Management of oral lesions in HIV-positive patients

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HIV/AIDS is currently the leading cause of death in Africa and the fourth leading cause of death worldwide. This systematic review of the literature was conducted to evaluate the evidence for treatment of the most common oral lesions associated with HIV: oral candidiasis with or without oropharyngeal involvement (OPC), oral hairy leukoplakia (OHL), recurrent aphthous-like ulcerations (RAU), oral Kaposi's sarcoma (OKS), orolabial herpes simplex infection (HSV), oral herpes zoster infection (VZV), intraoral or perioral warts (HPV), and HIV-associated periodontal diseases. Treatment of HIV-associated salivary gland disease is addressed in a different section of this World Workshop. We found the largest body of evidence for treatment of OPC in HIV patients. Future trials will be needed to test drugs currently in development for treatment of *Candida* strains that are resistant to existing therapies. There were no double blind, placebo-controlled randomized clinical trials (RCT) for topical treatment of OHL, and only one RCT for systemic treatment of the lesion with desciclovir. Systemic thalidomide was the only drug tested in RCT for treatment or prevention of RAU. Only 1 double-blind RCT comparing vinblastine and sodium tetradecyl sulfate was identified for localized treatment of OKS. Three drugs (famciclovir, acyclovir, and valaciclovir) were shown to be effective in randomized, double-blind trials for treatment or suppression of mucocutaneous HSV lesions in HIV patients. In all 3 trials, the effects of these medications on orolabial HSV lesions were not reported separately. There were no double-blind, placebo-controlled RCT testing topical treatments for orolabial HSV lesions in HIV patients. No trials testing treatments of oral VZV were identified. There were no double-blind, placebo-controlled RCT for treatment of HIV-associated intraoral or perioral warts or periodontal diseases. In conclusion, there is a need for well-designed RCTs to assess the safety and efficacy of topical and systemic treatments of most oral mucosal and perioral lesions in HIV patients. There is also a need to develop newer drugs for treatment of resistant fungal and viral microorganisms. Finally, standardized outcome measures should be developed for future clinical trials to allow comparisons of studies using different populations. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103(suppl 1):S50.e1-S50.e23)**

HIV/AIDS is currently the leading cause of death in Africa and the fourth leading cause of death worldwide. It is estimated that more than 38 million people worldwide were living with HIV infection in 2003, including 25 million who live in sub-Saharan Africa.[1] In addition to drastically altering health, HIV infection impacts multiple aspects of society. HIV-related deaths and illnesses have crippled economic growth of several sub-Saharan countries, destroyed families, created over 14 million "AIDS orphans," and strained the health care systems of many nations. At present, the epidemic continues to extend into Asian countries inadequately equipped to limit its spread, although there are suggestions of modest decreases in the number of new infections in other parts of the world.[1,2] People with HIV infection are living longer,[1] meaning more will seek care for the oral complications of this disease.

Oral lesions, usually caused by opportunistic fungal or viral agents, occur often during HIV-infection. A key but not exclusive basis for pathogenesis involves reduced numbers and function of CD4+ T cells; the resultant decrease in systemic and mucosal immune integrity is in turn associated with an increased frequency of oral lesions.[3-5] In contrast, as a consequence of highly active anti-retroviral therapy (HAART), an increase in CD4+ T cell numbers and renewed ability to mount an inflammatory response, sometimes referred

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Table I. List of oral lesions reviewed

Candidiasis (oral, with or without pharyngeal involvement), including:
pseudomembranous, erythematous, hyperplastic, and angular cheilitis
Oral hairy leukoplakia
Recurrent aphthous-like ulcerations
Oral Kaposi's sarcoma
Oral herpes viruses (simplex and zoster)
Human papillomavirus (wart-like) lesions
Periodontal diseases
Linear gingival erythema
Necrotizing ulcerative gingivitis
Necrotizing ulcerative periodontitis

to as the immune reconstitution syndrome, may lead to increased frequency of selected oral lesions.[3-5] HAART therapy has thus decreased the prevalence of several but not all HIV-associated lesions.[3-8] However, worldwide, many patients with HIV infection do not receive HAART. Even in Western Europe and the United States, patients treated with HAART may develop drug-resistant strains of HIV and these individuals may newly infect other people with their already drug-resistant HIV strains. Oral lesions such as oral candidiasis can be signs of failing anti-retroviral therapy[9-12] emphasizing the need to assess the oral cavity during routine care of all those who are infected. Therefore, it is critically important that oral health care professionals in all parts of the world be competent in the diagnosis of HIV-associated oral lesions, be knowledgeable of evidenced-based treatments for these oral conditions, and be trained to provide patients with an appropriate referral for diagnosis and medical management, if undiagnosed HIV infection is suspected.

This systematic review of the literature was conducted to evaluate the evidence for treatment of oral lesions associated with HIV. We have limited our review to therapies for the most commonly found lesions worldwide in HIV that would be treated by an oral health provider (Table I). The review of treatment for HIV-associated salivary gland disease is included in a different section of this World Workshop. The practitioner should be aware that therapies tested in the United States and Western European populations, even those tested before the era of HAART, may not have the same efficacy in contemporary patients residing in Africa/Southeast Asia. These patients may have other risk factors such as malnutrition that predisposes them to opportunistic infections and further complicates HIV disease. For example, oral pharyngeal candidiasis (OPC) was present in 10 of 147 HIV-negative children in a South African clinical study testing the WHO Clinical Case Definition for pediatric HIV infection,[13] and malnutrition was an independent risk factor for death in HIV-infected children hospitalized with diarrhea in an area of Africa with a high prevalence of HIV.[14]

METHODS

The methodology used in this section follows the Reference Manual for Management Recommendations Procedures by Baccaglini et al. that was distributed to the World Workshop in Oral Medicine IV reviewer team. The manual was adapted from the Methodologies and Policies from the American College of Cardiology/American Heart Assocation (ACC/AHA) Task Force on Practice Guidelines (http://circ.ahajournals.org/manual/manual_I.shtml) and the Method for Evaluating Research Guideline Evidence by Liddle J, Williamson M, and Irwig L, NSW Health Department (http://www.health.nsw.gov.au/pubs/1996/methodeval.html).

The search for literature related to management of oral lesions in HIV-positive patients encompassed literature from 1966 through 2005. Searches were performed on Medline/PubMed, Embase, Cochrane Library, and Best Evidence online databases. Searches included meta-analysis, randomized controlled trials (RCT), cohort, before and after studies, and case reports in peer-reviewed journals, and were limited to the English language and human subjects. Additional studies were identified from the reference lists of these articles and selected reviews.

We conducted an independent review of all relevant literature, and have described studies not included in previously published acceptable systematic reviews or meta-analyses. Each article was reviewed independently by 2 reviewers. Articles that were not treatment trials or were outside the scope of this review were assigned a score of "F" and excluded. A quality score (study grade A, B, C, D) was given to each study using standardized evaluation forms, and the grades were combined as described in the Reference Manual (see Fig. 1).

Only evidence from A and B studies was used to formulate final treatment recommendations. Given the paucity of studies rated A or B, we opted to include studies rated "C" as preliminary evidence in the tables and studies rated "D" in the text. However, no final recommendations were derived from these studies. Results from these studies should be interpreted with caution given the moderate to high potential for bias.

Results, including a short review of the pathophysiology and future research recommendations, are given for each lesion. Treatment recommendations in the form of expert opinion are provided after the summary portion of each section to complement evidence derived

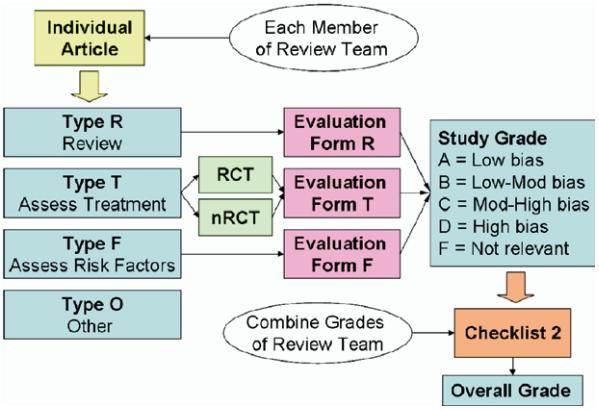

Fig 1. Literature review.

from published studies. This is meant to give guidance for treatment of oral lesions for which there are limited therapeutic trials, such as oral warts.

ORAL AND/OR OROPHARYNGEAL CANDIDIASIS (CANDIDOSIS) (OPC)

From review of articles: [8, 13, 15-66]

Pathophysiology

As recently as 1999, the pathophysiology of OPC in HIV-infected individuals was not comprehensively understood.[56] While candidal colonization was correlated with plasma HIV-1 RNA levels at the time, the CD4+ count and other factors related to systemic and mucosal immune status merited further research. Based on additional investigations, it is now evident that the fundamental causes of clinically significant OPC are related to decreased CD4+ count, anti-retroviral combination therapy, and, quite possibly, cigarette smoking.[11] These factors are briefly described in the following 2 paragraphs.

The impact of reduced numbers of circulating CD4+ cells in relation to emergence of oral lesions including OPC is well established.[57,58] The resultant compromise in mucosal immune surveillance and function is a direct contributor to increased risk for opportunistic infection, including OPC.

Mechanistic relationships between antiretroviral therapies and causation of OPC are perhaps more paradoxical, as presented in the literature. It appears that, in the early years of clinical use of these agents, there may have been less than optimal suppression of viremia. This in turn could have contributed to continued decrease in CD4+ number, and resultant persistence of OPC. Other factors associated with these antiretroviral interventions in the early clinical years include (1) timing of administration of the agent in relation to HIV status, and (2) therapies without protease inhibitors, versus combined therapies that have more recently included protease inhibitors.[11]

Many HIV protease inhibitors have an anti-candidal effect that is independent of immune reconstitution. Protease inhibitor targets include secretory aspartyl proteinase (Sap), enzymes of the *Candida* Sap family that belongs to the same family as HIV-proteinase.[63] While Saps are essential virulence factors for mucosal infection by *Candida albicans*, HIV protease inhibitor-related Sap inhibition alone is not capable of eliminating *Candida* from the oral cavity and does not alter OPC antimycotic susceptibility.

The potential pathogenic basis for smoking in relation to OPC causation is less clear; further study is warranted. In addition, additional research relative to yeast virulence factors, including the possible roles of phenotypic switching and/or genetic variations, is also needed.

Readers are directed to a more comprehensive review of the pathobiology of candidiasis in another section of this workshop entitled "Use of prophylactic antifungals in the immunocompromised host."

Treatment

This review is limited to trials testing treatments for oral candidiasis with or without assessment of oropharyngeal candidiasis. Trials testing treatments for esophageal candidiasis only were excluded. The 3 most common clinical presentations of candidiasis in the oral cavity of HIV-infected individuals are pseudomembranous, erythematous, and angular cheilitis. Hyperplastic or chronic candidiasis is the fourth and rarest form. The primary clinical outcome used in many antifungal clinical trials was a decrease in pseudomembranous candidiasis. If no plaques or white lesions were visible after therapy, this was termed "clinical cure." A few trials, such as the study by Pons et al.,[22] evaluated all forms of OPC but did not report the effects of the study medication for each clinical presentation. However, we did not find reports suggesting that the different clinical forms of OPC were more or less susceptible to antifungal treatment.

Candidal cultures or rinses were obtained in some trials, and the effect of therapy on the growth of *Candida* was determined. The absence of *Candida* species in culture was termed "mycologic cure."

Objectives

- To assess the efficacy of available antifungal agents for the *treatment* of oral candidiasis in persons diagnosed with HIV/AIDS.

- To assess the efficacy of available antifungal agents as *prophylactic* measures to prevent oral candidiasis in persons diagnosed with HIV/AIDS.
- To assess the effects of prophylactically administered antifungal agents on the development of resistant strains of *Candida* colonizing the oral cavity of HIV-infected patients.
- To assess the efficacy of available antifungal agents for *treatment of azole-resistant* oral candidiasis in persons diagnosed with HIV/AIDS.

Findings

- Three systematic reviews on treatment and prevention of OPC were published between 2000 and 2005.[38,54,59] Together, these reviews provide a comprehensive summary of important trials on treatment and prevention of OPC. Our independent search did not identify additional randomized clinical trials with the exception of the following studies worthy of mention:

  OPC treatment

  - A randomized clinical trial comparing a 1-week course of *miconazole* tablets (250 mg every 6 hours) and *nystatin* tablets (1,000,000 IU every 8 hours) in 85 Ugandan patients showed clinical cure of oral candidiasis in all the patients when reevaluated at a mean follow-up of 7.6 days (SD 0.9). Notably, concurrent esophageal candidiasis, present in 91% of patients, responded more favorably to treatment with miconazole (92.5% cure versus 21.6% cure in the Nystatin group). No adverse events were observed in either group [rated B].[28]
  - A randomized, single-blind trial compared *fluconazole* tablets (100 mg daily; n = 13) and *clotrimazole* troches (10 mg 5 times per day; n = 11) for 14 days for treatment of pseudomembranous OPC. At the end of treatment results showed that fluconazole (15% colonized, 100% clinically cured) was more effective than clotrimazole (38% colonized, 73% clinically cured), and resulted in fewer relapses at days 28 and 42. Limitations of this study were the significantly lower compliance in the clotrimazole versus fluconazole group, and the lack of a placebo control [rated C].[52]
  - An open-label, comparative, phase IIIb RCT conducted in 4 Kampala hospitals (Uganda) compared once-daily slow-release mucoadhesive tablets of *miconazole* (10 mg, applied 30 minutes after breakfast; n =178) versus *ketoconazole* tablets (400 mg QD; n = 179), the Ugandan standard of care. Patients not responding at 7 days were treated another 7 days. Patients were adults (age 18+) with OPC. At day 7, clinical cure occurred in 87% of miconazole-treated and 90% of ketoconazole-treated patients ($P = .029$, <10% clinical difference). At the end of treatment (14 days), there were statistically significant differences (–3.5%; $P = .005$) in the proportion of clinical cure between the 2 groups (miconazole 93% and ketoconazole 96%), but the authors did not feel this was clinically significant [rated B].[32]

  OPC prevention

  - A randomized, multicenter, open-label study comparing continuous prophylaxis (200 mg PO 3x/wk; n = 413) versus episodic treatment (for episodes only; n = 416) with fluconazole for OPC showed no difference in time to development of fluconazole-refractory oral candidiasis (FROC) within 24 months [rated B].[26]

  Fluconazole-refractory OPC (FROC)

  - A prospective, multicenter, open label trial evaluated the use of *amphotericin B* oral suspension (ABOS, 100 mg/mL, 5 mL 4x/d for 14 days) for treatment of FROC in 54 HIV subjects. Given the low response rate (43%), the authors concluded that ABOS should be used as a second line of therapy for FROC, when itraconazole solution treatment fails [rated C].[64]
  - A small prospective, randomized single-center, open-label clinical trial of a 2-week course of alcohol-free (5 mL qid; n = 13) versus alcohol-based (15 mL qid; n = 14) *malaleuca* for treatment of FROC showed that at the 2-week evaluation 6 patients had improved and 1 was lost to follow-up in each group [rated C].[53]
- The Centers for Disease Control and Prevention (CDC) recently published evidence-based online guidelines for treatment of oropharyngeal candidiasis in adults and adolescents[62] or children and infants.[36,65,66] CDC guidelines for drugs with moderate to strong evidence for efficacy are summarized in Table II. Additional details are available from the CDC's Web site.

Summary and recommendations

Lesions due to opportunistic *Candida* infection are the most studied HIV-associated oral lesions in both children and adults. There have been numerous clinical trials published in the literature and summarized by 3 independent systematic reviews. This section provides additional evidence that was not included in the 3 reviews.

Table II. Centers for Disease Control and Prevention guidelines for treatment of oropharyngeal candidiasis (OPC) in patients with HIV (December 2004)

OPC treatment	
Adults and adolescents	*FROC treatment*
Fluconazole 100 mg PO QD for 7-14 days	Itraconazole oral solution ≥ 200 mg PO QD
Itaconazole oral solution 200 mg PO QD for 7-14 days	Amphotericin B deoxycholate 0.3 mg/kg IV QD
Clotrimazole troches 10 mg PO 5x/d for 7-14 days	
Nystatin suspension 4-6 mL QID or 1-2 flavored pastilles PO 4-5x/d for 7-14 days	
Children and infants	
Fluconazole 3-6 mg/kg body weight (max 400 mg/dose) PO for 7-14 days	Itraconazole cyclodextrin oral solution 2.5 mg/kg body weight PO BID (max 200-400 mg/day) for 7-14 days
Itraconazole cyclodextrin oral solution 2.5 mg/kg body weight (max 200-400 mg/d) for 7-14 days	Amphotericin B oral suspension 1 mL (100 mg/mL) PO QID for ≤ 14 days
Clotrimazole troches 10 mg PO QID for 14 days	
Nystatin suspension 4-6 mL PO QID or 1-2 flavored pastilles PO 4-5x/day for 7-14 days	

Adapted from the Centers for Disease Control and Prevention's Morbidity and Mortality Weekly Report.[62, 66] Note: Only drugs with moderate to strong evidence for efficacy were included in this table. FROC, Fluconazole-refractory OPC; PO, by mouth; QD, every day; QID, 4 times daily

- When evaluating the literature, consideration should be given to the possibility that conclusions from more recent trials may be the most generalizable to the current population, given changes in fungal resistance patterns and host defense capabilities over time.
- Recently published evidence-based CDC guidelines may be used to guide treatment decisions. The level of evidence for each drug is included in the CDC guidelines for HIV-positive adults and adolescents (http://www.cdc.gov/mmwr/PDF/rr/rr5315.pdf)[62] or infants and children (http://www.cdc.gov/mmwr/PDF/rr/rr5314.pdf).[66] We did not independently verify the accuracy of the level of evidence or drug regimens published by CDC.
- In summary, in both children and adults azole-susceptible OPC is preferably treated with topical (nystatin or clotrimazole) or systemic (fluconazole or itraconazole) drugs. For fluconazole-refractory OPC, itraconazole oral solution and amphotericin B oral suspension have been used. Intravenous amphotericin B can be used as a last treatment option.
- One study has suggested that miconazole may be considered for treatment of OPC in developing countries if a high percentage of patients is expected to have concurrent esophageal candidiasis and more expensive azolic drugs are impractical.
- Newer drugs, such as D0870 show promise in treating resistant OPC.[24]
- Recent studies have addressed the potential development of resistance in patients treated with fluconazole. Preliminary results suggest that development of resistance may not be higher in patients on prophylactic fluconazole, but long-term effects are unknown. Thus, most authors and CDC guidelines do not recommend OPC prophylaxis except for exceptional cases of severe or frequent recurrences.
- Patients with esophageal or invasive *Candida* infection should be referred to their primary physician for systemic therapy. Symptoms reported by patients with esophageal candidiasis may include odynophagia, dysphagia, and retrosternal burning pain.
- Treatment considerations should include (1) compliance, especially in children,[39] (2) drug interactions, (3) monitoring of side effects, and (4) cost.

Expert opinion

Use of topical agents for treatment of OPC in patients with a CD4 count higher than 200 cells/mm^3 is recommended as an initial therapy. This is advised since there are reported drug-drug interactions between systemic antifungal and antiretroviral medications,[61] and many patients with HIV infection are co-infected with Hepatitis C that further compromises drug metabolism in the liver. Culture is recommended for OPC that does not respond to therapy, as continued candidiasis after topical and systemic therapy may indicate colonization with a resistant strain of *Candida*.

Research needs

- Presently, there are adequate treatments for oral candidiasis. While older studies often had no information about viral load and most patients were not receiving concurrent modern antiretroviral therapy, there does not appear to be evidence that patients treated for OPC while receiving concurrent HAART have different treatment outcomes.
- The biggest limitation of studies reviewed for this paper is the lack of standardized outcome measures to judge partial and complete clinical response. In some trials, only the response of white plaques was considered, such as a decrease in number or size. Erythematous lesions were excluded by some inves-

tigators because the examiners felt they could not evaluate them adequately. A clinical trials working group could establish criteria including guidelines to judge extent of clinical lesions, partial clinical cure, and complete clinical cure. Guidelines for trials that only assess "clinical cure" would be of particular value for studies conducted in areas without resources to determine mycologic cure (the absence of yeast growth in culture).

- Given the widespread use of fluconazole in many immunocompromised individuals such as patients undergoing cancer therapy, azole-resistant candidiasis is expected to be a continuing problem.[16] Significant numbers of HIV patients taking fluconazole in studies testing prophylaxis versus episodic treatment of OPC had clinically resistant fluconazole infections (4.1%-8.7%).[26,33] Resistance to fluconazole was documented by increases of mean inhibitory concentrations in the majority of tested isolates. While at present there is no good evidence that prophylactic treatment versus episodic treatment of patients with low CD4 counts leads to increased antifungal resistance, multi-drug resistant strains of *Candida* can be isolated from patients.[33,55] Non-*albicans Candida* such as *C. kruzei*, intrinsically resistant to fluconazole,[60] and *C. glabrata,* a cause of refractory mucosal candidiasis, can cause persistent infections in patients with advanced immunosuppression.[62] While prophylaxis is not recommended to prevent oral candidiasis in HIV,[62] prophylactic doses of agents such as fluconazole may be prescribed to prevent invasive fungal infections such as cryptococcosis.

ORAL HAIRY LEUKOPLAKIA (OHL)

From review of articles: [5, 7, 8, 11, 67-82]

Pathophysiology

OHL is caused by Epstein-Barr virus (EBV).[80] This effect may in part be exerted via EBV-mediated blocking of several tissue-protective promoters, including interferon (IFN)-alpha4 and IFN-beta.

As with OPC, low CD4+ count remains the major risk factor relative to development of OHL.[81] It appears that other oral mucosal immune factors, including tissue-associated pro-inflammatory and T-helper cytokines, may also contribute to expression of disease. Smoking appears to be less of a risk factor with OHL than is the case for OPC.[11]

Treatment objective

- To assess the effectiveness of available systemic antiviral agents or topical therapies for the treatment of OHL in persons diagnosed with HIV/AIDS.

Findings

Topical treatments. Four limited reports have described the topical treatment of OHL with *podophyllum resin* (POD).

- Two men with biopsy-confirmed OHL and treated with a single application of POD 25% had complete or partial resolution of their lesions within 4 to 5 days. Remission ranged from 2 to 28 weeks. The contralateral side of the tongue in 1 man was used as a control and did not show any change. Unpleasant taste lasting up to 2 hours after the application was the only adverse effect reported. Limitations of the study include small sample size, unclear outcome definition, and no blinding or placebo [rated D].[71]
- A retrospective study of 9 patients (age 27-58, unknown gender) treated with POD 25% in benzoin compound tincture (applied 2-3 times with a cotton swab for 30-60 seconds followed by a rinse with water) for biopsy-confirmed OHL showed complete remission 1 week after a single application (n = 5) or 1 week after the second application (n = 4). Remission lasted 2 to 28 weeks. Adverse effects included altered taste and soreness of the tongue. Limitations of this study include the lack of description of results for the untreated contralateral side, small sample size, no blinding or placebo, and unknown total follow-up time [rated D].[69]
- A report of 6 men (aged 29-52 years) with OHL treated with a single application of POD 25% on the dried surface of the tongue produced resolution of all the lesions in 3 to 5 days. Remission lasted over 4 months in all 6 patients. Limitations of the study include biopsy confirmation of OHL for only 1 patient, no description of results for the untreated contralateral side of the tongue, small sample size, and no blinding or placebo [rated D].[67]
- Ten HIV patients with OHL had 1 side of the tongue treated with a single application of POD 25% with the other side acting as a control. An improvement of the lesions was seen after 2 days but the effects diminished over a 30-day follow-up period. Reported adverse effects included transient burning, taste changes, and pain. Limitations of the study include lack of description of participants' baseline characteristics, no biopsy confirmation of OHL, incorrect statistical analyses, and no placebo [rated D].[72]

Comparison of local therapy and systemic treatments. Two studies have compared systemic treatment of OHL with acyclovir to local therapy with surgery or tretinoin (Vitamin A):

- Thirty-eight HIV males with symptomatic, biopsy-confirmed, EBV-DNA–positive OHL were enrolled

in an open-label, 3-month, 3-arm trial comparing surgery (n=12), oral acyclovir (n = 14; 3.2 g/d for 20 days), and no treatment (n = 12). All surgery patients had clinical disappearance of the OHL with no recurrence at 3 months, although EBV DNA persisted, and new OHL foci appeared in 10 patients. Only 12 of 14 of the acyclovir arm had regression of OHL with 100% recurrence by 3 months. The untreated arm had no clinical changes in OHL. Limitations of the study include the absence of randomization and unclear baseline characteristics of the participants [rated C].[73]

- In a brief letter Schofer et al.[74] described treatment of OHL in HIV patients using Vitamin A 0.1% twice daily (n = 12) followed by intravenous (IV) acyclovir (n = 2; 7.5 mg/kg, every 8 hours for 7 days). Despite a response to both drugs within the first 2 weeks, recurrence of OHL was seen after discontinuation of treatment [rated D].

Systemic treatments

- A randomized, placebo-controlled, double-blind clinical trial of *desciclovir* for the treatment of OHL was published in 1990. HIV males (mean age 33.7) were randomly assigned to receive 250 mg of desciclovir (n = 8) or placebo (n = 6) TID for 14 days. Mean percentage reduction in lesion size in the treatment arm was greater than 60% at weeks 1, 2, and 4 compared to less than 20% reduction in the placebo group. Adverse effects in the treatment arm (3 aching and 1 tachycardia) and placebo group did not lead to a discontinuation of treatment. Limitations of this study include the lack of details about the source population from which the cases were drawn (including hospital location and years of enrollment), small sample size, unclear description of certain baseline characteristics (e.g., prior treatments, current medications, or CD4 count), and lack of statistical test results [rated C].[70]
- A study of 19 adult males (age 29-59) attending a dental clinic in Houston, Texas, and treated with high doses of oral *valacyclovir* (1000 mg q8h) for 28 days. Clinical response (defined as grossly normal epithelium and no typical OHL histological features on surgical biopsy) was seen in 89% of cases (16 of 18), and virological response (no EBV replication) was seen in 84% of the cases. At 28 to 42 days after treatment, clinical recurrence was 17% (2 of 12) and virological recurrence was 31% (4 of 13). Limitations of this study include lack of randomization, blinding, or placebo control [rated C].[82]
- An 8-week, open-label trial compared treatment with oral *acyclovir* (n = 6; 800 mg every 6 hours for 20 days) and no therapy (n = 7 who refused treatment) for biopsy-proven OHL in HIV males. Five of the 6 patients in the acyclovir arm had partial (n = 2; >50% decrease in size) or complete (n = 3) response after 2 to 4 weeks, whereas the untreated arm had no change or worsening (n = 1) of OHL. Recurrences occurred in all patients 14 to 18 days after discontinuation of the drug. Limitations of this study include lack of randomization, blinding, or placebo [rated C].[75]
- A report of 3 HIV males treated with *foscarnet* (4800 to 6000 mg IV twice daily) for CMV retinitis showed complete clearance of OHL within 2 to 3 weeks. No controls, blinding, or randomization were used [rated D].[76]

Summary and recommendations

Topical treatments

- There is a paucity of reports on topical OHL treatment in the literature. Among these, there are no randomized, double-blind, placebo-controlled trials.
- Four reports have suggested possible efficacy of podophyllum (POD). At the dosages used, adverse effects were mild and transient. In most cases, a small quantity of POD was briefly applied to just 1 side of the tongue during each session, possibly limiting its toxicity. However, serious systemic adverse effects and fatalities following the use of larger POD doses or after its ingestion have been reported. Toxic reactions may develop several hours after POD use. POD is also teratogenic in animals.[78]
- Reports of other local/topical treatments include surgery and topical tretinoin (retinoic acid, vitamin A). However, no well-designed studies of these treatment modalities have been published in the literature.
- Topical treatments may become impractical for very large lesions.
- Repeated treatments may be needed to induce complete remission and/or to treat recurrence. Recurrence is common after discontinuation of therapy.

Systemic treatments

- Among systemic antiviral therapies for treatment or prevention of OHL, only 1 drug (desciclovir) has been tested in a placebo-controlled, double-blind, randomized clinical trial [rated C].[70]
- Reports of other systemic antiviral treatments such as valacyclovir, acyclovir, ganciclovir (DHPG), foscarnet, and a recent case report on famciclovir [rated D][79] suggest that these drugs may improve OHL. It should be noted that some of these drugs (foscarnet and ganciclovir) were used to treat other conditions, and clearance of OHL lesions was a secondary effect.
- The results of all the studies published thus far in the literature on systemic antiviral treatment of OHL

Table III. Evidence table of treatments for oral hairy leukoplakia (OHL); A, B, or C level studies only

Agent tested	*Sample size*	*Study design*	*Outcome*	*Rating*
Greenspan et al. Systemic desciclovir, 250 mg tid, 14 days.[70]	8 desciclovir	Randomized, placebo- controlled, prospective, biopsy-confirmed OHL	Desciclovir: 60% decrease in lesion size; Placebo < 20%	C
	6 placebo			
Walling et al. Systemic valacyclovir, 1000 mg tid, 28 days.[82]	19 valacyclovir	Open label, no placebo control, prospective, biopsy-confirmed OHL	89% clinical cure; 17% clinical relapse	C
Herbst *et al*. Systemic acyclovir, 3.2 g/day for 20 days vs surgery patients vs no treatment.[73]	12 surgery	Open-label, prospective, biopsy-confirmed OHL	Surgery: 100% resolution with no recurrence at 3 months	C
	14 acyclovir		Acyclovir: 86% regression with 100% recurrence by 3 months.	
	12 no treatment		No treatment: No clinical changes	
Resnick et al. Oral acyclovir (800 mg every 6 h for 20 days) vs no therapy.[75]	6 acyclovir	Open-label, 8-week, prospective, no randomization, biopsy confirmed OHL	Acyclovir: 83% partial or complete response, with 100% recurrence after treatment	C
	7 no treatment		No treatment: No clinical changes	

tid, 3 times a day.

should be interpreted with caution because of several limitations in the study design and/or statistical analyses.

- The potential to develop drug resistance and side effects should be carefully considered among the risks and benefits when using systemic antiviral drugs for OHL.

Recommendations

- Overall, the highest level of evidence for treatment of OHL is "C" (see Table III). At present there is insufficient evidence to develop evidence-based treatment recommendations.

Research needs

- While reduction of HIV viral load is associated with a decrease in the prevalence of OHL, it is not a rare finding in patients taking modern antiretroviral therapies. It was the second-most common lesion in 3 studies examining oral lesion prevalence after wide spread use of HAART.[5,7,8] However, few therapies have been tested as treatments for OHL. This is most likely because the lesion is benign and is not associated with significant morbidity. Primary reasons for treatment are cosmetic or size reduction if the lesion interferes with eating. The therapeutic objective is to limit lesion size, rather than eradicate infection. Therefore, appropriate agents that produce an acceptable clinical outcome with minimal toxicity should be available for use. Toxicity of agents will be a significant issue, as it is expected that these lesions will recur frequently and need repeated treatment. Patients in trials should be evaluated for relapse as well as immediate clinical responses.
- Standardized outcome criteria such as change in lesion size should be established for trials. Biopsy should be used to confirm the diagnosis of OHL in clinical trials subjects, as oral candidiasis on the tongue can have a similar clinical appearance. A working group should also decide whether repeat biopsy is necessary to evaluate drug efficacy in therapeutic studies.

RECURRENT APHTHOUS-LIKE ULCERATIONS (RAU)

From review of articles: [7, 9, 13, 83-94]

Pathophysiology

To date, the cause of recurrent aphthous-like ulcerations has not been established. This limitation continues to compromise the clinician's ability to provide definitive therapy.[91] Once the lesion has been initiated, HIV disease–related changes in the immune system may exacerbate severity of RAU.[90]

Treatment objective

- To assess the effectiveness of available systemic or topical therapies for the *treatment* and *prevention* of RAU in persons diagnosed with HIV/AIDS.

Table IV. Evidence table of treatments for recurrent aphthous-like ulcerations (RAU); A, B, or C level studies only

Agent tested	*Sample size*	*Study design*	*Outcome*	*Rating*
Jacobson et al. Systemic thalidomide, 200 mg/d, 4 weeks.[86]	29 thalidomide 28 placebo	Randomized, placebo-controlled, double-blind prospective	Thalidomide: 55% complete healing; Placebo 7%	A
Jacobson et al. Systemic thalidomide, 100 mg 3 times/wk for 6 months as prophylaxis.[87]	23 thalidomide 26 placebo	Randomized, placebo-controlled, double-blind, prospective	Thalidomide no more effective than placebo	A
Ramirez-Amador et al. Systemic thalidomide, 400 mg/d 1 week, 200 mg/d 7 weeks.[84]	10 thalidomide 6 placebo	Randomized, placebo-controlled, double-blind	Thalidomide: 90% complete healing; Placebo: 33%	B

Findings

Three randomized, double-blind, placebo-controlled clinical trials have been published on the treatment or prevention of RAU using *thalidomide*:

- A 4-week trial comparing thalidomide (n = 29; 200 mg/d) or placebo (n = 28) for *treatment* of RAU showed a significantly higher percentage of complete healing of RAU in the thalidomide treated patients (55% versus 7% of placebo-treated) [rated A].[86]
- A single-center, 8-week trial comparing thalidomide (n = 10 males; 400 mg/d for 1 week followed by 200 mg/d for 7 weeks) with placebo (n = 6 males) for *treatment* of RAU found a significant reduction in the largest ulcer diameter in the thalidomide group (P = .02). A greater reduction in the number of lesions and total diameter of the lesions was also found in the thalidomide group, although not statistically different from the placebo group. A significantly higher percentage of patients in the thalidomide (90%) versus placebo (33%) group had complete healing of their ulcers at the end of the trial (P = .03) [rated B].[84]
- In a multicenter 6-month clinical trial comparing low intermittent doses of thalidomide (n = 23; 100 mg, 3 times per week) and placebo (n = 26) for *prevention* of oral and esophageal ulcerations in patients successfully treated with thalidomide in the past, the drug was ineffective [rated A].[87]

Summary and recommendations

- Two randomized, double-blind, placebo-controlled trials have shown effectiveness of thalidomide (200 mg/d) for treatment of RAU.
- Low intermittent doses (100 mg 3 times per week) were ineffective for prevention of RAU in 1 trial.
- Toxicity is a limiting factor for treatment. Risks and benefits should be evaluated carefully when considering thalidomide for treatment of RAU.
- There are no randomized clinical trials of other drugs for treatment or prevention of RAU in HIV-infected patients.
- Overall, the level of evidence is "A" for the use of thalidomide for *treatment* of RAU in HIV-positive patients (see Table IV). Thalidomide may be considered for treatment of RAU in those cases in which the benefits outweigh the risks. However, the use of thalidomide for *prevention* of RAU cannot be recommended at this time.

Expert opinion

Topical and systemic steroids have been used successfully by those experienced in the treatment of HIV-infected patients with RAU. The doses, agents, and duration are the same as those used for HIV-negative patients with recurrent aphthous ulcerations. Levamisole has been effective in select patients, but this agent has not been investigated in trials.[93]

Research needs

- There is good evidence only for use of systemic thalidomide to treat the oral ulcerations associated with HIV infection. A clinical trial testing topical thalidomide of RAU in patients with HIV has been completed, but its publication is pending (Dr. Sharon Gordon, personal communication). While systemic thalidomide does not appear to increase viral load, it has significant toxicities. The teratogenic effects of thalidomide are well described, making it unsafe for any woman who may become pregnant. Other side effects include rash, sedation, and neuropathy.[86,87] Nonteratogenic treatments should be available, given that almost 50% of persons infected with HIV are female.[2] Many of these women will give birth after infection.
- A small open-label trial of systemic steroids was published in 1994 as therapy for idiopathic esophageal ulcerations of HIV,[89,94] but there have not been studies examining systemic steroids in RAU. There also have not been trials testing agents such as topical clobetasol mixed with antifungal preparations, which is effective for treatment of many oral vesiculobul-

lous diseases (see other sections of this Workshop related to oral lichen planus).

ORAL KAPOSI'S SARCOMA (OKS)

From review of articles: [5, 7-9, 85, 95-123]

Pathophysiology

Kaposi's sarcoma–associated herpesvirus/HHV8 is an oncogenic virus that is consistently detected in virtually all clinical expressions of Kaposi's sarcoma (KS).[119] It is theorized that this virus, when infecting circulating KS cell-progenitors, predisposes KS development in the setting of exposure to Th1 inflammatory cytokines. Lytic replication caused by the virus can further promote tissue inflammation, thereby providing a proangiogenic stimulus that in part increases generation of matrix metalloproteinases.[121]

In this multifactorial model of infection, hypoxia and injury can lead to clinical expression of KS. The relationship of this model of pathogenesis to the "plasmablastic lymphoma" of the oral cavity[120] warrants further study.

Treatment

Most trials of systemic treatments for KS have not reported oral findings separately, or have focused on extraoral sites. Several drugs, including vincristine, vinblastine, adriamycin, doxorubicin, bleomycin, interferon alpha, alitretinoin, and pegylated liposomal doxorubicin (PLD) have been used for treatment of various forms and anatomic locations of KS. The primary physician should be informed if a KS lesion is detected intraorally since the patient may have concurrent cutaneous or visceral involvement that warrants detection and management. Given the potential for serious adverse effects from systemic drug treatment of KS, patients should be referred to their primary physician for management of KS lesions of the oropharyngeal region that exceed small focal lesions of the oral cavity. Thus, we have focused our review on local treatments of OKS.

Objective

- To assess the effectiveness of available local therapies for the treatment of oral Kaposi's sarcoma in persons diagnosed with HIV/AIDS.

Findings

Intralesional vinblastine and sodium tetradecyl sulfate. A series of small trials and reports suggested potential efficacy of 2 intralesional drugs for the treatment of OKS: (1) VNB (*vinblastine*, Velbe) and (2) STS (*sodium tetradecyl sulfate* 3%, Sotradecol). Among these were 6 reports:

- A report of 16 male patients (age unknown) with multiple OKS lesions treated with VNB (0.2 mg/mL in 0.1-mL amounts per 0.5-cm lesion, up to 0.8 mg per lesion) showed some response to VNB at 1 month (at least 50% regression in size in 12 of 21 treated lesions) compared to no regression in untreated lesions in the same patients. No blinding or randomization was used [rated C].[105]
- In a letter to the editor, Muzyka and Glick[122] described treatment of nodular OKS lesions (4-15 mm in size) with intralesional STS 3% in 12 AIDS patients. There was an 80% average reduction in size (including complete clearance in 4 patients) within 2 to 3 weeks of 1 to 2 treatment sessions 3 days apart, no untoward effects, and no further progression of the lesions at 24 weeks. Limitations of this study include no blinding, randomization, or controls, and unknown patient characteristics or clinical details, such as amount of STS injected [rated D].
- A report of 12 patients (age 28-56 years, unknown gender) treated with a sclerosing agent (STS, Sotradecol 3% up to 0.8 mL/lesion) for 1 to 2 OKS lesions less than 2.7 cm in size showed remission of all 15 lesions (9 complete by the fourth to sixth week and 6 partial requiring retreatment). Injections were made in the surrounding tissue as well as directly into the lesions. Some degree of ulceration was seen in all patients after the first week, including 1 patient with a superficial palatal bone sequestrum and extensive pain. In some patients remission lasted over 18 months, while others were lost to follow-up because they moved or died. No blinding, randomization, or controls were used [rated C].[108]
- Fifty males aged 26 to 50 years with 144 OKS lesions were treated with 1 to 6 (mean 2.4 times) intralesional injections of VNB sulfate (0.1 mg/cm^2 using a 0.2-mg/mL solution, 1 injection every 2 weeks) until resolution or until there was no change in lesion size and pigmentation, and followed for up to 64 weeks (mean follow-up 14 weeks). Results showed a mean reduction in lesional area of 93%, a recurrence rate of 25% (with the lowest recurrence rate seen in red macular lesions), and a mean time to recurrence of 13 weeks. Adverse effects were transitory pain (72%); ulceration (22%); paresthesia (12%); and sinusitis, fever, or localized ischemia ($<$10%). Limitations of this study were the lack of a control group, blinding, or randomization; loss to follow-up as a result of 19 AIDS-related deaths; and variable follow-up time since the last injection [rated C].[112]

Table V. Evidence table of treatments for oral KS (OKS); A, B, or C level studies only

Agent tested	*Sample size*	*Study design*	*Outcome*	*Rating*
Ramirez-Amador et al. Single dose of intralesional vinblastine (VNB) versus 3% sodium tetradecyl sulfate (STS) at a standard vol. and dose of 0.2 mg/cm^2 of lesion.[107]	8 VNB 8 STS	Randomized, double-blind, prospective	VNB and STS: Partial response in 88% in each group. One VNB patient with complete response	C
Flaitz et al. Intralesional VNB 0.1 mg/cm^2 using a 0.2-mg/mL solution, 1 injection every 2 weeks, 1-6 times (mean 2.4 times).[112]	50VNB	Open-label, nonrandomized, no placebo	VNB: Mean reduction in lesional area of 93%, recurrence rate of 25%	C
Epstein and Scully. Intralesional VNB 0.2 mg/mL in 0.1-mL amounts per 0.5-cm lesion, up to 0.8 mg per lesion.[105]	21VNB	Open-label, nonrandomized, no placebo. Other lesions in patient was control	VNB: 57% had at least 50% regression in size vs untreated lesion	C
Lucatorto and Sapp. 3% STS, up to 0.8 mL/lesion, 1 to 2 times.[108]	12 STS	Open-label, nonrandomized, no placebo	STS: 100% partial or complete response	C

- A report of 10 patients treated with up to 3 intralesional VNB injections at least 2 weeks apart (0.3 mg/mL, 2.0 mL total for all sites per visit) for OKS and followed for 2 years had shown a regression of the tumor. However, 8 additional patients were excluded from the analyses because of visceral spread of KS or death from their disease, and their response to VNB is unknown. The demographics of this sample are also unknown. No blinding, controls, or randomization were used [rated D].[104]
- Following these reports, the first double-blind, randomized trial comparing a single dose of intralesional VNB and STS 3% at a standard dose (0.2 mg/cm^2) for the treatment of OKS in adult (age >18) males was performed. Eight patients were assigned to each treatment arm (total n = 16). After 4 weeks there was some response in all but 1 patient in each group, although complete response was seen only in 1 patient in the VNB group who had a 1-cm macule at baseline. The 2 drugs were shown to be similar in efficacy and adverse events. Adverse effects included transient postoperative pain and ulceration. Limitations of this study include the inability to compare to a placebo, small sample size, and lack of follow-up [rated C].[107]

Other topical agents

- Two HIV males unresponsive to systemic interferon and treated for oral and cutaneous KS with intralesional *interferon alpha-2b* (3-5 million, 3 times/week for 4-5 weeks according to the extent of the lesions) showed clearance of the lesions, whereas untreated control lesions persisted [rated D].[118]

Effects of other treatments not specific for OKS

- A meta-analysis of randomized trials showed no difference in KS survival in patients treated with *acyclovir* versus controls [rated A].[103]

Summary and recommendations

- We found only 1 double-blind RCT comparing VNB and STS for local treatment of OKS. The effects of the 2 drugs appear similar, although STS may be more affordable because of its low cost and easy application and handling.
- Limited studies of single or multiple intralesional injections of VNB and STS have shown some efficacy and localized transient adverse effects from both drugs.
- Intralesional injection with interferon alpha needs further investigation.
- Only brief reports are available for other local treatments of OKS, such as radiation or laser surgery.
- No phase III clinical trials have been published thus far for systemic therapy of OKS.
- The level of evidence is "C" for treatment of OKS with intralesional injection of vinblastine or 3% sodium tetradecyl sulfate (see Table V). At present there is insufficient evidence to develop evidence-based treatment recommendations.

Expert opinion

Management is primarily palliative and directed toward alleviating pain and restoring normal function. Therapy directed to improve esthetics by reducing the color of pigmented lesions is especially important to

patients who have anterior gingiva or lip involvement. Small nodular lesions of the palate, not overlying a neurovascular bundle, and lesions of the lips, tongue, or buccal mucosa/vestibule that interfere with speaking and eating may be surgically resected or debulked. Alternatively and for larger lesions that are not surgical candidates, intralesional injections of VNB or 3% STS may be attempted. Referral to a medical specialist (e.g., infectious disease, medical oncology, or radiation oncology) for evaluation and possible systemic chemotherapy or local radiation therapy management of larger or multiple OKS lesions may be warranted. This may be done in consultation with the patient's primary care physician, who should perform a thorough review of systems for signs of possible visceral involvement and a complete skin-lesion screening.

Research needs

- The prevalence of KS in HIV-infected patients using HAART has decreased significantly, in part from antitumor effects of antiretroviral agents. HAART is significantly associated with a decrease the prevalence of OKS.[5,7,8] HHV-8 seropositivity has a strong association with a history of sexually transmitted diseases in men having sex with men,[123] so safer sexual practices may contribute to declines in KS.
- Despite advances in treatment of HIV, some infected patients still develop KS and need additional therapy, especially those with widespread disease or disease interfering with organ function. The therapeutic goals for these treatments are "long-term palliation with minimal toxicity."[115] Systemic paclitaxel and alpha interferon are effective in controlling widespread KS, but may have significant side effects such as neutropenia. The liposomal anthracyclines (pegylated liposomal doxorubicin or daunorubicin), while less toxic than their unencapsulated counterparts, have cumulative toxicities. A Phase II trial of 9-*cis*-retinoic acid completed in 2002 found partial response in 39% of enrolled patients, but there were significant toxicities with higher doses that limit its use.[97]
- Localized treatments associated with less toxicity are important for management of patients with small, focal KS lesions. Alitretinoin gel has been tested for treatment of cutaneous KS in Phase I and II studies,[116] but no well-designed, adequately powered trials exist for the various suggested treatments of OKS.[116] These include intralesional injections of chemotherapy (VNB) or sclerosing agents (STS); surgery; cryotherapy; localized radiation for large, bulky lesions; and topical retinoids. We could not find any trial for OKS treatment in which the active drug was tested against placebo.
- Future trials testing localized treatments for OKS should adapt the published standardized methods to judge responses in clinical trials.[117]
- Intraoral therapies tested in the past attempted to limit vascular growth (STS and VNB). Given the viral component of KS, new therapies directed at controlling Kaposi's sarcoma–associated herpesvirus/HHV8 also should be considered.

ORAL HERPES SIMPLEX (HSV) AND HERPES ZOSTER (VZV) INFECTION

From review of articles: [36, 51, 103, 124-151]

Pathophysiology

The mechanistic basis for development of recurrent oral herpes infection in HIV patients is linked to reduced CD4+ cell count.[148] Frequent mucosal herpes simplex virus (HSV) reactivation, including oral HSV infection, may lead to higher levels of plasma HIV-1 RNA.[127, 132] In this context, reactivation of herpes infection may contribute to the pathobiologic expression of HIV disease itself and increase the risk of HIV transmission.

Herpes zoster infection (VZV) of the oropharyrngeal regions results from reactivation of latent VZV, harbored in the trigeminal nerve, in response to immune deterioration as seen most commonly with the age-associated immunosenescence among the elderly. Low CD4 count (particularly between 50 and 200 cells/mm^3) and being on HAART appear to be significant risk factors associated with development of VZV among HIV patients of all ages and genders; HIV viral load is not associated with risk.[149-151]

Further research is needed relative to specific mechanisms that lead to reactivation of the latent HSV and VZV viruses.

Treatment objective

- To assess the effectiveness of available systemic or topical therapies for the treatment of oral herpes simplex and oral herpes zoster infection in persons diagnosed with HIV/AIDS.

Findings

Herpes simplex— adults

- Two randomized, double-blind clinical trials have been published on the treatment and/or prevention of orolabial and anogenital herpes simplex reactivation in adult HIV patients using *famciclovir*, the oral formulation of penciclovir.
  - Study 1 was a single-center, placebo-controlled, crossover, efficacy study. Forty-eight subjects were assigned to famciclovir (500 mg BID) or

placebo twice a week for 8 weeks, and then crossed over after a 1-week washout period. There was a significant decrease in viral shedding ($P = .02$) and oral symptoms ($P = .02$) in the treatment versus placebo groups. Limitations of this study included the high dropout rate (40%), and potential variation in sample collections by individual participants [rated B].[126]

- Study 2 was a multicenter, parallel-group, equivalency study comparing famciclovir and acyclovir. A total of 293 HIV patients (37.5% with orolabial lesions, 89% completed the study) were recruited from 48 hospitals in different continents between 1993 and 1996. Treatments with famciclovir tablets (500 mg BID) and placebo capsules (5 per day) or acyclovir capsules (400 mg 5 times a day) and placebo tablets (2 per day) were comparable in efficacy (i.e., prevention of new lesions, time to complete healing, cessation of viral shedding, and loss of lesion-associated symptoms) and tolerability. A limitation of this study was that outcomes for orolabial lesions were not reported separately [rated A].[124]

- An international, multicenter, randomized, placebo-controlled trial comparing *valaciclovir* (500 mg BID, n = 194) and placebo (n = 99) for up to 6 months for suppression of recurrent herpes in adult HIV patients showed that the time to recurrence was significantly shorter in the placebo versus treatment arm (HR = 5.3; 95% confidence interval [CI] = 2.0-14.3). A limitation of this study was that the design was based on the primary outcome being genital herpes [rated B].[134]
- One study of 2 HIV patients indirectly addressed treatment of acyclovir-resistant oral herpes with *foscarnet*. All patients had virological cure, but clinical oral findings were not reported. Lesions eventually recurred in every patient that responded initially [rated D].[136]

Herpes simplex— infants and children

- Evidence-based guidelines for the treatment of herpetic gingivostomatitis in children and infants were recently published by CDC. Recommendations include the use of *acyclovir* 20 mg/kg body weight (max: 400 mg/dose) by mouth 3 times daily for 7 to 14 days for mild gingivostomatitis, and intravenous acyclovir for moderate to severe cases.[36]

Herpes zoster

- There are no trials of local or topical treatments of *oral* herpes zoster in HIV patients.
- There are no trials specifically addressing systemic treatment of *oral* herpes zoster in HIV patients.

Summary and recommendations

Herpes simplex—adult/systemic

- Several studies have investigated the use of antivirals for the treatment and/or prevention of herpes simplex. After excluding studies conducted in immunocompetent patients or that did not include data about the presence of orolabial herpes, a few studies remained. All of these trials were testing systemic agents for treatment of mucocutaneous (genital and oral) HSV.
- Only 1 study has reported results on the use of valacyclovir for suppression of oral herpes in HIV patients, although the study was designed for genital herpes.
- Two well-designed studies have shown efficacy of famciclovir compared to placebo and equivalency compared to acyclovir for the prevention and treatment of HSV.
- In summary, 3 drugs (famciclovir, acyclovir, and valacyclovir) have been successfully used in HIV patients who may have had oral HSV lesions (see Table VI). These drugs are also CDC's recommended treatment options for treatment of orolabial lesions in HIV patients, although the reported regimens are slightly different from those described in the studies reviewed in this section.[62]
- No RCTs have been published on treatment of acyclovir-resistant oral HSV.
- Patients that do not respond to acyclovir should be referred to their physician for possible intravenous antiviral therapy.

Herpes simplex—adult/topical

- There are no randomized, double-blind, placebo-controlled trials of topical treatment of oral HSV lesions in HIV patients.

Herpes simplex—women and children

- The use and effects of acyclovir and valacyclovir in the general population of children and pregnant women was summarized by Tyring et al.[133] Additional information on the use of antivirals in these population subgroups is available from CDC.[36,62,66]
- Given the higher risk of complications, these patients should be referred to their primary physician for treatment.

Herpes zoster

- There are no trials on topical or systemic treatments of oral herpes zoster in HIV patients.

Table VI. Evidence table of treatments for oral herpes simplex virus (HSV) in HIV infected patients; A, B, or C level studies only

Agent tested	*Sample size*	*Study design*	*Outcome*	*Rating*
Romanowski et al. Famciclovir (500 mg BID) vs. acyclovir (400 mg 5x/d) to prevent recurrence of genital and oral herpes; 37.5% had orolabial lesions.[124]	150 famciclovir; 143 acyclovir	Randomized, placebo-controlled, double-blind, prospective	Famciclovir: 16.7% developed new lesions during study Acyclovir: 13.3% developed new lesions during study Equivalent time to healing in both arms	A
Schacker et al. Famciclovir (500 mg BID) or placebo twice a week for 8 weeks, and then crossed over after a 1-week washout period.[126]	48 famciclovir or placebo (crossover)	Randomized, placebo-controlled, double-blind prospective, crossover	Famciclovir: Statistical decrease in viral shedding and oral symptoms	B
DeJesus et al. Valacyclovir (500 mg BID) vs placebo for up to 6 months for suppression of recurrent herpes in adult HIV patients.[134]	194 valacyclovir 99 placebo	Randomized, placebo-controlled, double-blind	Valacyclovir: Longer time to recurrence Primary outcome genital herpes	B

BID, twice daily.

- Given the potential for spread to the ophthalmic branch of the trigeminal nerve, patients should be referred to their primary physician for systemic drug treatment of herpes zoster.

Expert opinion

Herpes simplex

- If the CD4 T-cell count is at or above 200 cells/mm^3, consider topical treatments first for perioral herpes simplex. Therapy should be continued until lesions are completely healed. If the count is below 200 cells/mm^3, the lesions are extensive, or the patient did not respond to topical therapy, prescribe a systemic antiviral drug.

Herpes zoster

- Given the higher rate of postherpetic neuralgia and other complications among patients with HIV[151] anti–herpes zoster therapy should be initiated as soon as possible for all cases
- Although no trials of oral VZV exist, experts would follow the current CDC guidelines[36] established based on evidence from trials of VZV affecting other dermatomes, and prescribe a 7- to 10-day therapeutic course of famciclovir or valacyclovir. There are suggestions of more toxicity with valacyclovir.

Research needs

- A few studies of systemic antivirals in HIV patients stated the baseline number of subjects with orolabial herpes simplex lesions. However, results were not reported by specific site. While famciclovir, acyclovir, and valacyclovir are effective in HIV patients with mucocutaneous HSV, the optimal drug and dosage for the HIV-infected patient presenting only with orolabial herpes is unknown.
- At this time, there appear to be effective therapies for treatment of herpes simplex virus and herpes zoster virus in patients with HIV infection. There will continue to be demand for newer antiviral agents in general as resistant strains of herpes viruses develop (see other sections dealing with herpes viruses in this World Workshop).

HIV-ASSOCIATED INTRAORAL OR PERIORAL WARTS (CONDYLOMA ACUMINATA, HUMAN PAPILLOMAVIRUS LESIONS)

From review of articles: [5,7-9,81,152-171]

Pathophysiology

Intraoral and perioral warts in HIV patients are caused by human papilloma virus. As with OHL, the condition occurs most frequently in the setting of reduced blood CD4+ T-cell counts.[81] There appears to be an overall lack of mucosal immune responsiveness to the lesion. Viral strain–related characteristics likely influence pathogenicity; for example, HPV32 seems to promote infection by selective enhancement of epithelial cell growth and differentiation within the stratum spinosum.[169]

Interestingly, oral HPV infection rates have not declined since introduction of HAART[156]; rates may have actually increased in white HIV-infected males.[170] These findings indicate the need for further research relative to relationships between HIV responsiveness to therapy and causation of intraoral warts by the virus.

Treatment objective

- To assess the effectiveness of available therapies for intraoral and perioral warts in persons diagnosed with HIV/AIDS.

Findings

- There are only a few case reports for treatment of HIV-associated oral warts. No randomization, placebo control, or blinding were included in the design of these studies, and sample size was very small.
- The first study in the literature on the treatment of HIV-associated warts with *bleomycin* was a single case report published in 2000. A 26-year-old woman with HIV with multiple warts that had only partially responded to prior therapy with cryotherapy, interferon-α 3 million U subcutaneously and surgical excision, was treated with intralesional bleomycin sulphate (1 U/mL diluted in sterile water) 0.5 mg/lesion up to 4 mg total on the first session. After 2 sessions 2 weeks apart, all warts had disappeared. The patient was lesion-free after 12 months of follow-up. Adverse effects included severe transient pain and necrosis at the injection site [rated D].[165]
- The results of 2 reports on 4 patients total have suggested that self-administered topical *cidofovir* (a purine nucleotide analog of cytosine) may be an effective treatment for refractory oral warts in HIV patients:
  - A case report of topical cidofovir gel 1% applied by a 36-year-old male patient with a cotton swab every night for treatment of recalcitrant HPV lesions on the gingiva showed 95% resolution of the lesions after 4 weeks, 100% improvement after an additional 4 weeks of treatment, and no recurrence for at least 12 months [rated D].[157]
  - A report of 3 men treated for refractory oral warts with cidofovir 1% to 3% solution once a day (prepared by diluting 1 vial of Vistide—cidofovir 375 mg/5 mL—in 20% propylene glycol aqueous solution), showed a complete resolution of all the lesions within 3 to 10 weeks. Except for 1 lesion that reappeared 4 months later and was retreated, no recurrence was seen for at least 18 months [rated D].[156]
  - Four male patients were treated with *interferon-α* intralesionally (weekly, 0.5-1.5 million units on average, no more than 0.1 mL/cm^2, total 6-24 treatments over a period of 1 month to 2.5 years), in combination with subcutaneous injections (2 of 4 patients, twice a week on alternate days) for recalcitrant oral warts previously treated with only partial success using electrosurgery, cryosurgery, podophyllum 25%, CO_2 laser, and/or excision. Counseling was also given. The lesions resolved and did not recur for 1 year or longer [rated D].[161]
  - A male with HIV treated with CO_2 *laser surgery* for perioral warts had no recurrence after 1 year [rated D].[166]
  - A male with HIV treated unsuccessfully with repeated curettage and cautery, cryocautery, and etretinate for oral and perioral warts, had a complete response to *cimetidine* 40 mg/day after 2 months, although recurrence was seen at lower doses [rated D].[168]

Summary and recommendations

- Several treatments for HIV-associated warts have been reported. However, most treatments have targeted extraoral warts (cutaneous or external anogenital) and may or may not be applicable to the treatment of intraoral warts. These treatments have included caustic/acid agents, cantharidin, podophyllin resin, tretinoin, intralesional bleomycin, topical 5-fluorouracil, surgical treatment (cryosurgery, CO_2 slush, electrosurgery and curettage, blunt dissection, CO_2 laser), imiquimod, vitamin A (oral etretinate), cimetidine, zinc sulphate, x-ray, heat and tape occlusion, excision, or a combination of the above.
- There are no randomized, double-blind, placebo-controlled trials for treatment of intraoral warts in HIV patients.
- A very limited number of case reports have addressed treatments specifically targeted at intraoral warts in HIV patients. These include pharmacotherapy (cidofovir, bleomycin, cimetidine, podophyllum, or interferon-α intralesional in combination or not with subcutaneous injections), surgery (excision, electrosurgery, cryosurgery, or CO_2 laser), or a combination of the above. In the absence of other study designs, we have reported the results of these case reports in this section.
- The treatment of oral warts is difficult because of the often widespread distribution of the lesions and high recurrence rate. Patient treatment should be accompanied by treatment of partners and counseling to prevent new lesions.

- Consideration should be given to the possibility of spreading the lesions to other surfaces during treatment. Cauterization may seed other mucosal surfaces with HPV, such as the nasal mucosa.[171]
- The highest level of evidence for treatment of intraoral or perioral warts in HIV-positive patients is "D." At present there is insufficient evidence to develop evidence-based treatment recommendations.

Expert opinion

- Surgery is currently the most common therapy for lesions that interfere with function or are of esthetic concern.

Research needs

- To date, there are no effective treatments for intraoral warts, an HIV-associated oral lesion that possibly has not decreased with HAART.[5,7,8] One retrospective study of lesions in an academic oral medicine clinic[9] reported increases of oral warts in their clinic population that was associated with HAART use, but this increase also may have been associated with patterns of referral.
- Future trials should consider analyzing outcomes for the various viral strains found within the warts.
- In general, human papilloma virus is implicated in HIV-associated malignancies of the anal/genital area in both males and females.[154] Another recent study of DNA extracted from 99 banked salivary specimens from HIV-infected patients found Caucasian males taking HAART were more likely to have HPV in their salivary samples than those who were not taking HAART.[163] However, these findings were not seen in samples taken from African Americans in this study. As HPV is associated with oncogenic processes in HIV-infected individuals, further studies of its pathogenesis and treatment are warranted.

HIV-ASSOCIATED PERIODONTAL DISEASES

From review of articles: [9, 172-187]

Pathophysiology

HIV infection is associated with a diverse expression of periodontal lesions, including unusual forms of gingivitis, necrotizing periodontal disease, and exacerbations of preexistent periodontal disease.[182] Risk factors include reduced CD4+ cell counts, coupled with more traditional risk factors including preexisting gingivitis, poor oral hygiene, smoking, and poor diet.[184,185]

Microbial pathogens are also a significant contributor to expression of clinical periodontal disease. Necrotizing periodontal disease does not appear to be principally caused by pathogens that are associated with periodontal disease in non–HIV-infected individuals, including Porphyromonas gingivalis.[183] In addition, profiles of subgingival microbial flora in HIV-positive patients are different and less complex than are subgingival microbial flora profiles in patients with a healthy periodontium.[183]

Treatment objectives

- To assess the effectiveness of available therapies for linear gingival erythema (LGE) in persons diagnosed with HIV/AIDS.
- To assess the effectiveness of available therapies for necrotizing ulcerative gingivitis (NUG) in persons diagnosed with HIV/AIDS.
- To assess the effectiveness of available therapies for necrotizing ulcerative periodontitis (NUP) in persons diagnosed with HIV/AIDS.

Findings

There are no randomized clinical trials for treatment of periodontal disease in HIV patients.

Summary and recommendations

At present there is insufficient evidence to develop evidence-based treatment recommendations.

Expert opinion

LGE, NUG, and NUP should be treated as they would be in non–HIV-infected patients. Adjunctive therapy, such as systemic antibiotics, chlorhexidine, or other drugs that target the responsible etiologic agent(s) should be prescribed when appropriate.

Research needs

- Anecdotal reports suggest NUG and NUP in HIV patients do not respond to conventional therapy,[173-176] but these assertions have never been substantiated in clinical trials. One of the biggest challenges for investigators conducting a treatment trial of periodontal diseases in HIV-infected adults would be subject accrual, as these lesions are relatively rare.[172]
- Multiple periodontal pathogens appear to be associated with these forms of gingivitis and periodontitis. *Candida* species, spirochetes, and more traditional periodontal pathogens have been cultivated from diseased periodontium of patients.[173] Human herpesviruses (HSV, EBV, and cytomegalovirus) have been suggested to be triggers or cofactors of periodontal disease activity. Research is needed that extends our understanding of the interaction between periodontopathic microorganisms and the host inflammatory response of adults and children with HIV/AIDS.

- Studies examining clinical attachment loss (CAL) longitudinally in HIV-infected cohorts[9,177-179] have reported greater loss in HIV-infected patients. All of these studies were small (total sample size of between 36 and 135), often with far more HIV+ patients than appropriate controls with similar risk factors. Studies with larger cohorts are needed to determine if HIV is an independent risk factor for increased CAL.
- LGE in selected age groups appears to be more common than ulcerative forms of periodontitis. A study of inner city children in New Jersey[180] found LGE in 22% of HIV-positive children versus 2% of age-matched controls living in the same household. Examiners were blinded to the child's HIV status during the examination, and conventional gingivitis, assessed at the same evaluation, was not different between patients and controls. It is not known if LGE leads to other forms of periodontitis as children with HIV infection age.

OVERALL SUMMARY OF RESEARCH NEEDS

- This review revealed that the vast majority of treatment studies were conducted with adult populations living in North America or Western or Central Europe. Individuals from these countries represent the minority of individuals infected with HIV. There were also very few studies of treatments for children, and women were underrepresented in earlier trials. At present, it is estimated that 2.3 million children worldwide are infected with this virus, and children born with HIV infection have broader infectious susceptibilities than adults acquiring infection after development of normal humoral immune responses.[186]
- Methodologically, there are not universally accepted outcome measures to monitor therapeutic responses in trials for treatment of oral HIV lesions, with the exception of KS. If standardized sets of outcome measures are developed, they should be flexible enough for use in underdeveloped nations that have the greatest concentration of HIV patients. Future therapeutic trials should also contain adequate representation from those patient groups that bear the greatest burden of this epidemic.
- HAART and/or persistent HIV infection have created a population of patients with different oral complications than those found in the late 1980s and early 1990s. There is a need for well-designed, controlled studies in which the examiner is blinded to the patient's HIV-status to estimate the current prevalence of oral lesions. Longitudinal studies documenting oral complications of children born with HIV infection are lacking. In general, HIV-infected patients are taking multiple medications. Therefore, meaningful clinical trials and prevalence studies need to be of sufficient size to control for the effect of medications, such as antibiotic usage and the prevalence of OPC.

AIDS immune reconstitution syndrome is now a recognized entity that occurs in a small subset of patients soon after institution of HAART. Patients who have been previously unable to mount an immune response to certain pathogens may have a renewed inflammatory response and a variety of clinical manifestations when the CD4 count rises. Oropharyngeal KS and herpes simplex infection have been reported to occur in these patients.[187] The frequency of oral lesions in this syndrome should be investigated.

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