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Original Research

Zidovudine Induced Oral Hyperpigmentation Among Hiv Patients In Kodagu region of India: A Clinico Epidemiological Study.

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ABSTRACT

Objective: The objective of this study is to determine the prevalence of oral pigmentation caused by Zidovudine in individuals with HIV infection in the Kodagu region of India.

Methods: The study included a total of 91 HIV-infected individuals who were undergoing treatment with Zidovudine. Thorough muco-cutaneous examinations were conducted to assess the presence of oral pigmentation. The location of the pigmented lesions, the duration since their appearance, and the duration of treatment were carefully documented. Subsequently, all the collected data were recorded and subjected to statistical analysis.

Results: Out of the 91 subjects receiving Zidovudine, 48 (52.7%) exhibited oral mucosal pigmentation, and 8 (8.8%) showed both intraoral and extraoral pigmentation. The most commonly affected intraoral sites were the buccal mucosa (47.3%), hard palate (30.8%), tongue (16.5%), gingiva (7.7%), lower alveolar ridge (3.3%), and upper alveolar ridge (1.1%). Additionally, 8 subjects (8.8%) exhibited pigmentation along the face and nails. Notably, 84.9% of individuals had been on Zidovudine for more than 5 years.

Conclusion: Prolonged treatment with Zidovudine is known to cause oral hyperpigmentation, which is a significant side effect. By providing prior explanations about the potential adverse reactions associated with the antiviral drug regimen, adherence to the treatment can be improved.

Key words: Anti retro viral therapy, pigmentation, Zidovudine-induced pigmentation, HIV.

Introduction:

Oral health reflects overall health, and HIV/AIDS often presents with oral manifestations. These manifestations not only indicate the disease but also predict disease progression and treatment response [1, 2]. Among the various oral lesions observed in HIV-positive patients, oral hyperpigmentation is significant [3].Several drugs, including antiretroviral therapy, have been associated with oral melanin hyperpigmentation. [1-4]. Zidovudine, a commonly prescribed antiretroviral medication, is known to cause hyperpigmentation. The mechanism of hyperpigmentation involves increased melanin production or the accumulation of the drug or its metabolites. [1,2]

The development and clinical presentation of pigmentation vary depending on the specific drug involved. Hyperpigmentation typically occurs as a result of increased melanin production, either due to the stimulation of melanocytes or as a consequence of pigmentary incontinence following cutaneous inflammation of unknown origin. Another possible mechanism is the accumulation of the drug or its metabolites in the dermis, where they can form complexes with melanin or iron. Microscopically, drug-induced melanosis is characterized by basilar melanosis without melanocytic proliferation. [1,2] The objective of this study was to determine the prevalence of Zidovudine-induced pigmentation among individuals with HIV infection in the Kodagu region of India.

Methods:

A cross-sectional study was conducted on a cohort of 91 HIV-seropositive patients who were receiving the Zidovudine regimen at the ICTC center in Kodagu. The study was carried out by the dental department, 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, participants received both verbal and written

information about the study in their respective mother tongues. Written informed consent was obtained, and strictconfidentiality 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, CD4+ T cell count, 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:

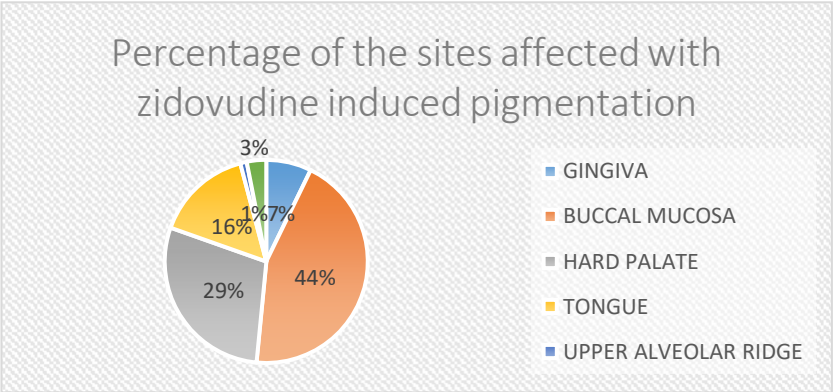
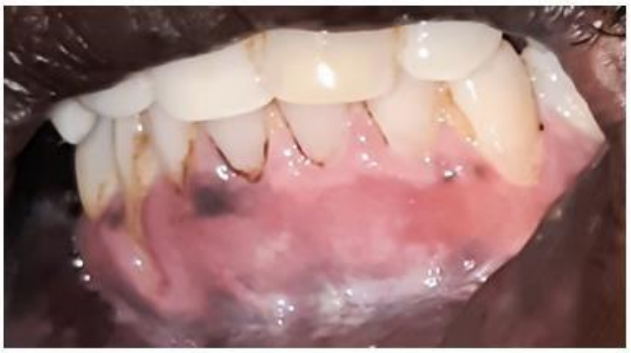


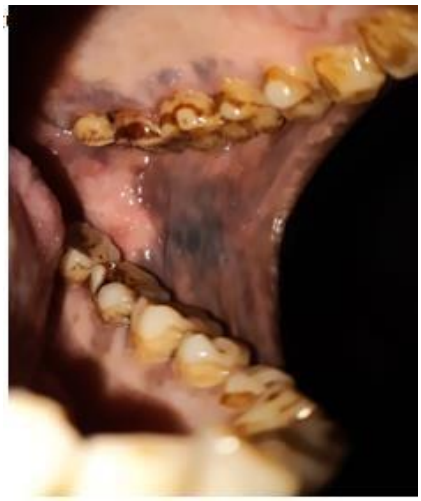
Figure 1: Intra oral sites with pigmentation in patients on Zidovudine

A total of 91 subjects (35.1%) who were receiving Zidovudine were included in the study. Among them, 48 subjects (52.7%) exhibited oral mucosal pigmentation, while 8 subjects (8.8%) had both intraoral and extraoral pigmentation, involving the skin, nails, and oral cavity.The most commonly affected intraoral sites were the buccal mucosa (47.3%), hard palate (30.8%), tongue (16.5%), gingiva (7.7%), lower alveolar ridge (3.3%), and upper alveolar ridge (1.1%) [Figure 1]. Patients noted 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}Asymptomatic, multiple, discrete, macular brownish-black to bluish discoloration of the oral mucosa was the distinct pigmentation pattern in individuals on Zidovudine therapy in our study (Picture 1-5), 8 (8.8%) subjects on Zidovudine therapy exhibited pigmentation along the face and nails (Picture 6,7).Our study included 91 HIV-seropositive individuals on the Zidovudine regimen, with 54 females and 37 males, female-to-male ratio :0.89. The mean age of the group without drug-induced pigmentation was 34.3 years (sd = 12.4), while the mean age of the group with pigmentation was 43.3 years (sd = 9) with no significant differences between both the groups.Among the patients on Zidovudine therapy with pigmentation, 26 individuals (44.8%) had low immunity (CD4 < 500), while 32 patients (55.2%) had CD4 counts > 500 with no significant differences.Regarding the duration of Zidovudine use, 49 individuals (84.9%) had been on the regimen for more than 5 years, while 9 individuals (15.5%) had been on the therapy for less than 5 years. Previous studies have reported that Zidovudine/azidothymidine can induce melanin hyperpigmentation within a month of starting treatment [5-8]
Statistical analysis did not reveal any significant associations between age, gender, CD4 count, duration of Zidovudine use, and the presence or absence of oral pigmentation.

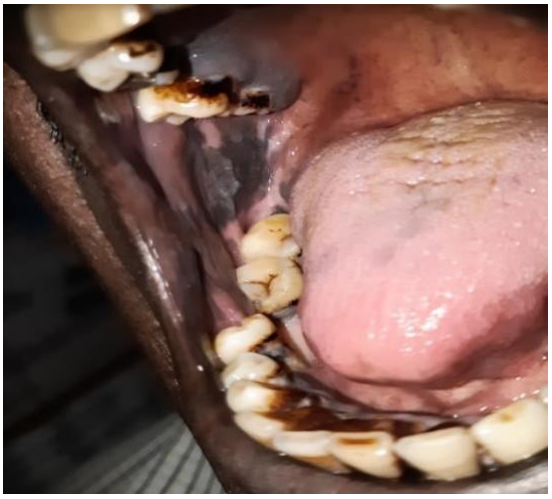
Picture 1: Discrete bluish black pigmentation of lower attached gingiva.



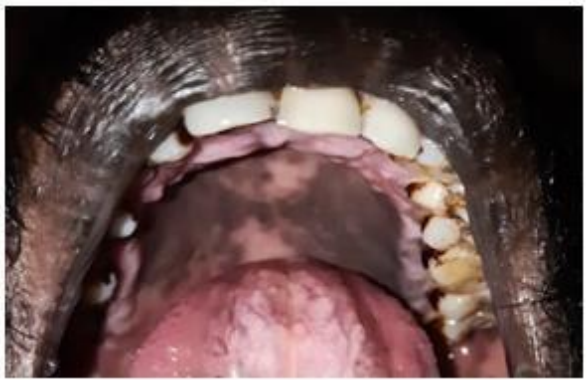
Picture 2: Discrete pigmentation along the palate and bluish black diffuse pigmentation along left buccal mucosa.



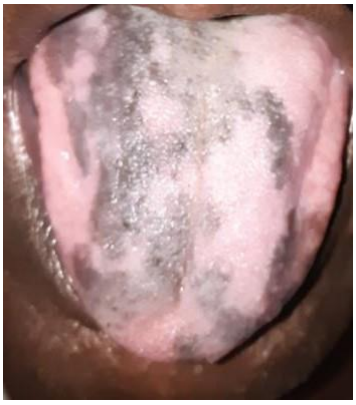
Picture 3: Discrete pigmentation along the palate and bluish black diffuse pigmentation along right buccal mucosa



Picture 4: Multiple discrete pigmentation bluish black along the palate



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



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

Picture 7: Discrete pigmentation seen on the face.

Discussion:

The prevalence of Zidovudine induced oral pigmentation in this study was 46%. This rate was significantly higher compared to the previous study conducted in Tanzania (4.7%)[2] , Kenya (6%)[9,10], Italy (6.4%),Greece (2%), Venezuela (38%)[10] India (26-35%)[5,11,12], Ethnic and racial backgrounds may contribute to the higher prevalence in the Kodagu population [2,5,11,12]The significant raise in the prevalence can also be due to the difficulty in differentiating between drug-induced pigmentation (Zidovudine) 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 drug Zidovudine. 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. 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.[13] 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. [4,11,14] hence histopathological evaluation is recommended in further studies.In our study the most commonly affected intraoral sites were the buccal mucosa (47.3%), hard palate (30.8%), tongue (16.5%), gingiva (7.7%), lower alveolar ridge (3.3%), and upper alveolar ridge (1.1%) which was higher 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. [1] 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. Drug-induced labial hyperpigmentation is not limited to specific races or genders. [4]

Asymptomatic, multiple, discrete, macular brownish-black to bluish discoloration of the oral mucosa was the distinct pigmentation pattern in individuals on Zidovudine 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.[5]Intraoral slate grey pigmentation 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. [2,3,15]Additionally, in our study, we found that 8 (8.8%) subjects on Zidovudine 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.[5] (Picture 6,7). It is important to distinguish this pigmentation from the brownish hyperpigmented stripes observed in HIV patients not receiving any drugs. [5,6] 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. [16] Therefore thorough drug history is required before arriving at a diagnosis.

Conclusion:

Prolonged treatment with Zidovudine can cause oral hyperpigmentation, a significant side effect. By informing patients about potential adverse reactions associated with the antiviral drug regimen, adherence to treatment can be improved.Histopathological evaluations and further studies are recommended to confirm the underlying causes and investigate the potential effects of Zidovudine pigmentation on oral health and quality of life.

References:

1. Giménez García RM, Carrasco Molina S. Drug-Induced Hyperpigmentation: Review and Case Series. J Am Board Fam Med [Internet]. 2019 Jul [cited 2023 Jan 29];32(4):628–38. Available from: http://www.jabfm.org/lookup/doi/10.3122/jabfm.2019.04.180212
2. Alawi F. Pigmented lesions of the oral cavity: An Update. Dent Clin North Am [Internet]. 2013 Oct [cited 2022 Feb 2];57(4):699–710. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3775277/
3. Ranganathan K, Reddy BV, Kumarasamy N, Solomon S, Viswanathan R, Johnson NW. Oral lesions and conditions associated with human immunodeficiency virus infection in 300 south Indian patients. Oral Dis. 2000 May;6(3):152–7.
4. Dereure O. Drug-induced skin pigmentation. Epidemiology, diagnosis, and treatment. Am J Clin Dermatol. 2001;2(4):253–62.
5. Singh SK, Rai T. A case of zidovudine induced pigmentation on palms and soles. Indian Dermatol Online J [Internet]. 2014 [cited 2022 Feb 2];5(1):98–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3937508/
6. Black and Brown: Non-neoplastic Pigmentation of the Oral Mucosa - PMC [Internet]. [cited 2023 Jan 29]. Available

from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6405786/
7. Sreeja C, Ramakrishnan K, Vijayalakshmi D, Devi M, Aesha I, Vijayabanu B. Oral pigmentation: A review. J Pharm Bioallied Sci [Internet]. 2015 Aug [cited 2021 Dec 18];7(Suppl 2): S403–8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4606629/
8. Capelli L, Garuti RA, Carmona Cuello LE, Sanz A, Oborski MR, León SA, et al. Hiperpigmentación cutáneo-mucosa y ungular secundaria a tenofovir. Arch Argent Dermatol [Internet]. 2013 [cited 2023 Jan 29];23–6. Available from: https://pesquisa.bvsalud.org/portal/resource/pt/lil-766765?lang=es
9. Moore DE. Drug-induced cutaneous photosensitivity: incidence, mechanism, prevention, and management. Drug Saf. 2002;25(5):345–72.
10. Chawre SM, Pore SM, Nandeshwar MB, Masood NM. Zidovudine-induced nail pigmentation in a 12-year-old boy. Indian J Pharmacol [Internet]. 2012 [cited 2022 Feb 2];44(6):801–2. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3523514/
11. Chandran R, Feller L, Lemmer J, Khammissa RAG. HIV-Associated Oral Mucosal Melanin Hyperpigmentation: A Clinical Study in a South African Population Sample. AIDS Res Treat [Internet]. 2016 [cited 2022 Feb 2]; 2016:8389214. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4783540/
12. Hamza OJM, Matee MIN, Simon ENM, Kikwilu E, Moshi MJ, Mugusi F, et al. Oral manifestations of HIV infection in children and adults receiving highly active anti-retroviral therapy [HAART] in Dar es Salaam, Tanzania. BMC Oral Health. 2006 Aug 18; 6:12.
13. Bravo IM, Correnti M, Escalona L, Perrone M, Brito A, Tovar V, et al. Prevalence of oral lesions in HIV patients related to CD4 cell count and viral load in a Venezuelan population. Med Oral Patol Oral Cirugia Bucal. 2006 Jan 1;11(1): E33-39.
14. Singal A, Bisherwal K. Melanonychia: Etiology, Diagnosis, and Treatment. Indian Dermatol Online J [Internet]. 2020 Jan 13 [cited 2023 Feb 4];11(1):1–11. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7001389/
15. Sharma G, Pai KM, Suhas S, Ramapuram JT, Doshi D, Anup N. Oral manifestations in HIV/AIDS infected patients from India. Oral Dis. 2006 Nov;12(6):537–42.
16. Hassan S, Zhou XA. Drug Induced Pigmentation. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [cited 2023 Jan 29]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK542253/