



Oral Health and HIV Infection: A Chronic Disease Model

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ABSTRACT HIV disease is now considered a chronic illness requiring continued management and monitoring. However, for those with poor access to anti-retroviral medications, the disease continues to be associated with higher morbidity and mortality. With the expansion of the HIV pandemic into vulnerable subpopulations, HIV care requires coordinated and integrated care for a complex mix of psychosocial and clinical services that must include oral health care.

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The HIV pandemic remains the most serious infectious disease challenge to global public health. Worldwide, more than 6,800 people become infected with HIV every day and more than 5,700 individuals die from AIDS leading to an ever-growing number of individuals living with HIV.¹

The incidence of HIV has decreased in many parts of the world including North America, Western Europe, and even in sub-Saharan Africa. However, in Latin America, Asia, and Eastern Europe, new patterns of the HIV epidemic have emerged.

Despite a decline in prevalence that has continued since the year 2000, sub-Saharan Africa remains the hardest-hit region in the world where the adult prevalence is estimated at 5 percent and HIV accounted for 76 percent of all deaths in 2007.² In Eastern Europe, the total number of people with HIV increased

150 percent between 2001 and 2007, and 90 percent of the new cases (about 150,000) occurred in the Russian Federation and Ukraine in 2007.¹ The estimated number of people living with HIV/AIDS is 7.4 million in Southeast Asia, 1.8 million in Latin America, and 1.6 million in Eastern Europe and Central Asia.¹ Globally, since 1990, almost half of the world's AIDS cases have been women.¹

In the United States, cumulative data from 1981 to 2007 shows reports of more than 1,051,000 cases of AIDS and more than 560,000 AIDS-related deaths.³ It is estimated that almost 1.2 million individuals are currently living with HIV in the United States, with more than 25 percent undiagnosed and unaware of their infection.³ In August 2008, the Centers for Disease Control and Prevention reported the use of new epidemiologic methods that led to a significant

revision in the estimated number of new HIV infections in the United States.⁴

Based on extrapolations from the estimated number of new infections in 2006, the previous estimated incidence rate of 40,000 was adjusted to 56,300, a rate that it is believed has been relatively stable since the late 1990s. In California, there are more than 66,000 individuals living with HIV/AIDS.⁵ In 2006, an estimated 935 new HIV cases were reported in San Francisco, an incidence rate that is most likely stable for this geographic area.⁶ In Los Angeles, an accurate HIV incidence rate is not yet available. However, at the end of 2008, a total of 23,679 people were reported to be living with HIV/AIDS and another 18,124 people were reported to be living with HIV/no AIDS (unpublished data).⁵

Worldwide, the predominant HIV transmission mode is heterosexual, with two broad patterns identified. The first pattern is a generalized epidemic sustained in the general populations of many sub-Saharan African countries; the second is the epidemic most common in the rest of the world, primarily concentrated among populations most at risk.¹ The at-risk populations include men who have sex with men, injecting drug users, and sex workers and their sexual partners. The most common form of transmission in the United States HIV epidemic is men having sex with men, MSM. Of new HIV infections among males in 2006, 72 percent were MSM. Among MSM with new infections, 46 percent were white (67 percent of general population), 35 percent were black (13 percent of general population), and 19 percent were Hispanic/Latino (15 percent of general population).⁷ Of all new infections among women in 2006, 73 percent of transmissions occurred as a result of high-risk heterosexual contact and 68 percent were in black women.³

Current State of HIV Disease Management

HIV disease is a spectrum ranging from an asymptomatic phase to severe immunosuppression manifested by many types of opportunistic infections and malignancies. The mechanisms involved in immunologic suppression comprise a variety of immunologic defects that include severe reduction in the CD4 positive T-lymphocytes, cytokine dysregulation, and defective innate immune

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responses.⁸ It is now widely accepted that intervention with anti-retroviral (ARV) drugs and adherence to appropriate medications can prolong life and delay HIV disease progression.

Since the discovery of the very first anti-HIV compound, Zidovudine (AZT), more than 21 years ago, great advances have been made in understanding the disease pathogenesis. The translation of that knowledge into practical therapeutics has led to the development of more than 30 individual drugs and combinations for treatment of HIV infection. Despite these advances, disease management remains challenged by toxicities, treatment maintenance and adherence, clinical manifestations of the disease and the drugs used to treat it, and the threat of drug resistance.⁸ In recent years,

newer formulations of ARVs have been developed that are more potent, produce durable results, and are less toxic.⁸

Current HIV/AIDS treatment guidelines recommend that anti-HIV treatment should be initiated for all symptomatic patients and asymptomatic individuals before the CD4 count goes below 350/mm³.⁸ Studies showed that if left untreated at this marker, the risk of the disease progressing to opportunistic infections and death within two years approximates 30 percent.⁸ As even the CD4 counts higher than 350/mm³ have been shown to be associated with increased mortality, malignancies (lymphomas, lung, anal, head and neck cancers), and major organ system dysfunction (cardiac, hepatic, renal), whenever possible, ARVs should be considered as early as possible.⁹⁻¹⁶ A decision to begin ARV for higher CD4 counts depends on patient readiness, drug interactions, adherence challenges, toxicities, and costs of treatment, recognizing that treatment must be sustained.⁸ Factors that call for earlier therapy include rapidly declining CD4 count, high viral load, the presence of comorbid conditions, and other clinical indications, such as chronic HBV infection and HIV-associated nephropathy.⁸ In addition, risk factors for cardiovascular disease, such as hypertension, hyperlipidemia, diabetes, and tobacco use, should be aggressively managed in all patients.⁸

Mechanisms of Anti-Retroviral Treatment

Strategies in HIV disease treatment involve intervention at several junctures of HIV infection and replication. The HIV life cycle includes six main stages: entry, reverse transcription of RNA into DNA, integration of proviral DNA into host DNA, transcription back to mRNA, viral assembly, and host cell lysis. Currently,

there are 32 FDA-approved ARV agents and combinations that address several of these replicative stages. The classes of those ARVs include 1) nucleoside reverse transcriptase inhibitors (NRTI), 2) non-nucleoside reverse transcriptase inhibitors (NNRTI), 3) protease inhibitors (PI), 4) entry and fusion inhibitors, and 5) integrase inhibitors.¹⁷

The primary aim of anti-HIV treatment is to provide a durable suppression of HIV replication that is below detection limits of plasma HIV RNA assays.¹⁸ Durable viral suppression results in fewer drug-resistant viral variants that occur through random mutations during the high rate of HIV replication and mostly because of poor patient adherence to medication regimen. The current ARV combination regimen for treatment-naïve patients is two NRTIs and either one NNRTI or two PIs (protease inhibitor-boosted regimen) (TABLE 1).

Baseline genotypic testing for resistance should be performed in all treatment-naïve patients to determine the best choice for the ARV regimen.⁸ The other classes of drugs, fusion, and integrase inhibitors are used in treatment-experienced patients after other regimens have failed (salvage therapy). Combination formulations of two NRTIs (Combivir, Epzicom, Truvada), three NRTIs (Trizivir), two PIs (Kaletra), or multiclass combinations of two NRTIs and one NNRTI (tenofovir + emtricitabine + efavirenz or Atripla) have made medication adherence easier for many patients.

Long-term use of ARVs may be associated with a number of clinical sequelae, including metabolic complications, cardiovascular disease, musculoskeletal presentations, and certain types of cancers. Metabolic complications include hyperglycemia, insulin resistance, and hyperlipidemia (elevations

in total cholesterol, LDL, and triglycerides) mostly caused by older formulations of PIs.¹⁹ Lipoatrophy or peripheral fat-wasting occurs with NRTI use while visceral fat deposition is associated with hyperinsulinemia and dyslipidemia.^{20,21}

Increased risk for coronary heart disease may be attributed to a number of factors, including metabolic alterations, changes in body composition (with loss of subcutaneous fat and/or accumulation of visceral fat), inflammation, the direct

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effects of the virus on the vasculature, and as a result of specific anti-retroviral drugs.²² Specific guidelines for reducing the risk of these complications have been published.^{23,24} Other consequences of ARV use include osteoporosis and avascular necrosis in bones, prostate neoplasia, and lethal solid tumors such as NHL associated mostly with NNRTIs.²⁵⁻²⁷

New Intervention Strategies

Current ARV drug development focuses on HIV entry into host cells and the specific regulatory mechanisms necessary for either successful viral replication or its release from the host cells. An entry inhibitor has already been marketed for clinical use, and new therapeutic agents targeting HIV regulatory gene products are in development. As reviewed by Greene et. al., some of

the specific new therapeutic targets include the integrase enzyme cofactor LEDGF/p75; several innate immune factors, such as TRIM5 α that restrict HIV integration; APOBEC 3G that interferes with viral DNA synthesis; and Tetherin that blocks viral release.²⁸

Viral Entry

HIV attacks CD4 receptors on the surface of cells like lymphocytes and macrophages, and attaches to the receptor through gp120. There is evidence that there are additional receptors involved in the attachment process. The natural chemokine receptors, such as CCR5 and CXCR4, act as coreceptors for HIV anchorage and host cell entry²⁹ (FIGURE 1). The R5 strain of HIV has an affinity for the CCR5 receptor and is the predominant type of HIV in mucosal transmission — distinct from the X4 strain of HIV that is primarily transmitted through blood exposure and with the primary CXCR4 coreceptor.

Due to genetic variability, people who do not fully express these coreceptors on the HIV target cells are either immune to HIV infection or their HIV disease does not progress as rapidly compared to people with full coreceptor expression. One of the reported genetic mutations involves a 32-base pair deletion in CCR5 receptor (CCR5- Δ 32 allele) that infers resistance in those who are homozygote for the mutation and slow progression for the heterozygotes.^{30,31} The CCR5- Δ 32 allele is mainly present in Europeans (10 percent on average); the allele frequency is highest (>15 percent) in the areas surrounding the Baltic and White seas, and in Central Russia.³²

The mutation frequency gradually decreases in all directions across Europe and is found with the lowest frequency in the Mediterranean area, North Africa, Middle East, Central Asia, and is absent in sub-Saharan Africa, east and Southeast

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TABLE 1

Major FDA-Approved Anti-HIV Medications

Drug Class	NRTIs	NNRTIs	PIs	Integrase Inhibitors	Entry Inhibitors
Main formulations	<p>AZT – zidovudine (Retrovir) ddI - didanosine (Videx) ddC - zalcitabine (Hivid) d4T - stavudine (Zerit) 3TC - lamivudine (EpiVir) ABC - abacavir (Ziagen) TDF - tenofovir (Viread) FTC – emtricitabine (Emtriva)</p> <p>Combinations Zidovudine + lamivudine (Combivir) Abacavir + lamivudine (Epzicom) Abacavir + zidovudine + lamivudine (Trizivir) Tenofovir + emtricitabine (Truvada)</p>	<p>ETV – etravirine (Intelence) DLV – delaviridine (Rescriptor) EFV – efavirenz (Sustiva) NVP – nevirapine (Viramune)</p>	<p>APV - amprenavir (Agenerase) TPV - tipranavir (Aptivus) SQV – saquinavir (Invirase) IDV – indinavir (Crixivan) FPV - fosamprenavir (Lexiva) RTV – ritonavir (Norvir) DRV – darunavir (Perzista) ATZ – atazanavir (Reyataz) NFV – nelfinavir (Viracept)</p> <p>Combination Loprinavir + Ritonavir (Kaletra)</p>	<p>Raltegravir (Isentress)</p>	<p>ENF – enfuvirtide (Fuzeon) Maraviroc (Selzenti)</p>
Advantages	<ul style="list-style-type: none"> • Easy dosing schedule • Little food effect • Dual NRT established as the backbone of combination therapy • Fewer drug interactions 	<ul style="list-style-type: none"> • Low toxicity • Impressive long-term results • Less lipid abnormalities • Saves PIs for future use 	<ul style="list-style-type: none"> • High genetic threshold 	<ul style="list-style-type: none"> • Useful for treatment experienced patients with multiple drug resistance 	<ul style="list-style-type: none"> • Useful for treatment experienced patients with multiple drug resistance
Disadvantages	<ul style="list-style-type: none"> • Some members lead to serious side effects 	<ul style="list-style-type: none"> • Low genetic barrier for mutation • Cross-resistance • Potential for CYP450 drug interactions • Side effects 	<ul style="list-style-type: none"> • Complex food requirements • Cross-resistance is common & have severe side effects • CYP3A4 inhibitors and substrate • Drug interaction • Side effects 	<ul style="list-style-type: none"> • Effectiveness in treatment naïve patients still being studied 	<ul style="list-style-type: none"> • Effectiveness in treatment naïve patients still being studied • Maraviroc only effective against R5 strain
Major side effects	<ul style="list-style-type: none"> • Peripheral neuropathy • Myopathy, cardiomyopathy & myositis • Lactic acidosis (lactate >2-5 mmol/dL plus symptoms) • Nausea, vomiting, abdominal pain, muscle weakness • Hepatic steatosis (adiposis) • Lipodystrophy • Pancreatitis • Bone marrow suppression <p>Side effects worse w/ older formulations</p>	<ul style="list-style-type: none"> • Rash • Drug-drug interactions <p>Nevirapine</p> <ul style="list-style-type: none"> • Hepatotoxicity • Stevens-Johnson syndrome <p>Efavirenz</p> <ul style="list-style-type: none"> • Neuropsychiatric effects • Teratogenic in primates (FDA Pregnancy Class D) 	<ul style="list-style-type: none"> • Insulin resistance and relative insulin deficiency • Hyperlipidemia • Lipodystrophy • Elevated liver function tests/ hepatotoxicity • Osteonecrosis & osteoporosis (increased in corticosteroid tx, alcohol abuse) • Hyperlipidemia, • Possible increased bleeding risk in hemophiliacs • Drug-drug interactions <p>Side effects worse w/ older formulations</p>	<ul style="list-style-type: none"> • Depression • Suicidal tendencies • Diarrhea • Headaches • Stevens-Johnson syndrome 	<p>Fuzeon</p> <ul style="list-style-type: none"> • Injection-site reactions • Hypersensitivity reaction • Increased risk of bacterial pneumonia • Risk of kidney dysfunction <p>Maraviroc</p> <ul style="list-style-type: none"> • Bladder irritation • Hepatitis • Hypercholesterolemia

Note: Table does not include multiclass combination drug Atripla (efavirenz [NNRTI] + tenofovir [NRTI] + emtricitabine [NRTI]).

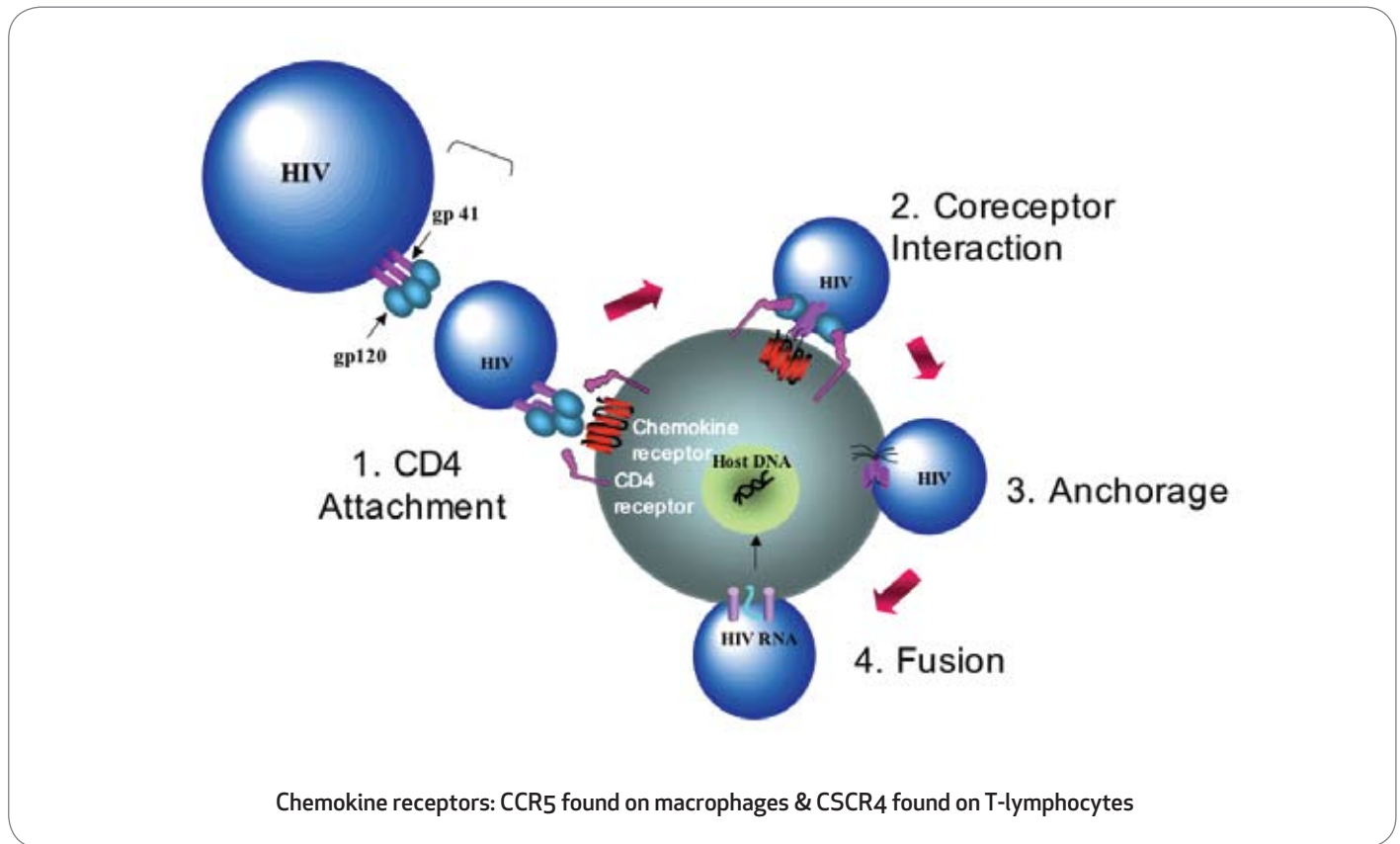


FIGURE 1. HIV entry.

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Asia, and in indigenous populations of the Americas and Oceania.³² Considering these observations, developing compounds capable of blocking the HIV-coreceptor interaction has been one of the main targets of anti-HIV drug development for years. With the creation of Maraviroc (Selzentry), a medication that causes a structural change in the CCR5 coreceptor, a new approach has become available in blocking HIV infection or progression.¹⁷

In addition, monoclonal antibodies (mAbs) against CCR5 have entered clinical testing as potential therapeutic agents in the near future.³³ A viral assay (Trofile Assay, Monogram Biosciences) has been developed to determine the proportion of the HIV viruses in an individual with the R5 strain. Using information obtained from this assay, Maraviroc may be used to block HIV entry in individuals infected with the R5 strain.

HIV Regulatory Genes

The very simple HIV genome consists of three structural and at least six regulatory genes. The structural genes include *env* encoding for the viral capsid proteins (gp 120 and gp 41, the main sites for interactions with CD4 receptors); *gag* encoding for the matrix and core proteins (p17 and p24); and *pol* encoding for the key viral enzymes (protease, reverse transcriptase, and integrase). As described earlier, current anti-HIV drugs mainly target the key viral enzymes that are necessary for replication and assembly.

However, with greater understanding of the role of HIV regulatory genes, Tat, Rev, Nef, Vif, Vpr, Vpx, Vpu, novel approaches to treatment may be on the horizon. The HIV regulatory genes and their protein products interfere

with a number of host immune mechanisms that help enhance viral RNA transcription and processing, lead to cytokine dysregulation, or induce host cell cycle arrest and apoptosis.³⁴⁻³⁷

Of all the regulatory genes, Vif has been shown to have great efficiency crippling an innate host defense molecule "Apolipoprotein B" or "APOBEC 3G," a polypeptide responsible for amino acid substitution on newly synthesized viral DNA that interrupts HIV replication^{38,39} (FIGURE 2). Viral Vpr gene appears to aid in this process as well.⁴⁰ Vpu is effective against another host defense molecule, "Tetherin," a membrane protein (CD317) with nonspecific anti-viral properties that blocks the envelope protein release⁴¹ (FIGURE 2). Vif and Vpu function are among several prime targets for new classes of anti-HIV drugs.²⁸

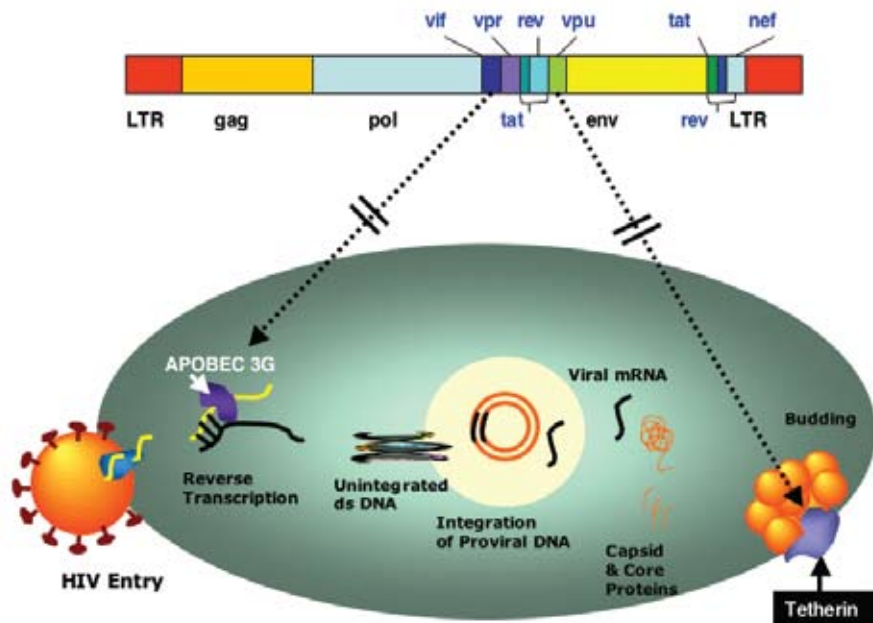


FIGURE 2. HIV genes and life cycle.

HIV Infection and Oral Health

Scientific discoveries in HIV medical management have transformed HIV infection from a rapidly progressive terminal disease to a chronic illness that can be compatible with a long and productive life for patients. The role of oral care providers in overall HIV management has evolved consistent with the changing face of the disease and its comorbid conditions. In patients who are receiving appropriate medical care, oral health care is focused on treating chronic oral diseases, restoring function, and improving a patient's quality of life. This is in stark contrast with the urgent oral care needs of individuals who are not receiving adequate or appropriate medical care, are failing ARV treatment, or are experiencing oral side effects of HIV-related or unrelated treatments.

Epidemiologic reports have indicated that with adequate ARV treatment, the incidence and prevalence of many HIV-related soft tissue pathologies have significantly decreased.⁴²⁻⁴⁷ Clinical detection of oral soft tissue lesions is associated with

a low CD4 count and high HIV viral load, inferring inadequate treatment, development of resistance, and therapeutic failure among those receiving ARVs.⁴⁸⁻⁵⁵ However, with optimal ARV treatment, the decline in prevalence is not uniformly observed for all types of HIV-related head and neck manifestations. Among patients receiving ARVs, an increase in prevalence of human papilloma virus (HPV)-related lesions and salivary gland disease (HIVSGD) has been reported.^{42,43,56-58} In addition, approximately 20 percent of patients who start ARV treatment experience specific clinical events associated with immune reconstitution inflammatory syndrome, IRIS.⁵⁹⁻⁶³

This phenomenon, reported among people who start treatment when their CD4 counts are very low and their viral loads are high, consists of clinical emergence of a prior subclinical infection or severe recurrence of an old condition.⁶³ Manifestations of IRIS have been reported to include mostly dermatologic lesions such as anogenital herpes, genital warts, molluscum contagiosum, and varicella zoster, as well as

other conditions like mycobacterial infections, hepatitis B and Kaposi's sarcoma.^{62,63}

Opportunistic oral infections and parotid enlargement have also been implicated in the clinical spectrum of IRIS.^{64,65} In considering oral soft tissue lesion prevalence rates, another caveat is the pattern observed in the developing world, where the level of access to ARVs is extremely variable among different countries.⁶⁶⁻⁶⁹ With less access to fewer ARVs, HIV-related oral manifestations continue to be reported in high prevalence rates in many regions of the world.⁷⁰⁻⁷⁷ In a comprehensive review of HIV-related oral lesions worldwide, oral candidiasis was noted as the most common opportunistic infection reported in high rates among the adult and pediatric populations.⁷⁷

HIV Disease Management Models of Care

The many medical advances in HIV disease management described in this paper have contributed to the evolution of HIV infection into a chronic disease where infected persons who can ac-

cess proper medical treatments can live longer, more normal lives. On the other hand, like other complex chronic diseases, HIV infection may be associated with a myriad of clinical presentations that occur at any point in the course of the disease that can lead to severe complications, morbid conditions, and major disabilities. As a result, preventive measures, early detection, timely intervention and long-term monitoring are key components of HIV care. Concurrently, ethnic minority populations, the poor, and people living with co-occurring illnesses, substance abuse and/or mental health diagnoses are increasingly more vulnerable to HIV exposure and infection. Overall, treatment of HIV seropositive patients and the affected, complicated subpopulations has become more challenging, requiring integrated and coordinated approaches to care.⁷⁸

There are numerous models for managing patients' care and treatment, including integrated care, disease management, chronic care, and care coordination that may be considered for implementation in the HIV field as HIV is increasingly characterized as a chronic, rather than terminal, disease. *Integrated care* actively combines interventions in order to treat presenting disorders and the needs of the whole person more effectively.⁷⁹ *Disease management* emphasizes evidence-based interventions and outcome evaluation.⁸⁰ The *chronic care model* represents a shift from acute episode-based service delivery to a holistic approach that includes biological, psychosocial, social, and environmental needs of an individual.⁸¹ *Care coordination* involves the development of a comprehensive assessment as the patient enters care, of all of their biological, psychological, and social needs so they can be addressed, as needed, concurrently.⁸²

Incorporating Oral Health Care in the HIV Continuum of Care

Oral care providers must remain knowledgeable about HIV-related head and neck manifestations and their relationship with HIV disease status. The presence of oral opportunistic infections and malignancies not only correlates with the effectiveness of anti-HIV treatments and the degree of immunologic suppression or rebound described earlier, but also has new implications for oral health itself. For

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instance, the higher prevalence of HPV-related lesions may contribute to oral cancer development.⁸³ Similarly, the presence of xerostomia and its deleterious effects on dentition, periodontal structures, and oral mucosa must be considered when monitoring for caries, periodontal conditions, and oral mucosal diseases. For all people living with HIV/AIDS, PLWHA, vigilance in detection, prevention, and treatment of all oral diseases remains critical. Therefore, access to routine dental care, as well as referral to specialty clinics, must remain a priority in the overall spectrum of HIV care.

Studies in the United States have consistently shown significant disparities in PLWHA accessing and utilizing oral health services; these disparities are primarily driven by an individual's socioeconomic characteristics.⁸³⁻⁸⁹ Most recently, in a na-

tional survey of 1,802 respondents, dental care was identified as the highest unmet need for all participants.⁹⁰ These observations are reported while there are public dental insurance programs and funding under the Ryan White HIV/AIDS Treatment Modernization Act that support, in part, the provision of oral health services for PLWHA.^{91,92} For many who depend on public programs, referral and utilization of dental services is mostly episodic and only for urgent-type care.⁹³ Therefore, in designing, funding, and implementing an HIV spectrum of care, in both private and public insurance systems, timely access to routine dental care and referral to specialty clinics must be considered a priority and oral health services should be included in the overall HIV care scheme.

The authors propose a model of care that was recently developed within the Ryan White Care system in Los Angeles County.^{94,95} This model of care involves a system of care coordination where every patient entering care is assessed, comprehensively, for all their needs and is guided through collaborative service delivery to ensure optimal health outcomes.⁹⁶ The new care coordination model allows for a significantly enhanced prominence for oral health care — a long-identified unmet need of HIV patients in the region. Previously, oral health needs were only addressed when the patient requested them or a medical provider identified them during the medical exam. In the new continuum, oral health care is included in the medical cluster as part of core medical services and oral health examination and determination of a patient's need for oral health services are a part of the initial comprehensive patient assessment. Furthermore, in planning the medical care coordination model and the new comprehensive HIV continuum of care, outcomes-based evaluation and assessment methods for clinical

service delivery have emerged. Specific oral health measures are included as a part of the overall health outcomes targeted for this local HIV service delivery system.

Conclusion

Recent advances in HIV medical management have transformed HIV infection from a terminal disease into a chronic illness requiring continued management and careful monitoring. The improved general health observed in patients is also associated with lower prevalence rates for many HIV-related oral soft tissue lesions, while new oral health implications have emerged. In the current state of the HIV epidemic, the link between oral and systemic health is especially important because of the relationship between oral findings and HIV status, as well as the impact of oral health in a patient's functional state and quality of life. HIV care exceedingly requires coordinated care and oral health care must be viewed as a critical component of the overall HIV disease management. As many HIV/AIDS services programs around the country are developing and adopting chronic disease models of care, dental care providers must remain engaged in the process to ensure the integration of oral health services in the HIV continuum of care. ■■■■■

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