ORIGINAL RESEARCH

Prevalence of drug induced oral hyperpigmentation among hiv patients in KODAGU: A clinico epidemiological study

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ABSTRACT
Objective: To assess the prevalence of drug induced oral pigmentation among HIV-infected patients in Kodagu and evaluate its clinical characteristics. **Methods:** A total of 259 HIV patients receiving highly active antiretroviral therapy were included in this cross-sectional prospective study. Comprehensive mucocutaneous examinations were conducted, recording the site, extension, and duration of oral lesions following the initiation of antiretroviral treatment. The collected data were statistically analysed. **Results:** Among the study population, 168 patients (64.9%) were on TLE regimen, while 91 patients (35.1%) were on Zidovudine, Lamivudine, and Nevirapine regimen. Oral mucosal pigmentation was observed in 100 patients, and 14 patients exhibited both intraoral and extraoral pigmentation involving the skin, nails, and oral cavity. **Conclusion:** Prolonged treatment with highly active antiretroviral therapy is associated with drug-induced oral hyperpigmentation. Proper patient education regarding potential adverse reactions can help alleviate unnecessary concerns and improve adherence to the antiviral drug regimen.

Keywords: Antiretroviral therapy, Oral pigmentation, Drug-induced pigmentation, HIV.

INTRODUCTION
Systemic disorders often have manifestations in the oral cavity, providing valuable insights into an individual's overall health. Among these disorders, human immunodeficiency virus (HIV) infection is a global pandemic that can progress to Acquired Immuno Deficiency Syndrome (AIDS).[1] With millions of people affected worldwide, the prevalence of HIV/AIDS is a significant concern. In India, it ranges from 23% to 30%.[2] Oral manifestations are common in HIV/AIDS patients and can serve as important indicators of disease progression and treatment response.

One of the frequently encountered oral manifestations in HIV/AIDS patients is drug-induced oral hyperpigmentation, especially as a result of highly active antiretroviral therapy (HAART). Oral hyperpigmentation refers to the discoloration of the oral mucosa, teeth, or surrounding tissues. Although various factors can contribute to oral pigmentation, drug-induced pigmentation is a notable cause. It can occur due to the usage of specific medications, including antimalarials, antiretrovirals, antibiotics, psychotropic drugs, and others. Therefore, understanding the etiology, clinical presentation, and management of drug-induced oral pigmentation is crucial for healthcare professionals involved in oral health care and medication management for HIV/AIDS patients, [1,3,4]

The etiology of drug-induced oral pigmentation involves several mechanisms. Some drugs, such as antimalarials, accumulate in the dermis and form complexes with melanin or iron, leading to pigmentation. Others stimulate melanocytes, resulting in increased production of melanin. Additionally, certain drugs can cause pigmentation due to pigmentary incontinence resulting from cutaneous inflammation. [3,5].

By exploring the prevalence and clinical characteristics of drug-induced oral pigmentation in HIV/AIDS patients, healthcare providers can effectively manage patient expectations and optimize treatment adherence. Understanding the factors contributing to drug-induced pigmentation enables informed decision-making regarding medication choices, potentially minimizing the occurrence and impact of oral hyperpigmentation. Additionally, recognizing and addressing drug-induced oral pigmentation can improve patient communication and alleviate unnecessary apprehension, enhancing treatment outcomes and overall quality of life.

METHODS

A cross-sectional study was conducted on a cohort of 259 HIV-seropositive patients who were receiving the highly active anti-retroviral therapy at the ICTC center in Kodagu. The study was carried out by the oral physician following the approval of the Institutional Ethical Committee (KOIMS/IEC/05/2018-19). The HIV status of all participants had previously been established using two enzyme-linked immunosorbent assays (ELISA-HIV). The study spanned a period of 6 months.

To ensure informed participation, subjects received both verbal and written information about the study in their respective mother tongues. Written informed consent was obtained, and strict confidentiality of personal information was maintained.

An oral physician examined and interviewed all subjects, documenting relevant clinical data. Supplementary medical history was obtained by consulting the medical records, adhering to WHO criteria. The collected data included age, gender, history of systemic disease, drug history, and the location of pigmentation both intraoral and extraoral.

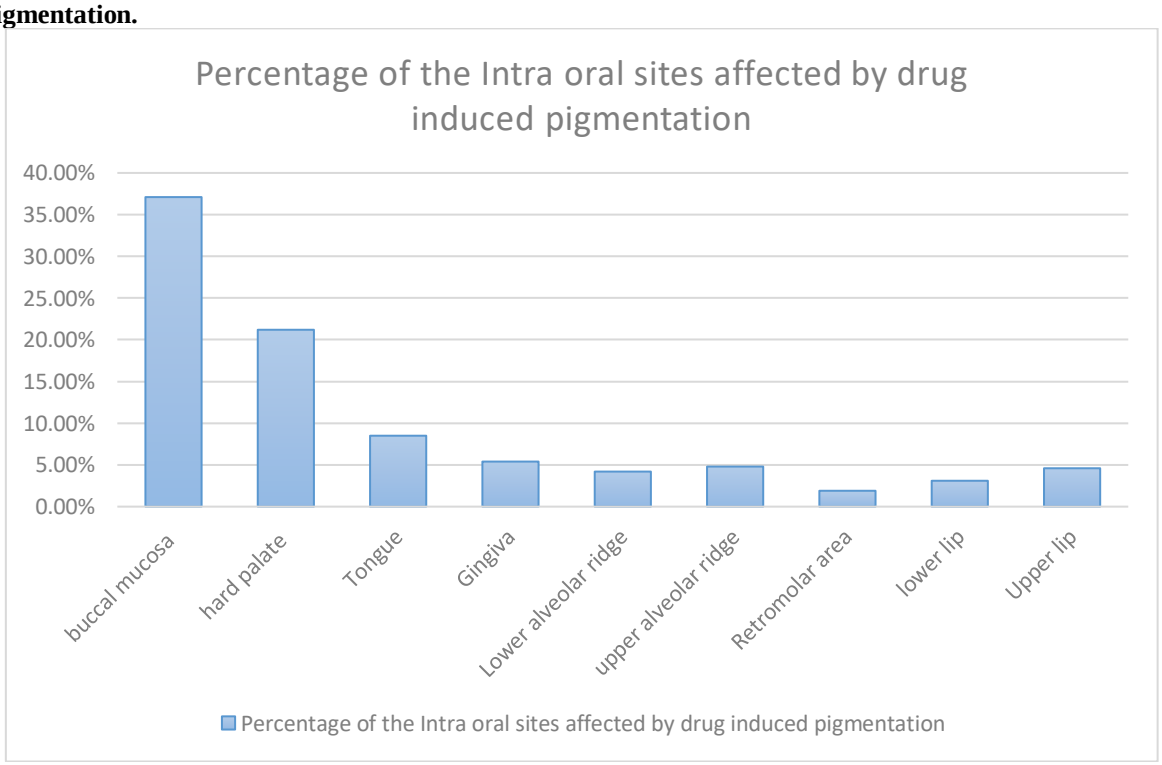
Statistical analysis was performed using the Chi-square test to assess the relationship between categorical variables in different groups.

RESULTS

A total of 259 HIV infected patients on highly active retroviral therapy were included in the study. All the patients were on HAART, and there were 15 HAART combinations made up of 11 drugs. Majority of the study population 168 (64.9%) were on TLE , 91(35.1%) were on Zidovudine, lamivudine and nevirapine regimen.

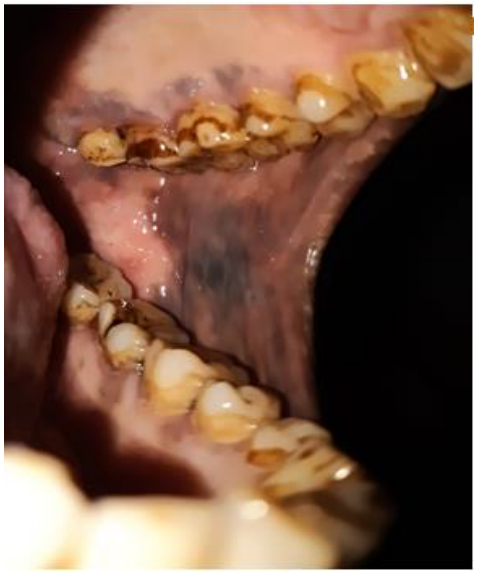
Oral mucosal pigmentation was seen in 100 patients and 14 patients had both intra oral and extra oral pigmentation i.e pigmentation of skin, nail and oral cavity was noted . The most commonly involved intra oral sites were buccal mucosa 96(37.1%), hard palate 55(21.2%) , tongue 22(8.5%) , gingiva 14 (5.4%) , upper lip 12(4.6%) ,lower lip 8(3.1%), upper alveolar ridge 8 (4.8 %), lower alveolar ridge 7 (4.2 %), retromolar area 5 (1.9%), ,.{ figure 1}. { Picture 1,2,3,4,5}

Figure 1: Percentage of the intra oral sites affected by highly active anti-retroviral drug induced pigmentation.

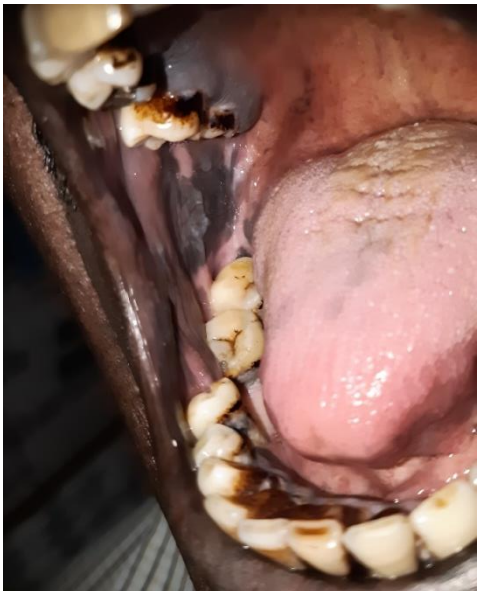


Picture 1: Discrete bluish black pigmentation of lower attached gingiva.

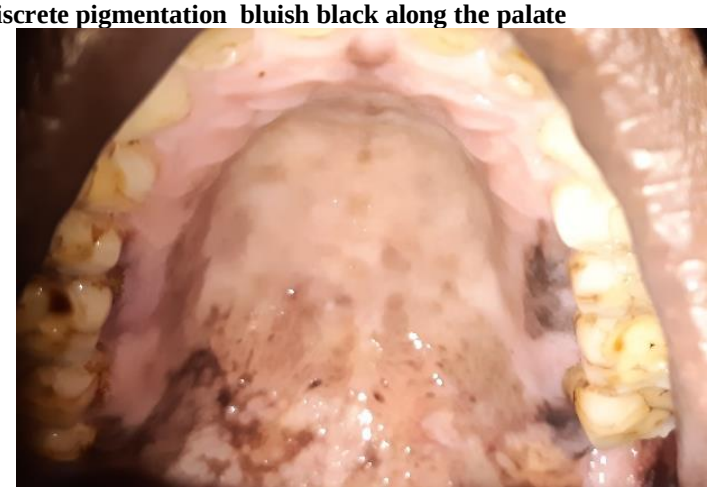
Picture 2: Discrete pigmentation along the palate and bluish black diffuse pigmentation along left buccal mucosa.



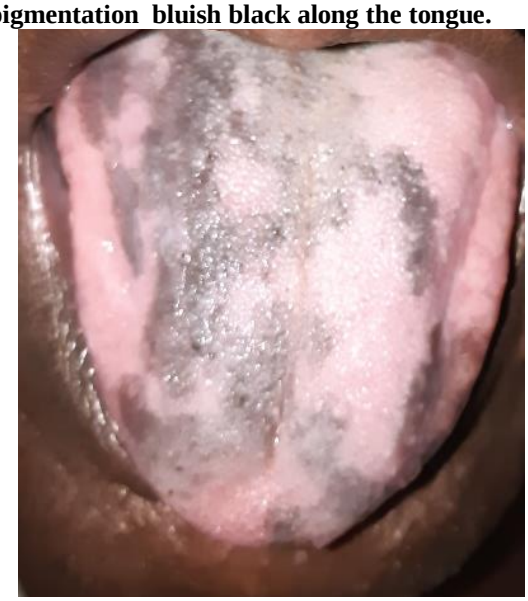
Picture 3: Discrete pigmentation along the palate and bluish black diffuse pigmentation along right buccal mucosa



Picture 4: Multiple discrete pigmentation bluish black along the palate

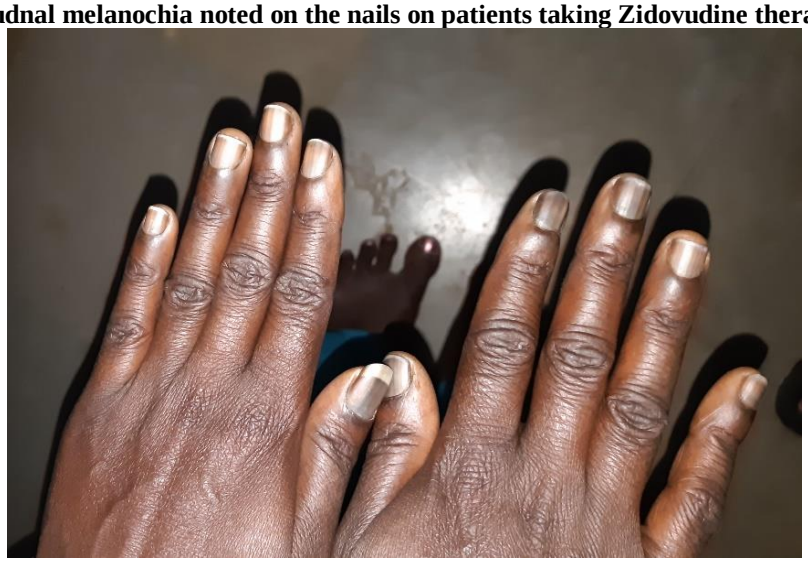


Picture 5: Multiple discrete pigmentation bluish black along the tongue.

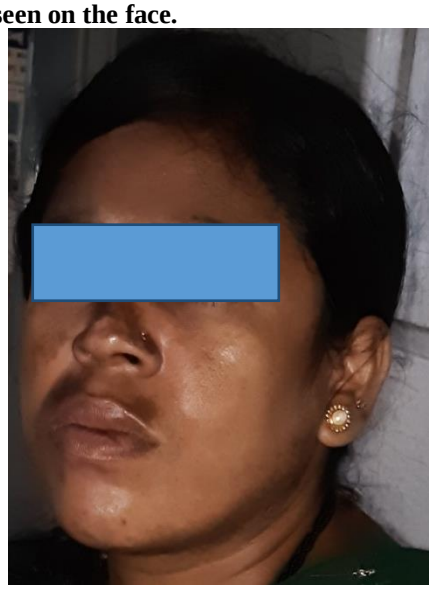


Asymptomatic, multiple, discrete, macular brownish-black to bluish discoloration of the oral mucosa was the distinct pigmentation pattern noted in individuals on Highly active anti-retroviral therapy in our study (Picture 1-5), They also exhibited pigmentation along the face and nails (Picture 6,7).

Picture 6 : longitudnal melanochia noted on the nails on patients taking Zidovudine therapy.



Picture 7: Discrete pigmentation seen on the face.



Out of two hundred and fifty-nine HIV-seropositive subjects on Antiretroviral therapy , 127(49.03%) females and 132 (50.97%) males, were included in this study (F : M = 0.89). The No oral mucosal hyperpigmentation was noted in 81 (63.8%)females and 78 (59.1%) males (F : M = 3.5 : 1) whereas oral mucosal hyperpigmentation was noted in 46 (36.2%) females and 54 (40.9%) males (F : M = 1.31 : 1) There was no significant association between the two groups with regard to gender

The mean age of the group with no drug induced pigmentation was 37.26 years (sd = 11.8); range 51) whereas the mean age of the group with drug induced pigmentation was 39.6 years (sd = 10.7) There was no significant difference in the mean age or in the age categories between the no drug induced pigmentation group and the one with pigmentation.Over all patients with Oral mucosal hyperpigmentation were in the age group of 25-55.

Out of which 158 people were on ART for more than 5years and 101 people were on HAART for less than 5 years.

Statistical analysis did not reveal any significant associations between age, gender, duration of Zidovudine use, and the presence or absence of oral pigmentation.

DISCUSSION

The prevalence of Zidovudine induced oral pigmentation in this study was 54%. This rate was significantly higher compared to the previous study conducted in Tanzania (4.7%)[5] ,Kenya (6%)[5,6],Italy (6.4%),Greece (2%), Venezuela (38%)[7] India (26-35%)[8-10],Ethnic and racial backgrounds may contribute to the higher prevalence in the Kodagu population [1,11,12]

The significant raise in the prevalence can also be due to the difficulty in differentiating between drug-induced pigmentation (highly active anti-retroviral therapy) and HIV oral mucosal hyperpigmentation as the study relies on self-reported patient histories, which may not always be reliable. As oral pigmentation is often asymptomatic and the affected sites may not be readily visible, a large number of subjects were unable to confidently state whether they had pigmentation before or after starting the drugs. Histopathological examination to confirm the lesions was not performed due to their asymptomatic nature, and conducting an invasive procedure like biopsy for confirmation would have been unethical.

The observed increase in prevalence could be attributed to the challenge of distinguishing between drug-induced pigmentation (resulting from highly active anti-retroviral therapy) and HIV oral mucosal hyperpigmentation[13]. This difficulty arises because the study relies on self-reported patient histories, which may not always be accurate or dependable. Additionally, oral pigmentation is often asymptomatic, and the affected areas may not be easily visible, making it challenging for many subjects to confidently determine whether they experienced pigmentation before or after initiating drug treatment. Since the lesions were asymptomatic, performing histopathological examination for confirmation would be unethical as biopsy would be an invasive procedure.

Previous studies have shown that oral pigmentation is common in dark-skinned patients on Zidovudine and may be reversible. It is believed that the upregulation of IL-1, IL-6, and TNF-α associated with HIV infection triggers keratinocytes and melanocytes to produce alpha melanocyte stimulating hormone (αMSH), leading to increased melanogenesis and clinical manifestation of oral pigmentation.[5]

The oral pigmentation may be drug induced, a consequence of adrenal insufficiency or idiopathic . In HIV-seropositive subjects, oral mucosal hyperpigmentation may also be induced by HIV-associated systemic conditions. Evidence have shown that the prevalence of oral pigmentation is higher in

HIV-seropositive subjects on HAART than in HIV-seropositive patients who haven't started HAART. [4,6,14] hence histopathological evaluation is recommended in further studies.

In our study the most commonly affected intraoral sites were the buccal mucosa 96(37.1%), hard palate 55(21.2%) , tongue 22(8.5%) , gingiva 14 (5.4%) , upper lip 12(4.6%) ,lower lip 8(3.1%), upper alveolar ridge 8 (4.8 %), lower alveolar ridge 7 (4.2 %), retromolar area 5 (1.9%), Patients reported that the discoloration appeared after initiating therapy, particularly in more visible areas such as the buccal mucosa, hard palate, and tongue.. { Picture 1,2,3,4,5}

Our study had a higher prevalence compared to a study conducted on 1217 patients on various drug therapies in a dermatology clinic in whom 16 patients (1.31%) were diagnosed with drug-induced hyperpigmentation. Among them, 4 patients had hyperpigmentation of the oral mucosa, 6 had hyperpigmentation in photograph-exposed areas, 4 had labial hyperpigmentation similar to our study, and 1 had nail hyperpigmentation.[13] Labial hyperpigmentation is associated with various conditions, including drug use (minocycline, zidovudine, cyclophosphamide, doxorubicin, citalopram, levodopa, nicotine, and tacrolimus), genodermatoses, inflammatory diseases, endocrine disorders, and neoplasms.Further drug-induced labial hyperpigmentation is not limited to specific races or genders. [14]

Asymptomatic, multiple, discrete, macular brownish-black to bluish discoloration of the oral mucosa was the distinct pigmentation pattern in individuals on highly active anti-retroviral therapy in our study (Picture 1-5). Previous studies have also reported a similar asymptomatic, greyish-black discoloration of the tongue in individuals on Zidovudine without any toxicity.[12]Intraoral slate graypigmentation was noted in individuals taking antimalarials such as quinacrine, chloroquine, and hydroxychloroquine. Tetracyclines cause pigmentation of the teeth and bones, while minocycline causes brownish pigmentation of soft tissues, including the hard palate, gums, mucosa, and tongue. [1,15,16]

Additionally, in our study, we found that 14 subjects on highly active anti-retroviral therapy exhibited pigmentation along the face and nails (Picture 6,7).Longitudinal melanonychia (Picture 7) was observed in our patients, consistent with findings reported in other cases of Zidovudine-induced pigmentation Notably, individuals with darker skin tones showed a higher incidence of nail pigmentation.[12] (Picture 6,7). It is important to distinguish this pigmentation from the brownish hyperpigmented stripes observed in HIV patients not receiving any drugs.[12,17] There have been reported cases of oral mucosal hyperpigmentation due to hydroxychloroquine, as well as cases of nail or nose hyperpigmentation due to quinacrine or quinidine. [7] Therefore thorough drug history is required before arriving at a diagnosis.

CONCLUSION

Drug-induced oral hyperpigmentation is a significant side effect of highly active antiretroviral therapy. Educating patients about potential adverse reactions can help alleviate concerns and improve treatment adherence. Further research is required to understand the underlying mechanisms and determine the pathological significance of drug-induced oral hyperpigmentation.

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