablets, take 1 tablet twice daily for 7 to 10 days. Other antibiotic options include clindamycin and amoxicillin
- Pain management is extremely important
- Nutritional supplementation or counseling may be necessary

Follow-up visits

- Detailed periodontal care, such as scaling and root planing

Kaposi’s sarcoma can be macular, nodular, or raised and ulcerated, with color ranging from red to purple (Figure 10); early lesions tend to be flat, red, and asymptomatic, with the color becoming darker as the lesion ages. Diagnosis is frequently missed in African-American patients due to lesion coloration. Progressing lesions can interfere with the normal functions of the oral cavity and become symptomatic secondary to trauma or infection. Definitive diagnosis requires biopsy. Treatment ranges from localized injections of chemotherapeutic agents, such as vinblastine sulfate, to surgical removal. Oral hygiene must be stressed. Systemic chemotherapy may be the treatment of choice for patients with extraoral and intraoral Kaposi’s sarcoma.

Oral Warts—Human Papilloma Virus

The incidence of oral warts due to human papillomavirus (HPV) has dramatically increased in the potent antiretroviral therapy era. Studies at the author’s institution indicate that the risk of HPV-associated oral warts is associated with a 1-log₁₀ or greater decrease in plasma HIV RNA level within the 6 months prior to oral HPV diagnosis, suggesting that the develop-

ment of warts may be related to immune reconstitution. The warts may be cauliflower-like, spiked, or raised with a flat surface (Figure 11). Treatment may involve surgery, laser surgery, or cryotherapy. It should be noted that HPV survives in aerosol. Topical 5-fluorouracil treatment has been used on external lesions, but should be avoided in African-American patients since it can cause hyperpigmentation. It should be noted, however, that this is a specialized treatment and should only be used by those experienced with the use of this topical medication. Lesions tend to recur after treatment.

Ulcerative Diseases

Herpes simplex virus

Herpes simplex virus (HSV)-1 infection is widespread and oral lesions are common. Recurrent intraoral HSV outbreaks start as a small crop of vesicles that rupture to produce small, painful ulcerations that may coalesce. Lesions on the lip are fairly easy to recognize. In the mouth, lesions on keratinized, or fixed, tissues, including the hard palate and gums, should prompt suspicion of HSV infection (Figure 12). Herpetic ulcerations are often self-limiting, although the use of an antiviral medication such as acyclovir is sometimes necessary to control the outbreak.

Aphthous ulcerations

Recurrent aphthous ulcerations appear on non-keratinized, or non-fixed, tissues, such as the labial or buccal mucosa, floor of the mouth, ventral surface of the tongue, posterior oropharynx, and maxillary and mandibular vestibules (Figure 13). Their cause is unknown. The lesions are characterized by a halo of inflammation and a yellow-gray pseudomembranous covering. They are very painful, especially during consumption of salty, spicy, or acidic foods and beverages, or hard or rough foods. In immunocompromised patients, these lesions tend



Figure 1. Cervical caries occurring in association with xerostomia.



Figure 5a. Pseudomembranous candidiasis—mild or moderate disease.



Figure 8. Linear gingival erythema.



Figure 2. Dental decay in less than 1 year (from left to right) with “meth mouth.”



Figure 5b. Pseudomembranous candidiasis—more severe disease.



Figure 9. Necrotizing ulcerative periodontitis.



Figure 3. Angular cheilitis.



Figure 6a. Oral candidiasis due to fluconazole-resistant *Candida albicans*.

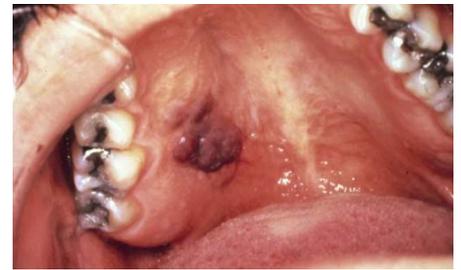


Figure 10a. Kaposi's sarcoma.



Figure 4a. Erythematous candidiasis.



Figure 6b. Oral candidiasis due to fluconazole-resistant *Candida glabrata*.



Figure 10b. Kaposi's sarcoma.



Figure 4b. Erythematous candidiasis.



Figure 7. Oral hairy leukoplakia.



Figure 11a. HPV-associated warts.



Figure 11b. HPV-associated warts.



Figure 13b. Aphthous ulceration.



Figure 11c. HPV-associated warts.



Figure 14a. Neutropenic ulcerations in a patient before therapy.



Figure 12a. HSV-1 lesion.



Figure 14b. Neutropenic ulcerations in the patient shown in Figure 14a after therapy.



Figure 12b. HSV-1 lesion.



Figure 13a. Aphthous ulceration.

to persist for longer than the 7- to 14-day period observed in immunocompetent individuals. Treatment for milder cases involves the use of topical corticosteroids such as dexamethasone elixir (0.5 mg/5 mL) 5 mL swished for 1 minute and then expectorated, 2 to 3 times daily until symptoms resolve. For more severe occurrences, systemic corticosteroids such as prednisone are used.

Neutropenic ulcerations

Neutropenic ulcerations are very painful ulcerations that can appear on both keratinized and non-keratinized tissues, and are associated with absolute granulocyte counts of less than 800/ μ L (Figure 14). These lesions are being found with increasing frequency in the HIV-infected population, although

the cause of this increase in frequency remains unknown. Large, unusual-looking, or fulminant ulcers in the oral cavity that cannot otherwise be identified or explained should prompt suspicion of this condition. Patients should receive granulocyte colony-stimulating factor treatment prior to systemic or topical steroid treatment, depending on the size and location of the lesion.

Pain in ulcerative disease

Pain management is a crucial component of treating ulcerative oral diseases. Pain usually is treated with topical anesthetics or systemic analgesics. However, relief provided by topical anesthetics is usually of short duration. Furthermore, anesthetic mouth rinses numb the taste buds, resulting in a decreased desire to eat, and diminished nutritional intake can have a significant negative impact on overall well-being for many patients. Systemic analgesics are also somewhat effective, but do not specifically address localized pain. One product that has been found to be effective in ulcer pain control is a rinse composed of polyvinylpyrrolidone, hyaluronic acid, and glycyrrhetic acid. If other topical treatments are to be used (eg, topical steroids), they should be applied prior to use of this rinse, since the barrier formed by the product will prevent penetration of the other topical medications.

Conclusion

Oral conditions seen in association with HIV disease are still quite prevalent and clinically significant. A thorough examination of the oral cavity can easily detect most of the common lesions. An understanding of the recognition, significance, and treatment of said lesions by primary health care providers is essential for the health and well-being of people living with HIV disease.

Presented by David A. Reznik, DDS, in June 2005. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Reznik in November 2005.

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Perspective

Dermatologic Manifestations of HIV Infection

Although some dermatologic diseases have decreased markedly in frequency in the potent antiretroviral therapy era, other conditions remain common. Among patients with low CD4+ cell counts who are not on or not adherent to antiretroviral therapy, notable conditions include psoriasis, photodermatitis, prurigo nodularis, molluscum, and adverse drug reactions. Conditions that remain relatively common despite adequate antiretroviral therapy include eczema, xerosis, warts, and Kaposi's sarcoma. Disorders that are associated with immune reconstitution under potent antiretroviral therapy include acne, staphylococcal infections, and erythema nodosum. In addition, HIV and hepatitis C virus (HCV) coinfection is associated with a number of skin disorders. This article summarizes a presentation on dermatologic manifestations of HIV disease by Toby A. Maurer, MD, at the 8th Annual Clinical Conference for Ryan White CARE Act clinicians in New Orleans in June 2005.

In many locales in the United States, the frequency of dermatologic diseases in HIV-infected patients—including seborrheic dermatitis, fungal diseases, psoriasis, and opportunistic infections with skin manifestations—has declined with the use of potent antiretroviral therapy. However, dermatologic disorders remain common in the HIV-infected population.

Conditions in Patients With CD4+ Cell Counts Below 200/ μ L Who Are Not on Antiretroviral Therapy

Common conditions in patients with CD4+ cell counts less than 200/ μ L who are not on antiretroviral therapy include severe psoriasis (usually affecting more than 50% of the body), extreme photodermatitis, prurigo nodularis, molluscum, and recurrent drug reactions.

Psoriasis

With the institution of antiretroviral therapy, psoriasis can be controlled with topical treatments, such as clobetasol and calcipotriene and ultraviolet light. Before adequate immune reconstitution under antiretroviral therapy

occurs or in cases of complex or more severe psoriasis, treatment with the retinoid agent acitretin at 10 to 25 mg/d can be considered; it should be noted that this agent is associated with increases in triglycerides and cholesterol. Psoriasis in HIV disease can have unusual presentations. Figure 1 shows inverse psoriasis of the feet and underarm, differing from the common presentation of psoriasis on extensor surfaces.

Photodermatitis

Figure 2 shows photodermatitis of the face, the “vee” of the neck, and the arm and hand, with the typical darkening of skin that is exposed to sun. Persons with background pigment of the skin (ie, people of color) are more photosensitive than persons without background pigment in the skin. HIV infection itself is photosensitizing, and patients with low CD4+ cell counts may be receiving photosensitizing drugs such as trimethoprim/sulfamethoxazole (TMP/SMX). Antiretroviral therapy allows patients to go off photosensitizing drugs and also decreases the reaction through immune reconstitution. Treatment includes sunscreen, potent topical steroids (eg, clobetasol), lubricants, and antihistamines. The tricyclic doxepin (25 mg qhs) is useful for its strong antihistamine effects.

Prurigo nodularis

Figure 3 shows prurigo nodularis (“itchy bumps”) of the arms and trunk. The disorder, which may have a photo-component, is more frequently seen in patients with CD4+ cell counts below 50/ μ L and is more common in persons of color. Patients are consumed by itching, which is not relieved with antihistamines. Institution of antiretroviral therapy is helpful in resolving the condition. Potent topical steroids should be used, and thalidomide is effective when it is started at a dose of 50 mg/d and titrated for response (rarely above 100 mg/d). Careful monitoring for development of peripheral neuropathies is suggested. In addition, thalidomide is a teratogen and special precautions need to be taken in women of childbearing potential.

Figure 4 shows a condition characterized by numerous papules smaller than those typically seen in prurigo nodularis; for years, this condition has been unhelpfully described as “pruritic eruption of HIV.” This is a common condition in areas of Africa, and a study was recently performed in Ugandan patients to determine the cause of the disorder (Resneck, *JAMA*, 2004). Of 102 lesion biopsies, 86 showed evidence of bug bites. A lower CD4+ cell count was significantly associated with greater severity of eruption, and the condition appeared to improve in patients started on antiretroviral therapy. The condition may thus represent hypersensitivity to bug bites secondary to immune deficiency.

Molluscum

Figure 5 shows severe facial molluscum. Molluscum is frequently seen in HIV-infected young women and men of any age who are not on antiretroviral therapy or are not adherent to their regimen. Its appearance fairly assures

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Figure 1a. Inverse psoriasis of the feet.



Figure 3. Prurigo nodularis.



Figure 7. Mosaic warts.



Figure 1b. Inverse psoriasis of the underarm (underarm psoriasis is also bilateral).



Figure 4. Pruritic papular eruption that appears to be due to hypersensitivity to bug bites.



Figure 8. Kaposi's sarcoma as it characteristically appears in the potent antiretroviral therapy era.



Figure 2a. Photodermatitis of the face and "vee" of the neck.



Figure 5. Severe facial molluscum.



Figure 9. Perioral dermatitis.



Figure 2b. Photodermatitis of the arm and hand.



Figure 6. Drug reaction producing full-body erythema.



Figure 10. Eosinophilic folliculitis.



Figure 11d. Staphylococcal infection can occur as cellulitis.



Figure 13c. Infection due to *Campylobacter* species can mimic erythema nodosum in appearance. Reprinted from Rajendran et al, *Arch Dermatol*, 2005.



Figure 11a. Staphylococcal infection can occur as abscesses.



Figure 12. HSV infection that was initially mistaken for staphylococcal infection.



Figure 11b. Staphylococcal infection can occur as ulcers.



Figure 13a. Erythema nodosum.



Figure 11c. Staphylococcal infection can occur as folliculitis.



Figure 13c. Infection due to *Helicobacter cinaedi* can mimic erythema nodosum in appearance.



Figure 14. HIV and hepatitis C virus coinfection-associated lichen planus (A) and vasculitis (B).

that the patient has a CD4+ cell count of less than 100/μL. First-line treatment is antiretroviral therapy. Liquid nitrogen provides only temporary treatment for the condition. We have found that curettage is successful in removing larger lesions and can be done without scarring.

Drug reactions

Figure 6 shows full-body erythema in a patient after starting a new drug. There is a group of patients with very low CD4+ cell counts (usually <50) who exhibit reactions to virtually every drug they are given, including antibiotics and antiretrovirals. Because of their low CD4+ cell counts, these are the very patients who require antiretrovirals and prophylactic antibiotics and are therefore at higher risk for drug reactions. A successful approach to reinstating drug treatment has been to put these patients on prednisone with a slow taper over 12 weeks while other drugs are individually added (Dolev, *Arch Derm*, 2004). In cases of drug reaction apart from such chronic reactions, steroids should be used only if the patient has a hypersensitivity reaction marked by elevated liver function test results or increased creatinine levels. Even in cases of erythema multiforme, Stevens-Johnson syndrome, or when urticaria is present, the best approach is simply to remove the offending drug and wait until the reaction resolves. Drug clearance may take time for some drugs used in HIV-infected patients (eg, TMP/SMX). Doxepin can be used for itching.

Diseases That Do Not Go Away Even With Antiretroviral Therapy

Some HIV-related dermatologic conditions occur and recur even with appropriate antiretroviral therapy.

Eczema and xerosis

Eczema and xerosis are common conditions, particularly in patients in whom

the CD4+ cell count nadir was less than 200/μL. Treatment consists of mid-potency steroids (ointment is better than cream, since it contains lubricant) and antihistamines. Tacrolimus and pimecrolimus, newer topical steroid formulations for eczema, have black box warnings regarding use in patients with altered immune function, although no specific degrees of immune deficiency are cited as contraindications for use.

Human papilloma virus-associated warts

Human papilloma virus (HPV)-associated warts are also highly recurrent despite adequate antiretroviral therapy, with some evidence indicating that eradication is difficult if the CD4+ cell count nadir was below 50/μL. Figure 7 shows mosaic warts on the bottom of the foot. No matter which is tried, treatment is only successful about 50% of the time. Treatments include liquid nitrogen, podophyllin, laser treatment, and surgery. A recent study suggests that once genital warts are removed by cryotherapy or surgery, imiquimod is often successful at preventing recurrence. Some patients report that application of duct tape is successful at removing warts, although this approach has not yet been formally studied in HIV-infected patients. Whatever eradication treatment is used, it should be repeated every 3 weeks, with successful treatment usually requiring an average of 12 treatments. We currently are investigating CD38 as a functionality marker of T cells in patients who have warts despite immune reconstitution under antiretroviral therapy.

Kaposi's sarcoma

Kaposi's sarcoma (KS) occurs throughout the course of HIV infection at CD4+ cell counts of anywhere from 0 to 800/μL. It remains an open question whether antiretroviral therapy, the first-line therapy for KS, should be started in a patient with KS but higher CD4+ cell counts than those counts

currently serving as indicators for starting antiretroviral therapy. KS occurs even in patients with profound suppression of HIV replication. As with HPV-associated warts, it may be the case that alterations in functionality of T cells in HIV disease inhibit immune response to human herpesvirus 8, the causative agent of KS. Currently, KS tends to present as subtle purple patches (Figure 8) rather than the large fixed plaques characteristic of the disease in the pre-potent antiretroviral therapy era. From a dermatologic perspective, treatment usually is considered to consist in careful monitoring of CD4+ cell count and plasma HIV RNA levels, and topical treatment (eg, aliretinoin) in patients with CD4+ cell counts greater than 400/μL and plasma HIV RNA levels below detection limits. Potent antiretroviral therapy should be started in patients with CD4+ cell counts less than 400/μL. Liposomal doxorubicin or paclitaxel infusions should be given in patients with eruptive KS or lymphedema who are on antiretroviral therapy.

Conditions Emerging With Immune Reconstitution Under Antiretroviral Therapy

Diseases that are now being seen with immune reconstitution under antiretroviral therapy include: acne, which must be differentiated from eosinophilic folliculitis; staphylococcal infections (frequently methicillin-resistant strains), which need to be differentiated from herpes simplex virus (HSV) and fungal diseases; and erythema nodosum, which needs to be differentiated from *Helicobacter cinaedi* infection.

Acne

Acne is seen as acne vulgaris, acne rosacea, and perioral or periorbital dermatitis in HIV-infected patients. Treatment consists of tetracycline or minocycline, and isotretinoin for cystic acne. Acne rosacea is characterized by redness, papules, and broken blood vessels. Figure 9 shows perioral dermatitis, with characteristic scaliness

and acneiform papules around the mouth.

Acne is to be differentiated from eosinophilic folliculitis, shown in Figure 10. This condition consists of multiple extremely itchy urticarial bumps that can be found on the face, neck, scalp, chest, and back. Although the condition was once typically seen in patients with CD4+ cell counts less than 200/ μ L, it has become common during immune reconstitution in the first 3 to 6 months of antiretroviral therapy. Treatment consists of the antifungal itraconazole 200 to 400 mg/d, not because the condition is fungal but because of the antieosinophilic effect of this agent. Permethrin can be used from the waist up every other day to dry the papules. Patients can also simply be observed to determine if the condition resolves after the initial 3 to 6 months of antiretroviral therapy.

Staphylococcal infection

There has been an increased frequency of staph infections with the decreased need for prophylaxis with TMP/SMX or other antibiotics during the antiretroviral therapy era. Staph infections can manifest as abscesses, ulcers, folliculitis, or cellulitis, as shown in Figure 11. It is important to obtain a culture from pus when possible. First-line treatment for abscesses is incision and drainage; antibiotic treatment is not required. If there is no pus available and the infection is not recurrent, treatment should first be attempted with an antibiotic active against methicillin-susceptible staph strains, with the patient returning during treatment for an evaluation of their response. If the infection is recurrent, treatment should be started with an antibiotic active against methicillin-resistant strains: TMP/SMX, doxycycline, and clindamycin still have activity against such strains; resistance is an ever-expanding problem with ciprofloxacin and levofloxacin. The addition of rifampin (600 mg every day for 5 days) can also be considered; potential drug-drug interactions with protease inhibitors need to be consid-

ered if this drug is to be used. Mupirocin ointment is also effective. In recurrent disease, it is important to look for and treat underlying skin disorders that could provide a portal of entry for staph, including dry skin, eczema, tinea, and psoriasis. If there is no response to treatment, the sufficiency of treatment duration should be considered. Prolonged treatment usually is required when hair structures or deep tissues are involved in infection. A 3-week course of treatment should be considered in cases of folliculitis.

Care must be taken to distinguish staph infection from HSV infection, which can mimic several types of skin conditions. HSV culture, direct fluorescence antibody testing, or skin biopsy for histology should be performed for suspicious lesions. HSV infection can present as scaly, impetiginized lesions, as shown in Figure 12. HSV infection should be treated with appropriate antiviral medication. Similarly, suspicious lesions or nonresponding infection should prompt skin biopsy for histology and tissue culture for fungal or mycobacterial infection.

Erythema nodosum

Erythema nodosum is frequently confused with cellulitis (Figure 13). The condition can occur during immune reconstitution in patients with a diagnosis of sarcoidosis. It can also be associated with other etiologies, including streptococcal or *Yersinia species* infection or inflammatory bowel disease. Diagnosis is made by biopsy. Treatment includes bed rest, prednisone, and potassium iodide.

Infection with *Helicobacter cinaedi* mimics erythema nodosum (Figure 13). This gram-negative infection can be characterized by fever, bacteremia, and diarrhea. However, blood culture can be positive in the absence of fever. Stool can also produce positive culture. Skin biopsy shows a suppurative process. Treatment consists of 8 weeks of doxycycline or erythromycin. A recent report indicates that a similar presentation (Figure 13) can be caused by

Campylobacter species infection. Diagnosis is made by blood culture. Treatment consists of ciprofloxacin.

HIV and HCV Coinfection

Coinfection with HIV and HCV is fairly common and is associated with a number of skin conditions, including lichen planus (Figure 14), xerosis, leukocytoclastic vasculitis (Figure 14), and itch without rash. Lubricants and steroid treatment should be used for xerosis. In cases of vasculitis, it is important to first rule out other potential causes, including: drug reactions; other infections (including streptococcal infection, endocarditis, and hepatitis A and B virus); collagen vascular disease and cryoglobulinemia; and leukemia and lymphoma. HCV viral load and liver function test results are not necessarily elevated in cases of active cutaneous vasculitis due to HIV and HCV coinfection. Treatment of vasculitis with colchicine has been helpful, and treatment of the HCV infection should be considered. The role of systemic steroids in treatment is not clear and may exacerbate the liver disease. The itch in HIV and HCV coinfection appears to be a central nervous system itch. Use of the opioid antagonist naltrexone (starting at 50 mg qhs) may be helpful. Neither antihistamines nor ultraviolet light have proved helpful in treatment. Treatment for HCV infection is also helpful.

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Suggested Reading

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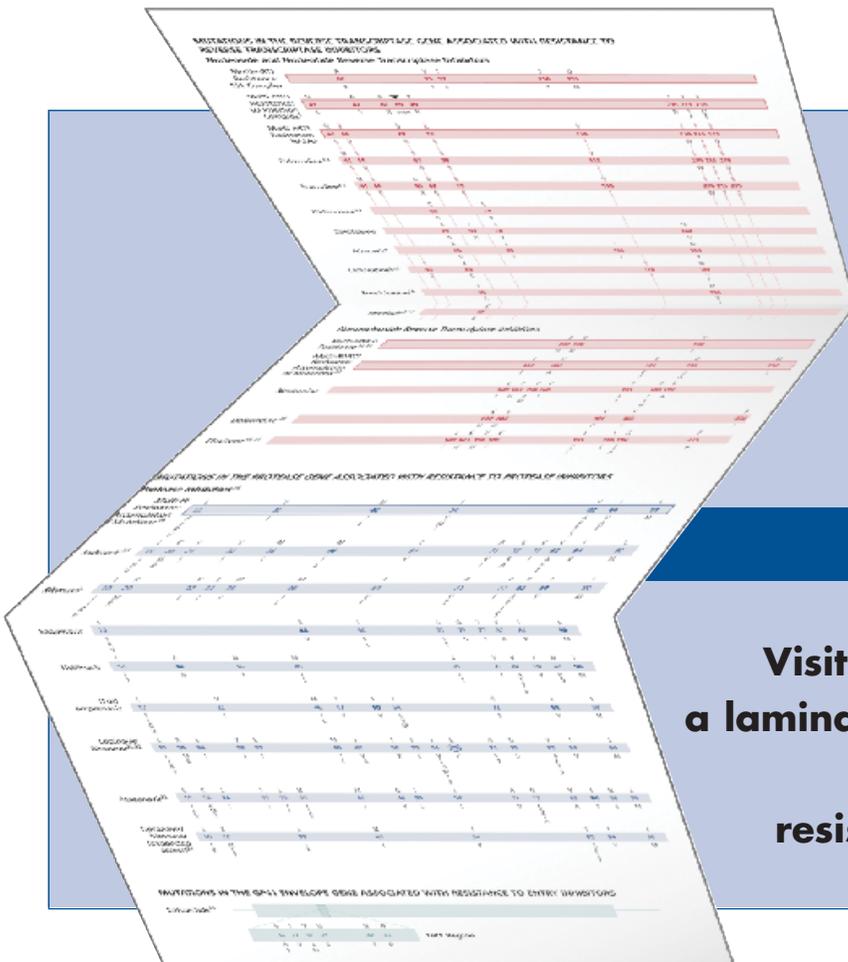
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- “The Importance of Viral Fitness and Drug Resistance in Chronic and Recent HIV Infection,” by Mark A. Wainberg, PhD, and Dan Turner, MD
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