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Review Article

Association of CD4 Count and Clinical Manifestations of Oral Lesions in HIV+ Children

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Abstract

Several studies have reported that up to 90% of HIV-infected patients exhibit one or more oral lesions at some time during their disease. Oral lesions are widespread in patients suffering from HIV infection. Oral health care workers caring for HIV-afflicted people/children ought to be aware of the various oral manifestations of HIV and detailed knowledge about staging and managing the same.

Children with HIV/AIDS are usually infected due to vertical transmission from mother to child or due to being victims of sexual exploitation. Owing to their innocent age and lack of awareness, they may not even understand the gravity of their health condition and suffer during the advanced stages of immunosuppression.

Increasing the intensity of immunological suppression leads to pronounced and characteristic oral changes. Early detection is the key to diagnosis and management, and it helps to reduce morbidity and improve the quality of life in these unfortunate children.

Keywords: *HIV; AIDS; Children; Candidiasis; Infection*

Introduction

It is universally accepted that HIV is a zoonotic viral disease that leapt species from chimpanzees to humans from the middle part of Africa. HIV is usually a lentivirus. It can lead to a chronic, slowly progressive, irreversible decrease in the patient's immune response, leading to morbidity and mortality in humans and other mammalian species. This viridian group includes the human immunodeficiency virus (HIV), which initiates AIDS. The virus equally attacks the human system. It is understood that HIV started first in the independent nation of Congo around 1920 and then traversed to humans and consequently scattered in other parts of the world.

History: In what method did HIV cross from chimpanzees to humans?

A) Various theories have been put forth for the onset of HIV in humans. One of the furthermost debatable claims about the origin of HIV is that the virus may have been communicated to humans through trials of the first polio vaccine in western Africa through the late 1950s. Studies of some of the known initial cases of HIV deliver evidence about the onset of the infection in humans and its

progression. The first confirmed case of HIV was from blood samples obtained at a place called Kinshasa in 1959 from a man in the autonomous republic of Congo. The sample was investigated, and the presence of HIV was detected retrospectively.

B) Another theory postulates that hunters with a break in the continuity of skin due to abrasions or lacerations may have contracted the virus through wild animals. Although the initial host response should have eliminated the virus, on a few occasions, the virus showed early mutations within the host and transformed into HIV-1 [1]. There are four variant strains of HIV (M, N O and P). Each variant has a slightly different genetic makeup. The presence of multiple strains supports the hunter hypothesis, as a different mutation would have generated these variations of HIV-1[2]. The most widespread strain is HIV-1 is Group M; this is the predominant strain worldwide (Figure 1A and 1B). The other variants are rarer and less transmissible than HIV-1. As a result, it infects far fewer people and is found in a few countries in West Africa, like Mali, Mauritania, Nigeria, and Sierra Leone [3].

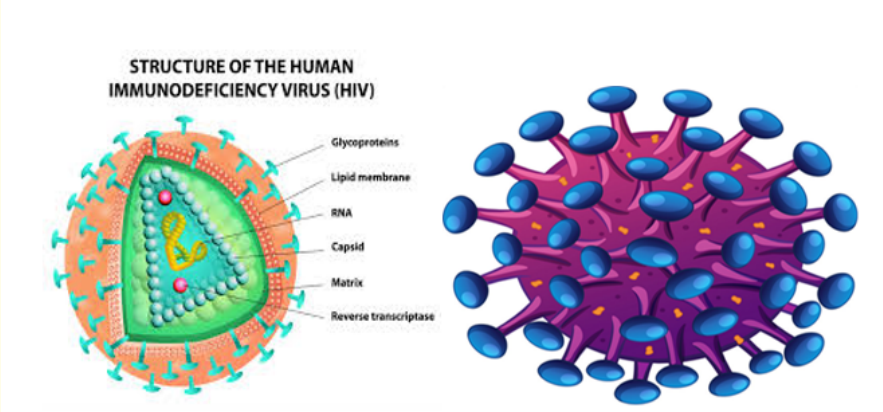

Figure 1A and 1B: *Structure of human immunodeficiency virus.*

2018 global HIV statistics

HIV remains a major worldwide public health issue. "In 2018, an estimated 37.9 million people were living with HIV (including 1.7 million children), with a global HIV prevalence of 0.8% among adults. Around 21% of these people did not know they had the virus" [4]. "An estimated 74.9 million people have become infected with HIV, and thirty-two million have died of AIDS-related illnesses since the first case was reported. In 2018, 770,000 people died of AIDS-related illnesses. This number has decreased by more than 55% since the peak of 1.7 million in 2004 and 1.4 million in 2010" [4]. "Most people living with HIV are in low- or middle-income countries, with an estimated 68% living in sub-Saharan Africa. Among this group, 20.6 million live in East and Southern Africa, which saw 800,000 new HIV infections in 2018" [5]. Recent studies support that, in all recognized HIV cases, antiretroviral treatment should be started where there is detectable viremia regardless of CD4 cell count.

Reasons for switching therapy involve local guidelines, alteration in drug regimen guidelines, the introduction of newer drugs, pregnancy or plans for pregnancy, elimination of food restriction, virologic failure or drug toxicity. Criteria for starting Antiretroviral Therapy (ART), monitoring the efficacy of therapy, patient compliance in taking proper medications, adverse effects and drug toxicity can be monitored by appropriate laboratory tests [6]. Presently, healthcare efforts are directed toward providing patients with HIV with a healthcare facility where they can receive counselling, medications, and support. Patients are also encouraged to report to the same facility to

establish rapport and familiarity with healthcare workers. Drugs like tenofovir, disoproxil fumarate/emtricitabine are recommended as preexposure prophylaxis in people at substantial risk. When indicated, post-exposure prophylaxis should be initiated as early as possible. The use of ART has succeeded in reducing HIV-1 mortality but cannot eliminate the virus due to the persistent and stable latent reservoir (LR) (long-lived CD4 T cells that harbour transcriptionally silent HIV virions). The global disease burden of 36 million infected individuals warrants the continued search for a therapeutic method that can eradicate the virus or encourage sustained viral diminution without therapy. Infant mortality due to pediatric HIV has been a concern addressed in the past couple of decades. However, pediatric morbidity has been controlled by better prenatal and perinatal procedures and drugs that prevent vertical transmission [4].

HIV/AIDS scenario in children

Even though mother-to-child transmission (MTCT) is the most common mode of spread of HIV-1 among infants and children, it can occur in utero, intrapartum, and post-natal. Breastfeeding is a significant cause of vertical transmission, and mothers should be counselled. The use of ART during pregnancy, postpartum, and breastfeeding reduces the risk of transmission to the child through elective caesarean delivery and also helps reduce a reduction in MTCT [7]. Maternal or infant factors affecting the risk of MTCT, like host genetic factors, maternal and infant co-infection, maternal behaviours, and nutritional supplementation, are important points to consider.

Almost ninety per cent of pediatric HIV infections are acquired or transmitted from mother to infant. The child may also get infections during pregnancy (30 to 35%), childbirth (60 to 65%) or breastfeeding (10 to 15%). Internationally the annual number of pediatric HIV has halved since 2010 [8,9]. Despite improvement in global HIV statistics in children, almost 24% of expectant mothers living with HIV do not have access to ART [9]. Two thousand sixteen out of an estimated 1.8 million children affected by HIV, only 43% had access to ART [9,10]. Most of the pediatric HIV burden is shared by African countries. AIDS continues to be among the most important cause of death in young people. 1,20,000 children died due to AIDS-related infections in 2016. These numbers average approximately 328 pediatric deaths every day. The mortality rate due to HIV in children aged 0 - 4 years is the highest among all age groups. However, there has been a 62% reduction in overall AIDS-related deaths internationally between 2010 to 2016 [7]. Most statistics focus on children infected by HIV; some children have been affected by HIV due to losing one or both parents who have succumbed to the infection [6].

Why are children at risk of HIV?

MTCT is the most common mode of infection in children. This is also called vertical transmission or parent-to-child transmission (Table 1). Breastfeeding also contributes to acquiring HIV infections in children. Promoting infant formula feeding may not be viable in many underdeveloped nations. Mothers on ART can reduce the risk of transmission to their children. The risk of acquiring HIV through breastfeeding is more in recently infected mothers due to a high viral load [3-5]. Hence HIV positive mothers need to be educated about maintaining appropriate ART to prevent the transmission of infections to their children. If appropriate ART is not given, a third of the infants who acquire HIV die before their second birthday [9-12].

It has been reported that 40 to 50% of HIV-infected individuals have oral or dental problems. Oral lesions are a source of substantial HIV-associated morbidity, even in those who are on modern HIV therapy. In addition, specific oral lesions are markers for progressive immunologic dysfunction and HIV disease progression [13-17]. It has been observed that oral lesions are the primary indicators of HIV/AIDS. Some common problems associated with HIV/AIDS are the development of fever, blisters, Kaposi's sarcoma, oral warts, canker sores, oral hairy leukoplakia, gingival and periodontal diseases, thrush, swelling in salivary glands, enlarged lymph nodes, dry mouth, oral viral lesions, and herpes simplex lesions etc. [5,18,19]. The side effects of medications commonly used may also affect oral health. Salivary flow may be diminished by anticholinergics or adrenergic inhibitors resulting in xerostomia. Antibiotics may exacerbate oral candidiasis. Didanosine (ddI) and zalcitabine (ddC) may cause painful oral ulcers. Other side effects of medications commonly used in the treatment of HIV, such as anaemia, thrombocytopenia, and neutropenia, may be manifested in the oral cavity through bleeding or infection [20-22]. The

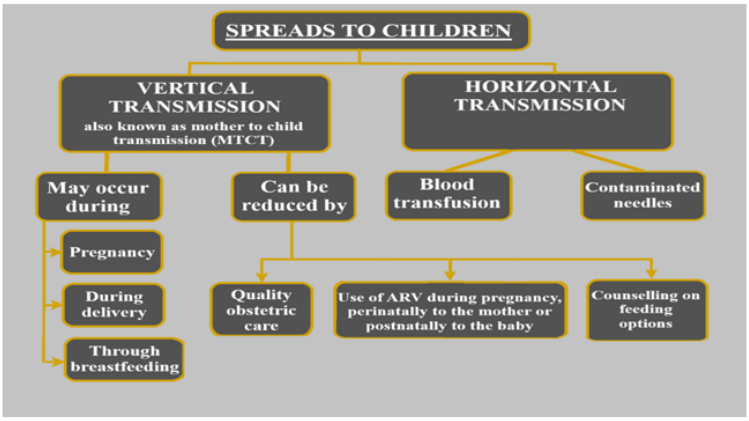

Table 1: *Exhibits transmission.*

sweeteners used in pediatric syrups contribute to the development of dental caries. Several studies have been reported about the general health status of HIV-positive children. Still, no exclusive research has been carried out to ascertain oral health status as an indicator of disease progression. Available information suggests that HIV-infected children have many oral manifestations similar to HIV-infected adults, but distinguishing features have been noted [23]. Most children with HIV infection present oral manifestations among the first signs of illness [24]. Parotid hypertrophy is present more exclusively in children, whereas periodontal bacterial infections and Kaposi's sarcoma predominate in adults. Prospective studies are needed to determine the prevalence and natural history of oral lesions to examine the relationships between immunologic and virologic markers of HIV disease status and the occurrence of oral manifestations, to evaluate changes in the oral microbial flora of HIV-infected individuals over time, and also to assess the causative nature of oral lesions broadly.

We dwelled into this aspect by carrying out an independent study in which 234 HIV+ children attending the ART Centre of infectious diseases in a tertiary care hospital (medical college) were studied; we confirmed that nearly 6.4% of HIV-positive children demonstrated association with perioral lesions (Figure 2A to 2I).

The lesions most commonly appear on the tongue and buccal mucosa (Figure 2A to 2I).

Figure 2A: *Aphthous ulcer due to HIV.*

Figure 2B*: Angular cheilitis due to HIV.*

Figure 2C: *Linear gingival erythema.*

Figure 2D: *Linear gingival erythema.*

Figure 2E: *Herpes zoster recurrent or chronic rtis (Otitis media, otorrhoea, sinusitis).*

Figure 2F: *Fissured tongue due to HIV/oral candidiasis.*

Figure 2G: *Tongue I HIV Children Oral Candidiasis (Outside Neonatal Period).*

Figure 2H: *Oral hairy leucoplakia*

Figure 2I: *Severe recurrent presumed.*

Candidiasis, Linear gingival erythema and aphthous mucosal stomatitis are frequently seen. Children with a CD4 count of fewer than 200 cells/mm^3 were more susceptible to developing these lesions. During the oral examination, children had a CD4 count t less than 200, whereas 106 had a CD4 count of 200 to 500. The Dental Caries occurrence ratio was high, and most were untreated. The deft /DMFT, defs/ DMFS scores in the HIV-positive children recorded were high, possibly due to increased intake of carbohydrates and sweetened medicines and xerostomia (Figure 3A and 3B). The findings of the present study are similar to those reported in other developed and developing countries and emphasize the need for education on the appropriate management and referral of patients presenting with oral manifestations of HIV infection [24-29].

Figure 3A and 3B: *Exhibiting tooth decay.*

It is vital to ensure that, whenever possible, sugar-free medications must be prescribed to children. Also, they must receive appropriate advice and necessary support to access dental care services. Oral manifestations are common in children infected with HIV and are associated with severe immunosuppression and AIDS. They are indicators of the infection with an analytical value of its progression. In the study, we confirmed oral candidiasis in 20.6% of the cases. Pseudomembranous candidiasis was the most common type. The frequency of gingivitis was also high; this could be attributed to dryness of the mouth. Ulcerative and painful oral lesions were frequently observed, which interfered with the performance of daily oral hygiene procedures. The average CD4 percentage was low for children with gingivitis; most had severe immunosuppression. New lesions were present in the oral cavity in immunologically compromised patients. A low value for CD4 characterizing the presence of immunosuppression is a predisposing factor for the development of opportunistic infection. The study also validates a relation between increased immunosuppression and the presence of candidiasis. Even though the children were on antiretroviral therapy, it was seen that some of them exhibited candidiasis. One explanation for this could be their low CD4 count and immunocompromised status. The introduction of HAART is associated with a significant decrease in the prevalence of opportunistic diseases, including oral mucosal lesions. HAART is also associated with substantially reducing the majority of [29,30]. In contradiction, these findings increased prevalence of oral warts has been noted by some investigators despite a marked improvement in CD4 count.

However, the link between human papillomavirus suggests that oral cancer may become a clinically significant long-term complication with the increasing life expectancy of HIV-infected patients. Results of the investigation by other authors [30,31] confirmed a decline in the prevalence of oral mucosal lesions in industrialized countries with the introduction of better retroviral therapies. However, an increase in salivary gland disease, xerostomia and oral warts was observed. The occurrence rate of Oral mucosal lesions in the post-HAART era indicates that (Table 2 and 3). Oral mucosal lesions are less frequent, but new and poorly understood paradigms are emerging [32].

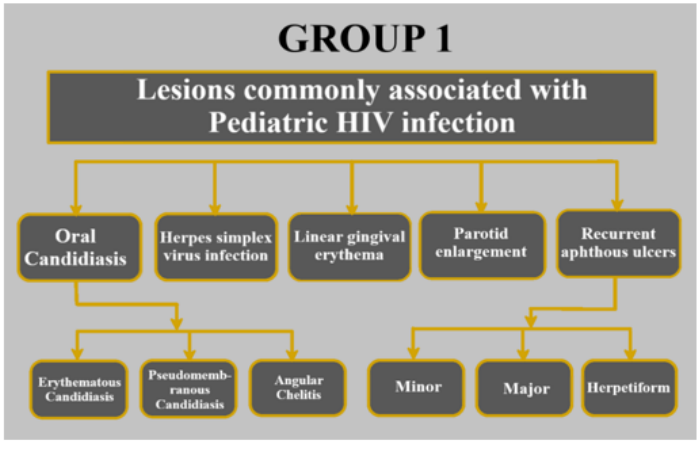

Table 2: *Exhibiting commonly affected lesions.*

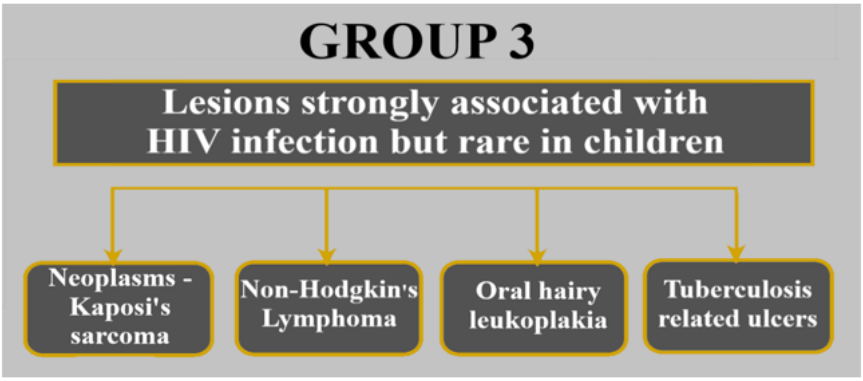

Table 3: *Exhibits lesions strongly associated with HIV infection but rare in children.*

Therapeutic management of HIV/AIDS in children (Table 4 and 5)

A combination of anti-viral drugs is used in the management of HIV. The treatment protocol depends on the time from the expected acquisition of infection to the initiation of treatment. It also depends on the presenting patient's signs and symptoms. Single-drug therapy may start in asymptomatic patients, while Highly Active Anti Retro Viral Therapy (HAART) is indicated in newborns. HAART aims to prevent progression and improve the existing host immune response to prevent progressive HIV encephalopathy. (The management of such children is depicted in table 4 and 5).

ARV Drug	Abbreviation	Action
Nucleoside Nucleotide Reverse Transcriptase Inhibitors	NRTIs Nucleotide Analogue Nukes	NRTIs, interfere with the action of HIV protein called reverse transcriptase, which the virus needs to make a new copy of itself.
Non-Nucleoside Reverse Transcriptase Inhibitors	NRTIs Non-Nucleotide Non-Nukes	NNRTIs also stop from replicating within cells by inhibiting the sense to transcriptase protein.
Protein Inhibitors	PIs	PI inhibits protease which is another protein involved in HIV replication.
Fusion or entry inhibitors		Fusion or entry inhibitors prevent HIV from binding to entering human immune cells.
Integrase Inhibitors		Integrase Inhibitors interfere with the integrase enzyme, which HIV needs to insert its genetic materials into human cells.

Table 4

NRTI	NNRTI	Protease Inhibitors	Fusion Inhibitors
Zidovudine (AZT)	Efavirenz (EFV) Nevirapine (NVC) Delavirdine (DLV)	Ritanovir (RTV) Saquinavir (SQV) Indianavir (IDV) Nelfinavir (NFV) Fosamprenavir (APV) Lopinavir (LPV) Atazanavir (ATV) Duranavir (DRV)	Enfuvirtide
Lamivudine (3TC)			
Emtricitabine (FTC)			
Stavudine (D4T)			
Didanosine (DDL)			
Tenifovir (TDF)			
Zalcitabine (ABV)			
Abacavir (DDC)			

Table 5: *HIV antiretroviral drugs [11].*

Most ART regimens start with two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) like zidovudine and lamivudine. The NRTI may be combined with a third NRTI or a protease inhibitor like ritonavir which is used as a booster [29-31].

Management of HIV in children (Table 4 and 5)

1) It is important to establish early identification of maternal HIV status.
2) Early testing of infants born to mothers who are known to be HIV positive.
3) Nutritional records of infants need to keep diligently guided on growth and development.
4) Early identification of infections and fevers of unknown origin.
5) Regular examination of lymphadenopathy, hepatic-splenomegaly.
6) Regular laboratory blood studies for CD4 counts.
7) Examination of oropharynx and mouth for secondary candidal infections.
8) Evaluate the family's knowledge about the child's condition and preparedness for care needs and access to medical care.
9) Evaluate the family's psychological coping.
10) Evaluate the health of the primary health giver and discuss alternate plans in case the primary caretaker is also positive with deteriorating health [16-19].
11) It is also important to know a child's level of knowledge about the disease and to explain it in easy terminology.
12) Assess the level of discomfort of the child.
13) Counsel the child/parent about the need for invasive methods as part of the management protocol.
14) Identify any potential concomitant infections (like TB) due to potential exposure from travelling to endemic areas.
15) In the case of adolescents, identify the history of substance abuse, piercings, tattoos, and sexual activity [7-19].

Prevention of HIV

As HIV is a potentially fatal disease with rapid progression to the symptomatic phase in the absence of treatment measures. Even with appropriate care, there is a slow deterioration of the host immune response, leading to systemic diseases and secondary infection.

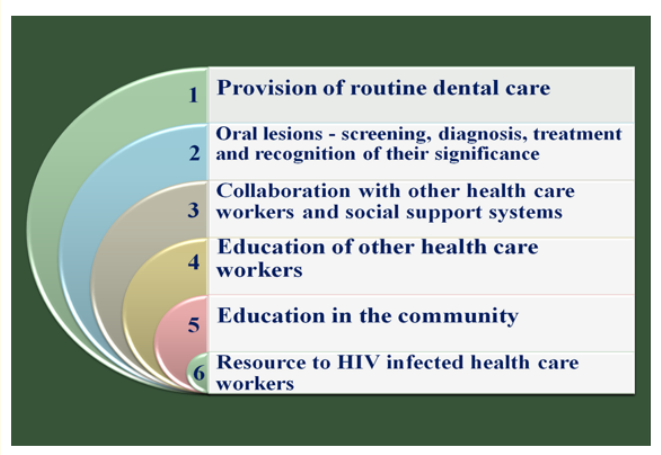

Figure 4: *Oral and dental health care for HIV/AIDS children.*

The basic approach to the control and prevention of HIV/AIDS:

- Prevention of acquisition of HIV infection is the primary goal.
- Health education focused on prevention to avoid blood-borne infection.
- Early-onset of ART or post-exposure prophylaxis.
- Prophylactic management of tuberculosis, candidiasis, and prevention of secondary infections.
- Primary health care integrated care for maternal child health education.

Prevention of mother to child transmission (MTCT)

There are two regimens for the prevention of MTCT:

A) "Regular AZT (AZT, also called Zidovudine (ZVD) and Retrovir, was the first approved HIV/AIDS drug.) in antenatal time blend of one dose of NVP at the commencement of labour and dose of AZT and 3TC throughout labour followed by a combination of AZT and 3TC for seven days in the postpartum period".

B) "Triple ARV drugs starting as early as 14 weeks of gestation until one week after all exposure to breast milk has ended (AZT+3TC+LPV or AZT+3TC+ABC) where ABC is abacavir, LPV lopinavir [3-6,20-23].

Procedure for infants born to HIV-positive mothers

1) Mother taking ART during the antenatal period:
   A) For breastfeeding infants: daily Nevirapine (NVP) (10 mg/day orally for infants < 2.5 kgs and 15 mg/day for infants > 2.5 kg) from birth till exposure to breast milk has been ended.
   B) For non-breastfed infants: Zidovudine or NPV () from birth to 6 weeks.
   C) During pregnancy: The mother should be on triple-drug ART during pregnancy and throughout breastfeeding duration [1,2].
2) Some physicians and paediatricians recommend altogether avoiding breastfeeding and using infant formulae for a child's nutritional needs to avoid the risk of transmission [7].

Conclusion

HIV infection carries a stigma, and patients are often reluctant to disclose their HIV status. Caretakers of children who have lost one or both parents due to HIV also display avoidance tactics when asked about the child's parents. Oral health care providers' respectful, compassionate, and understanding approach is essential to encourage obtaining an accurate history. Dental surgeons and oral health professionals can contribute a crucial role in the overall health infrastructure for early identification, counselling, educating, and caring for children who have HIV. The investigation done by us emphasizes a need for further longitudinal studies with a frequent oral examination of children to establish a relationship between HIV and the oral health status of HIV positive; it is recommended that the professionals focus on spreading awareness amongst medical and their counterparts and thereby improving their knowledge of the oral manifestations of HIV/AIDS.

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