



RESEARCH ARTICLE

CHRONICITY OF HIV INFECTION AND ORAL HEALTH: UNVEILING EMERGING PERSPECTIVES

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ABSTRACT

The quest for HIV eradication has seen significant progress with the advent of highly active antiretroviral therapy (HAART), transforming HIV infection from a life-threatening condition to a manageable chronic disease. Recent research endeavors have focused on understanding HIV pathogenesis, exploring novel therapeutic strategies, and addressing challenges associated with long-term treatment and eradication efforts. Clinical interventions aimed at curing HIV infection have been explored extensively, with trials testing various immune interventions and diagnostic systems to target latent viral reservoirs and improve clinical monitoring. While improvements in virological and immunological outcomes offer hope for increased life expectancy among PLHIV on ART, challenges remain in achieving parity with the general population. Timely diagnosis and treatment have been shown to enhance life expectancy, but the presence of comorbidities not linked to AIDS poses a significant risk, particularly among women. Efforts to eradicate HIV also encompass infections among PLHIV on ART, emphasizing the need for tailored treatment strategies to combat drug resistance and improve management outcomes. In addition to HIV eradication efforts, understanding the dissemination of the oral microbiota in the body has emerged as a crucial aspect of overall health. Dysbiosis of the oral microbiome has been linked to systemic diseases such as cardiovascular diseases, cancers, and respiratory illnesses. Studies highlight the intricate interplay between oral health and well-being, advocating for interdisciplinary approaches in healthcare. Overall, while significant strides have been made towards HIV eradication and understanding the systemic implications of oral health, continued research efforts and interdisciplinary collaboration are essential to address the evolving challenges and improve long-term health outcomes for PLHIV.

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INTRODUCTION

Developments in scientific research since the onset of HIV infection have significantly improved the well-being of those affected, particularly with the advent of antiretroviral therapy (ART).(1-3) Although ART has been successful in reducing HIV-related morbidity and mortality globally, the complex relationship between HIV, oral health, and overall quality of life requires further exploration. Adherence to ART is essential, given its direct impact on the immunovirological status and prolonged life expectancy of people living with HIV (PLHIV).(4,5) However, even with optimal treatment, PLHIV may present with oral and systemic manifestations, indicating the need for comprehensive health care beyond antiretroviral medications. This article looks at the oral health challenges faced by PLHIV, recognizing their potential to affect functional, psychological and social aspects of life. challenges faced by PLHIV, recognizing their potential to affect functional, psychological and social aspects of life.

In addition to health implications, PLHIV often faces discrimination and social rejection, creating barriers to accessing health care. Recognizing this, we aim to present a nuanced exploration of emerging ideas and knowledge regarding PLHIV receiving antiretroviral therapy and oral health. A series of searches were carried out in major scientific databases, such as PubMed and Google Scholar. The keywords of the searches carried out were as follows: HIV infection, HIV and oral diseases, HIV chronicity. A series of searches were carried out in major scientific databases, such as PubMed and Google Scholar. The keywords of the searches carried out were as follows: HIV infection, HIV and oral diseases, HIV chronicity. Included studies were independently selected by the authors.

Towards an eradication of HIV infection?: ART has significantly improved the immune function of PLHIV and transformed the life-threatening condition into a chronic infection for those with access to antiretroviral therapy (ART)(6,7).

Recent research endeavors have focused on advancing our understanding of HIV pathogenesis, exploring novel therapeutic strategies, and addressing the challenges associated with long-term treatment and HIV eradication. In a recent literature review conducted in Germany on clinical interventions in research around curing HIV infection, the authors provided an overview of the various clinical studies that have been conducted with the aim of reducing the frequency of latently infected cells or to prolong viral rebound time after interruption of ART. It emerged from this work that many HIV cure clinical trials have been conducted in small cohorts. These trials tested different immune interventions such as therapeutic T-cell vaccines, cytokine administrations, immune checkpoint inhibitors, and a plethora of drugs with varying safety profiles that are more or less effective in reactivating the reservoir latent viral.(8) Castro-Gonzalez *et al.* summarized in their work, the efforts that have been devoted to the eradication of HIV-1 from latently infected cells. They argued that to achieve a complete purge of the latent reservoir, it was necessary to first have a better understanding of the factors influencing the establishment and then maintenance of latency, the contribution of T cells, as well as T cells, non-T to the latent reservoir. These technical advances not only make it possible to specifically target latently infected cells with the aim of eliminating or containing them, but also to assess the exact size and distribution of the reservoir in a more personalized manner(9).

Chargin *et al.* developed a diagnostic system that could stimulate replication-competent HIV-1 reservoirs for improved clinical monitoring, including selection of antiretroviral treatment regimens. Since plasma viral load and CD4 counts were effective for clinical monitoring, they did not provide a complete representation of HIV-1 quasispecies in infected individuals. They thus showed that HIV-1 viral replication could be stimulated using PiraStim stimulation of whole blood. Sequencing results showed that three cases had additional drug resistance after stimulation. The technique described here had the potential to more accurately identify antiretroviral resistance and readapt treatment regimens for HIV-infected patients (10). As part of the search for a cure for HIV infection, progress in nanotechnology takes on its full meaning in the fight against the sexual transmission of HIV. In a setting where HIV sexually transmitted infection (STI) was responsible for approximately 80% of all infections, approximately half of those affected were women.(11,12) Sexual transmission was responsible for the majority of HIV infections due to sexual contact with infected cervicovaginal secretions or semen containing HIV-infected CD4 T cells.(13-15) Most microbicides have been shown to be ineffective in preventing the risk of HIV infection in clinical trials. A team of Spanish researchers worked with the polyanionic carbosilane dendrimer G2-S16 (PCD) as a possible new vaginal topical microbicide, based on its short reaction times, wide availability, high reproducibility and quantitative reaction yields. In their review, the authors analyzed the advances in the state of the art of G2-S16 as a possible innovative and promising microbicide on the verge of reaching clinical trials.(16) G2-S16 PCD provided remarkable insights into the future growth of multipurpose interventions to prevent HIV infection in women. A study was conducted in 2020 by a team of researchers on Alzheimer's disease disruptions in HIV-mediated neuronal dysfunctions in order to understand the mechanisms and develop therapeutic strategies. They concluded based on the available literature that HIV-

associated synaptic loss (HIV-associated neurocognitive disorders) and the etiology of Alzheimer's disease were an interconnected and orchestrated consequence of numerous neuropathogenic processes triggered by HIV-1. They argued that interactions between HIV-1 and host cells played a vital role in the pathogenesis of these abnormalities (17). The improvement in virological and immunological results and the reduction in the toxicity of antiretroviral therapy (ART) give hope that the life expectancy of HIV-positive people on ART will approach that of the general population. The authors therefore systematically reviewed the literature and summarized published estimates of life expectancy for HIV-positive populations on ART. They compared the life expectancy of PLHIV on ART to the life expectancy of the general population based on ten relevant studies, published between 2006 and 2015. The authors concluded that life expectancy of HIV-positive people on ART has improved globally in recent years, but significant gaps remain compared to the general and HIV-negative populations, as well as between regions and sexes (18).

A study was carried out in the United Kingdom to determine the impact of late diagnosis and treatment on the life expectancy of people living with HIV-. The investigation focused on a collaborative cohort of PLHIV with a CD4 count ≤ 350 cells/mm³ at the start of antiretroviral treatment, between 1996 and 2008. They deduced that timely and early diagnosis and prior antiretroviral treatment with good compliance could increase life expectancy.(19) In this context of increased life expectancy, the presence of comorbidities not linked to AIDS has become the most frequent cause of death among PLHIV on ART. They concluded that multi-morbidity was a strong independent predictor of mortality among adult PLHIV. Women in general and particularly women with fewer than three comorbidities had a lower mortality rate than men. However, their mortality risk was higher with an increased mortality rate compared to men when they had three or more comorbidities. A team of American researchers carried out work in 2020 on the probable cure of HIV-1 infection given the persistence of the pathology despite years of antiretroviral treatment. They reviewed fundamental studies and highlighted new perspectives in HIV cure research.

The authors concluded by arguing that the progress made thus far in deciphering HIV pathogenesis and developing treatment strategies represented hope that eradication of HIV infection was not a utopia, but an achievable goal in order to relieve society from the affliction of the HIV pandemic (20). Despite numerous trials exploring immune interventions, the path to HIV eradication requires a deeper understanding of the factors influencing the establishment and maintenance of latency, the role of T and non-T cells in the latent reservoir, and the identification of cellular biomarkers. Advances in diagnostic systems, such as those that stimulate HIV-1 reservoirs to improve clinical surveillance, are crucial steps toward the ultimate goal of eradication.

Infections among PLHIV on ART: The advent of highly active antiretroviral therapy (HAART) has heralded a new era in the management of human immunodeficiency virus (HIV) infection, offering infected individuals improved life expectancy and enhanced quality of life. However, as HIV-infected populations age and experience immune restoration, the landscape of morbidity and mortality has evolved, necessitating a shift in focus from AIDS-related to non-AIDS-

related conditions.(21) Several works have therefore been undertaken for this purpose. Studies conducted by Bonnet *et al.*,(22) Kumar *et al.*,(23) and Hessamfar *et al.*(24) shed light on the changing patterns of severe morbidity among HIV-infected individuals, highlighting a transition from AIDS-related to non-AIDS-related events. These findings underscore the importance of broadening endpoints beyond AIDS-related events to comprehensively describe disease progression in the HAART era. Furthermore, Luz *et al.*(25) explore the spectrum of morbidity experienced by HIV-infected individuals in Brazil, emphasizing the need for increased efforts to record and analyze serious non-AIDS morbidity. The study underscores the importance of understanding the evolving epidemiological trends and identifying priorities for improving patient quality of life beyond HIV-specific treatment. Liver-related deaths have emerged as a significant cause of mortality among HIV-infected individuals receiving combination antiretroviral therapy (CART), as demonstrated by Weber *et al.*(26) This underscores the importance of addressing comorbidities such as liver disease and the need for longer-term follow-up to assess treatment-related hepatic mortality. Additionally, Grulich *et al.*(27) highlight the association between immunodeficiency and cancer risk in HIV-infected individuals, emphasizing the importance of understanding the evolving landscape of cancer incidence in this population. In their study of serious fatal and non-fatal non-AIDS-defining illnesses in Europe conducted in 2010, Mocroft Amanda *et al.* (28) revealed that non-AIDS events (cardiovascular disease, non-AIDS malignancies, end-stage renal disease, liver disease, and pancreatitis) were common in the combined antiretroviral therapy (CART) era and were associated with considerable mortality.

The authors suggested that the increasing burden of other comorbidities would highlight the need for observational studies and clinical trials to collect this information in a standardized manner, as has been developed over the years for AIDS, and if necessary, integrate these comorbidities into studies taking into account the clinical progression of the disease and the impact of CART. Risk factors for non-AIDS events were varied, with multiple potentially modifiable risk factors related to immunodeficiency and lifestyle. Despite advances in HIV treatment, the infection still has a significant impact on life expectancy. Efforts to eradicate HIV also focus on infections among people living with HIV (PLHIV) on ART. This advance provides valuable information on adapting treatment strategies to combat drug resistance, ensuring more effective management of HIV infections among people on ART. In conclusion, while HAART has significantly improved outcomes for HIV-infected individuals, challenges remain in addressing the evolving spectrum of non-AIDS-related morbidity and mortality. Continued research efforts are needed to understand the underlying determinants of severe morbidity and mortality and to develop targeted interventions to improve long-term health outcomes in this population.

Dissemination of the oral microbiota in the body: The oral microbiota is a protective factor against colonization of extrinsic pathogens that can have an impact on systemic health.(29) Despite its complexity, the microbiota is normally in a state of equilibrium with the host called “microbial homeostasis”.(30) This balance can be destroyed by a number of factors.(31,32) Systemic diseases, medications and immunodeficiency are well-known general factors that could lead to an overgrowth of non-oral microorganisms (dysbiosis)

and opportunistic infections could follow.(33) The imbalance in the ecosystem, which can be caused by a weakened immune system, results in a challenge to oral and systemic health. The ecological conditions of these habitats are constantly changing, so the ecosystems are subject to frequent variations. The oral microbiome is a key factor in good or poor health.(34) Dysbiosis of the oral ecosystem is associated with diseases such as cardiovascular diseases, cancers and diabetes (35). Thus, several studies have highlighted a link between oral diseases and systemic diseases. Periodontal diseases are believed to be correlated with cardiovascular diseases, cancers, diabetes, lung diseases, risks of premature births, rheumatoid arthritis, digestive pathologies, lupus erythematosus, and Alzheimer's disease. Ahmed *et al.*(36) reviewed the literature on the association between periodontal disease and cardiovascular pathologies in 2015. Their research showed that there is increasing evidence regarding the association of periodontal disease and cardiovascular pathologies. In vitro studies also highlight a potential link between oral bacteria and atherosclerosis.

Also, they noted the urgent need for the selection of appropriate control cases and effective interventional trials to analyze how such interventions can produce a positive outcome on cardiovascular diseases. Recent interventional trials have shown that periodontal treatment could reduce the consequences of cardiovascular diseases. Respiratory diseases pose a significant health burden globally, contributing to numerous deaths and substantial morbidity. Bansal *et al.*(37) delve into the intricate interplay between oral bacteria and respiratory infections, shedding light on the epidemiological evidence and underlying mechanisms. They emphasize the pivotal role of oral disorders, particularly periodontal disease, in influencing the trajectory of respiratory illnesses such as bacterial pneumonia and chronic obstructive pulmonary disease (COPD).

The research underscores that oral periodontopathic bacteria, through aspiration, can infiltrate the lungs, precipitating aspiration pneumonia. Additionally, teeth act as a reservoir for respiratory pathogen colonization, potentially leading to nosocomial pneumonia. The study highlights parallels between the inflammatory processes in periodontal disease and emphysema, suggesting an overreaction of the inflammatory cascade culminating in connective tissue destruction, which may elucidate the association between periodontal disease and COPD.

This state of the art reinforces the urgent need to take care of any source of oral infections in this population whose immune system is being reconstituted. Indeed, the oral cavity is the main connection of our body with the surrounding environment, it is also an indicator of the general health of vital systems and organs. The mouth being the starting point of the digestive and respiratory tracts, it also represents the first protective barrier against the entry of pathogens such as viruses, bacteria, fungi and parasites. Given that the oral microbiota is also known as a reservoir of infection for other body sites(38), it is undeniable to work for the balance of this complex ecosystem, particularly among PLHIV on ARVs. This research should provide data that can enrich knowledge, reconsider the oral care of PLHIV on ART and shed light on this subject in Africa.

CONCLUSION

This literature review provides a comprehensive overview of the current HIV research landscape, emphasizing the multifaceted approaches used to eradicate the virus, manage infections in individuals on ART, and use nanotechnology for innovative preventive measures. Oral diseases have a considerable impact on general health, with disadvantaged, discriminated against, poor and aging populations being most heavily affected. Relatively simple and inexpensive measures, such as good oral hygiene, the use of fluoride, early detection and appropriate interventions, can prevent or limit serious consequences of oral diseases. Furthermore, chronic oral pathologies have been associated with systemic diseases, such as coronary heart disease and diabetes. Finally, oral diseases have a serious impact on quality of life, affecting physical, psychological and social well-being.

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Key Points

- The quest to eradicate HIV infection must take into account all sources of oral infections in people living with HIV (PLHIV) on antiretroviral therapy.
- Oral cavity is the body's main connection with the surrounding environment, it is also an indicator of the general health of vital systems and organs.
- Optimizing the oral care pathway for PLHIV on antiretroviral therapy constitutes a major public health challenge, especially in developing countries, with the need to encourage better cooperation between all health professionals working in the fight against HIV infection and dental surgeons.
- This review article presents the complex interweaving of oral health and general health in a context where HIV infection has become chronic.
- This observation implies a perpetual search for the well-being of PLHIV by the scientific community.

Glossary of Abbreviations

AIDS : Acquired immunodeficiency syndrome

ART: Antiretroviral therapy

CART: Combination antiretroviral therapy

CD4: Cluster of differentiation 4

COPD: Chronic obstructive pulmonary disease

HAART: Highly active antiretroviral therapy

HIV: Human immunodeficiency virus

PCD: Polyanionic carbosilane dendrimer

PLHIV: People living with HIV

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