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Do Highly Active Antiretroviral Therapy Drugs in the Management of HIV Patients Influence Success of Dental Implants?

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Abstract

HIV infection is a global pandemic that affects CD4 cells in the immune system and leads to lethal opportunistic infections. The advent of highly active antiretroviral therapy (HAART) has induced a marked reduction in the viral load and an increase in the CD4 cell count, thereby changing the course of the disease from an acute life-threatening condition to chronic disease. Accordingly, need and demand for oral rehabilitation in HIV positive population have increased in recent years. However, few drugs used in the HAART regimen have also known to be associated with osteopenia and osteoporosis. Although HAART reduces the morbidity in HIV patients, it remains unknown to what extent the therapy influences the implant healing. Few scientific literatures have identified osteoporosis and HIV infection as an unconducive milieu for dental implant placement and survival but demonstrated favorable outcomes in short-term assessments. The long-term impact of bone metabolic effects of HAART on implant success remains a conundrum.

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Key words

HAART drugs. HIV infection. Dental implants.

Introduction

HIV infection is a pandemic affliction that results in AIDS in humans. The hallmark of HIV infection and AIDS includes progressive failure of immune system and subsequent lethal opportunistic infections. This lentivirus can infect and kill many different types of cells in the body, but the primary targets are immune cells called CD4 T-cells. The CD4 T-cells are a type of T-lymphocytes that help to coordinate the immune system's response to infection and disease[1]. AIDS is attributed to HIV infection when the CD4 cell count drops below 200 (cell/mm^3)[2]. The treatment is focused to contain the infection by improving the CD4 cell count

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to normal levels (500-1500 cells/mm^3). The therapeutic management of HIV infection includes the use of a regimen popularly called as "Highly Active Antiretroviral Therapy" (HAART). This therapeutic regimen induces a marked reduction in viral load and increases in the CD4+ cell count, thereby changing the course of the disease from an acute life-threatening condition to chronic disease. Accordingly, need and demand for oral rehabilitation in HIV positive population have also increased in recent years[3].

Oral rehabilitation with dental implants for edentulous, HIV patients can be a good alternative to traditional removable prostheses. Expert opinions indicate no difference in post-surgical complications or osseointegration of implants in patients with or without HIV infection[4]. Baron et al. reported a complete oral rehabilitation using twelve Branemark implants in a female patient infected with HIV, hepatitis B and hepatitis C. At 2 years post-implantation, there was minimal peri-implant bone loss with no signs of peri-implantitis noted[5]. Although HAART reduces the morbidity in HIV patients, it remains unknown to what extent the therapy influences the implant healing. Further, it is a well-known fact that HAART per se demonstrates metabolic side effects such as osteoporosis and osteopenia[6-8]. However, few reports identified HIV infection as a relative contraindication to implant therapy provided the infected individual is free of severe immunosuppression and bleeding disorder[9,10]. Over the years, the literature has demonstrated equivocal evidence with reference to factors predicting the success of dental implants in HIV-infected patients[11,12]. Another concern that is often overlooked in the literature is the metabolic effects of HAART regimen and its implications with implant survival[13-16] (Fig. 1). The intent of this paper is to analyze and explore the implications of HAART and its side effects on dental implants and stimulates a scientific discourse among the researchers.

HAART and bone metabolism

HAART is a therapeutic formula that results from the triple combination of about 15 different antiretroviral drugs. It was put into practice in the mid-1990s and has become the mainstream therapy for HIV infection since then[17,18]. At present, there are seven classes of drugs to treat HIV infection[19]. These drugs are broadly classified by the phase of the retrovirus life-cycle that the drug inhibits. The classification includes nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), a fusion inhibitor, a CCR5 antagonist, and a CD4 post-attachment inhibitor. In addition, there are boosters or enhancers to improve the pharmacokinetic profiles of some HAART drugs[19]. The HAART regimen generally consists of two NRTIs as backbone, plus a drug from one of three drug classes: an INSTI, an NNRTI, or a boosted PI as a base drug[19]. HAART influences the viral count and the CD4 cell count. Disease morbidity and mortality have been drastically reduced after the introduction of HAART protocol. The prevalence of oral lesions has reduced to 30% after the HAART and improved the quality of life in HIV patients[20]. However, the HAART is not without any side effects. Certain NRTI drugs, tenofovir disoproxil fumarate (TDF), and PI drugs which are the first-line drugs in the HAART regimen demonstrated alterations in bone metabolism[21-23]. Osteopenia and osteoporosis are common inflictions in HIV infection itself[24,25], but literature has demonstrated a heightened incidence of bone metabolic concern in HIV patients under HAART[6-8,22-24]. About 50-71% of patients with HIV infection under HAART had reduced bone mineral density compared to controls[21-26]. Recently, the WHO and FDA recommended a second-generation – INSTI drug, dolutegravir (DTG) as the most effective drug to reduce the HIV viral load, with few known side effects[27,28]. Accordingly, DTG in combination with two NRTI is used for treatment-naive HIV-infected patients. DTG appears to have less effect on bone health[29-31]. Another drug, namely tenofovir alafenamide (TAF) is considered as successor for TDF due to its low toxicity to kidney and bone compared to TDF[32]. However, the guidelines advocated by the US Department of Health for the use of antiretroviral agents in adults and adolescents with HIV indicate that reduction in bone mineral density is observed after the initiation of any ART regimen[33]. The equivocal nature of the relationship between bone health and ART regimen needs to be studied further.

The underlying mechanism of bone loss in HIV positive patients under HAART is unclear and remains elusive. Overexpression of receptor for activation of nuclear factor-kappa B ligand (RANKL) has been documented in HIV positive patients. RANKL plays a crucial role in bone metabolism and acts as a critical mediator of bone resorption and bone density[6,34,35]. It is studied that HIV infection affects the memory B cells which switched from OPG production to RANKL production in animal models[36]. It has also been shown that NRTI treatment inhibits mitochondrial DNA (mt DNA) synthesis[6]. However, RANKL is believed to prevent mt

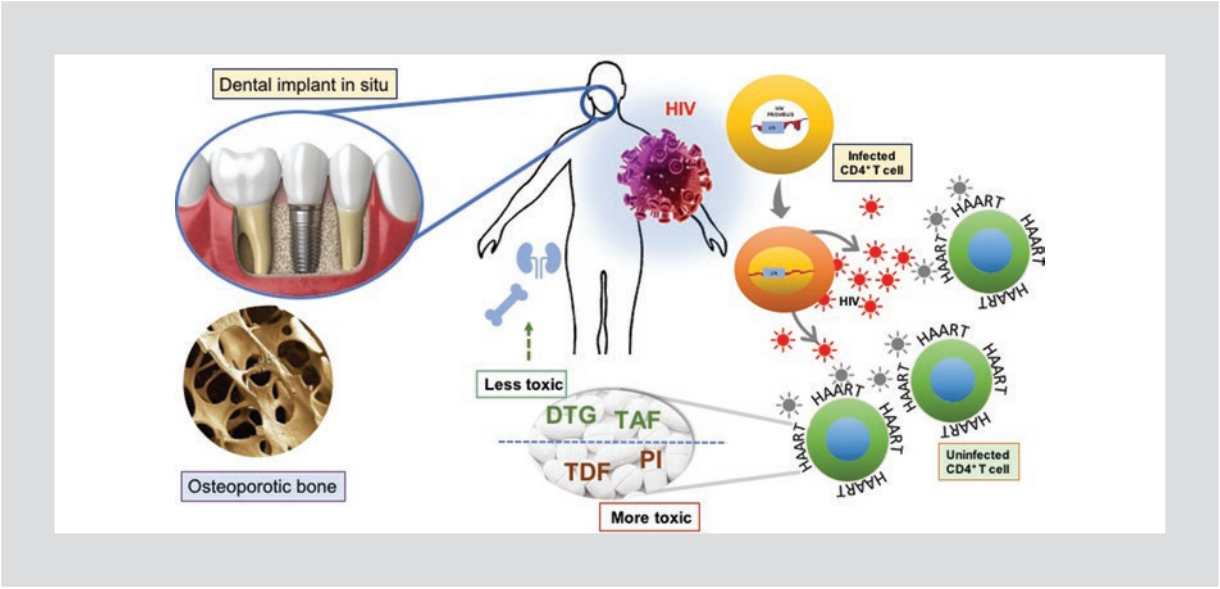

Figure 1. *Hypothetical schema representing the interaction between HIV infection, HAART drugs and a dental implant.*

DNA damage. Thus, the relationship between HIV infection and NRTI therapy seems to be ambiguous regarding the influence of overexpressed RANKL and mt DNA synthesis. The data are conflicting and vary by drug. However, there is emerging evidence that HIV-associated bone loss can be managed by the newer less toxic ART drugs[29-32].

Implant stability and osteoporosis

Osteoporosis is a common metabolic bone disease characterized by a reduction in bone density and alterations in the microstructure of the bone that leads to an increased risk of fracture of the bone. The alteration in bone metabolism in osteoporotic state may trigger metabolic events that could compromise healing of bone surrounding the implants[37]. Many researchers have attempted dental implant placement in patients with osteoporosis, but the findings of these studies are inconclusive. Some reported that diagnosis of osteoporosis and osteopenia in patients did not influence the increased risk of implant failure[38-42]. However, other studies contradicted the use of implants in patients with osteoporosis with the inference that the impaired bone metabolism led to reduced bone healing around the implants and affected the osseointegration with higher failure rates[43,44]. Nevertheless, few researchers and clinicians are of the opinion that the presence of osteoporosis may not be a definitive condition to contraindicate dental implant treatment[45,46]. They believed that the placement of dental implants with high degree of clinical acuity addressing methodical treatment planning tactics and choosing appropriate implant geometry and surface treatment is the key to successful osseointegration even in morbid conditions. Recent systematic reviews stated that the evidence for an association between osteoporosis and implant failure is weak[47,48], but recommended to adopt a safe surgical protocol and a longer healing period to achieve an adequate osseointegration[49,50]. There is equivocal evidence in the literature with respect to the side effects of the medication used in osteoporotic patients especially oral bisphosphonates, as a potential risk factor for implant stability rather than the osteoporotic condition itself[51].

Implant therapy in HIV patients under HAART

The use of dental implants in HIV patients was first reported by Rajnay and Hochstetter in 1998[14]. They placed an endosseous implant into a fresh extraction site and restored with a single crown that functioned well after 18 months of follow-up. Viral load and CD4 cell count are considered as important factors when placing implants in HIV positive patients under antiretroviral therapy. The success of implant osseointegration in HIV patients was dependent on low viral load and high CD4 cell count[15,16,52,53]. However, a recent prospective cohort study with a sample size of 16 noted a 10% failure rate in HIV patients compared with 5-7% in healthy patients[54]. In another investigation, HIV-positive heavy smokers (>10 cigarettes/day) demonstrated peri-implantitis and increased implant fail-

ures[55]. Oliveira et al. studied the relationship between levels of CD4+ cells, viral load, type of HAART regimen, baseline urinary pyridinoline and deoxypyridinoline bone marker levels, and osseointegration of implants in 24 HIV positive patients. The results demonstrated that the implants were asymptomatic without clinical complications at 12-month follow-up[56]. Although the subjects demonstrated an increased level of pyridinoline and deoxypyridinoline, the osseointegration was not affected. Some recent reports also documented successful implant oral rehabilitative therapies in HIV positive patients that are directed toward bone augmentation, immediate implant placement into fresh extraction socket, fixed implant-supported immediate loading, and mandibular implant-supported overdentures[57-60]. However, no case reports or studies have elaborated the stage of infection or duration of HAART regimen in HIV patients. The current evidence pertaining to the longevity of dental implants in HIV positive patients under HAART is limited and inconclusive. In cases, where dental implants are not a feasible option in patients with HIV infection, alternative treatment options such as fixed or removable dentures are advocated[9]. These treatment options have their own advantage as they are non-surgical procedures and disadvantages such as compromising the adjacent teeth for replacing the missing tooth and less compliant for patients compared to implant therapy.

Risk of infection

With a substantial increase in the life expectancy of the HIV population, they are prone to age-related noncommunicable comorbidities such as cardiovascular, renal, neurological, and metabolic diseases. In addition, coinfections such as tuberculosis, cryptococcosis, hepatitis B virus (HBV), hepatitis C virus (HCV), and malaria are common in these patients[61,62]. The WHO states that HIV patients are at 16-27 times at higher risk of developing tuberculosis, and those with latent tuberculosis infection experience reactivation of the infection by 20 folds[63]. HIV patients with HCV coinfection are at higher risk of developing chronic kidney disease and fractures[64]. Although HAART drugs significantly reduced the liver-related mortality rate by combating against the HBV in HIV patients, total and liver-related mortality remains an area of concern when HBV coinfection occurs[65]. A recent systematic review and meta-analysis suggested that HIV infection and HAART regimen including exposure to specific ART class (e.g., PIs) are associated with increased risk of myocardial infarction[66]. These coinfections are regarded as either absolute or relative contraindications for implant placement. Implant failure generally may arise from three major etiologies: impaired host healing, disruption of a weak bone-to-implant interface (failure to osseointegrate), and infection[67]. Although implant healing after surgical placement is not affected in HIV patients, failure from poor osseointegration and periimplantitis (infection around the implant) has been reported[67].

Complications of dental implants

Surgical placement of dental implants could cause complications as with any surgical procedure. Although most of the complications can be resolved without serious issues, some can lead to implant failure or even life-threatening events. During implant surgery, intraosseous hemorrhage due to arterial trauma can result in the formation of hematoma in the floor of the mouth[68]. Excessive hemorrhage can seep into the adjacent submandibular and sublingual spaces which may require intubation or tracheostomy. Nerve damage during implant surgery can cause mild paresthesia to complete anesthesia or dysesthesia. This could result from direct trauma to the nerve during surgery or indirect trauma from post-surgical intra-alveolar edema or hematoma[68]. Injury to the adjacent teeth, perforation of Schneiderian membrane, displacement of implants or graft material into the maxillary sinus, post-surgical maxillary sinusitis, and mandibular fracture in the atrophic mandible are other complications associated with implants[68]. Such complications are bound to occur in any patients regardless of the health and disease status. However, such occurrences in compromised patients may pose an additional threat to the milieu interior.

Conclusion

HAART regimen has revolutionized the palliative care for HIV-infected patients by bringing the disease to chronic state and reducing morbidity. Literature elaborated certain unexplained bone metabolic effects including reduced bone mineral density with HAART regimen, especially TDF and PI drugs. The newer drugs, especially DTG in combination with two NRTI that are used for treatment-naive HIV-infected patients appear to have less effect on bone health. However, the guidelines advocated by the US Department of Health for the use of antiretroviral agents in adults and adolescents with HIV indicate that reduction in bone

mineral density is observed after the initiation of any ART regimen. Oral health care needs for HIV positive patients include therapeutic procedures that address maintaining the integrity of oral structures and function. Dental implant care in such patients contributes to positive health-related quality of life. The impact of bone metabolic effects of HAART on implant success remains a conundrum. No studies dealing with dental implants have reported or analyzed the duration of HAART regimen and its effects on the bone mineral density. Further, the osteoporotic status in a long-term HAART regimen protocol was not analyzed before the implant therapy. Hence, there is a need to study the long-term side effects of HAART on bone metabolism and its implications for implants success and survival. Although the evidence is low with reference to survival of dental implants in HIV subjects under HAART regimen, it is utmost responsibility of the medical and dental practitioners to synthesize the possible links.

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