Antiretroviral therapy has added 14 million life-years in end of 2011—a 20-fold increase since 2003. Since 1995, antiretroviral therapy reached 8 million people by the mid-2000s because of the steady decline in HIV incidence and scaled-up antiretroviral therapy since the peak in 1997. As the oral palate, tongue and buccal mucosa have been documented as the oral cavity.

Antiretroviral therapy, though has its distinct advantages, it comes along with its due flip side. Numerous studies have time and again proved the effects of this therapy on the general body. But a minuscule of it is targeted on its effect on the oral tissues. Effects such as gingival epithelial changes to pigmentation of the palate, tongue and buccal mucosa have been documented and new studies are needed to highlight this aspect. These changes can be taken into highlight and be used as an important diagnostic aid and also indicating toward treatment failure. This review article encompasses the side effects and adverse effects of this type of therapy on the general body as well as the oral aspect.

Keywords: Antiretroviral therapy, Side effects, Adverse effects, Oral cavity, HAART.


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INTRODUCTION

Globally, 34.0 million (31.4-35.9 million) people were living with HIV at the end of 2011. Worldwide, the number of people newly infected continues to fall: the number of people (adults and children) acquiring HIV infection in 2011 was 20% lower than in 2001. The number of people dying from AIDS-related causes began to decline in the mid-2000s because of the steady decline in HIV incidence and scaled-up antiretroviral therapy since the peak in 1997. Antiretroviral therapy reached 8 million people by the end of 2011—a 20-fold increase since 2003. Since 1995, antiretroviral therapy has added 14 million life-years in low- and middle-income countries. Twenty-five years after the discovery of the antiviral effect of AZT (Broder, 2010; Mitsuya et al, 1985), there are 25 approved single antiretroviral drugs in 6 mechanistic classes. These six classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) (Cihlar and Ray, 2010) (Martin et al 2010), non-nucleoside reverse transcriptase inhibitors (NNRTIs) (de Bethune, 2010), protease inhibitors (Pis) (Wensing et al 2010), entry/fusion inhibitors (FIs) and CCR5 antagonists (Tilton and Doms, 2010), and integrase inhibitors (McColl and Chen, 2010).

In India, the National AIDS Control Organization (NACO) introduced inexpensive and generic ART drugs. So, with the availability of generic HAART at low cost, an increasing number of HIV-infected individuals in India are now receiving therapy. Adverse events are common and may lead to discontinuation of therapy, dose interruption, and significant reductions in quality of life. Adherence may be compromised because of adverse events, and adherence is increasingly recognized as an important determinant of successful antiretroviral therapy.

HIV care facilities in developing countries have witnessed dramatic decreases in mortality that are similar to those previously recorded in developed countries. One by-product of increased access to HAART, however, is that management of antiretroviral drug-related toxicities is becoming an important component of HIV care in developing countries.

Each antiretroviral medication is associated with its own specific adverse effects or may cause problems only in particular circumstances. Similarly, class specific adverse effects may occur. (Adverse effects of antiretroviral therapy for HIV infection). This review focuses on the well-known adverse and side effects of ART on the general body as well as the oral cavity.

A significant proportion of patients had adverse effects of a lower grade severity after HAART. A significant proportion of those started on ART substitute therapy due to adverse effects and those on NVP-based regimens are more likely to do so when compared with those on non-NVP-based regimens.

All antiretroviral drugs can have both short-term and long-term adverse events. The risk of specific side effects varies from drug to drug, from drug class to drug class, and from patient to patient.

Working Mechanism

Current treatments against human immunodeficiency virus type 1 (HIV-1) infections include six different classes of
drugs, targeting the three viral enzymes (more than 20 different compounds in clinical use target the protease, reverse transcriptase and integrase), the virus fusion process (enfuvirtide/T-20 targets the viral gp41) or viral entry (maraviroc targets the human CCR5 cellular coreceptors) [Novel targets for HIV therapy. Antiviral Res. 2008] Combinations of these drugs are used in a treatment strategy known as HAART.

NRTIs were the first class of drugs to be approved by the FDA (Young 1988). Reverse transcriptase (RT) inhibitors are divided into two classes: nucleoside and nucleotide RT inhibitors (NRTIs), and non-nucleoside RT inhibitors (NNRTIs). NNRTIs compete with the natural nucleoside triphosphate (dNTP) for binding the RT polymerase active site, and after their incorporation into the primer strand, act as terminator of DNA synthesis due to the lack of a 3'-hydroxyl group. NNRTIs do not interfere with dNTP binding, but rather lead to unproductive complexes by altering the conformation or mobility of RT, thereby exerting a noncompetitive inhibition. NNRTIs are highly specific for HIV-1 RT and result in less adverse effects than NRTIs.16

The stable integration of the reverse transcribed viral genome into host chromatin forms an important point-of-no-return during HIV infection. Strand transfer integrase inhibitors bind in the catalytic core domain of the enzyme and compete for binding with host DNA.17

The HIV protease is the enzyme responsible for the cleavage of the viral gag and gag-pol polyprotein precursors during virion maturation. HIV-protease inhibitors prevent cleavage of gag and gag-pol protein precursors in acutely and chronically infected cells, arresting maturation and thereby blocking the infectivity of nascent virions. The main antiviral action of HIV-protease inhibitors is thus to prevent subsequent waves of infection; they have no effect on cells already harboring integrated proviral DNA.18

The fusion inhibitor enfuvirtide and the small-molecule CCR5 antagonist maraviroc are the first two licensed entry inhibitors. They bind to different regions of CCR5 and thereby disruption of sequential steps on viral entry.19

Maturation inhibitors are a novel mechanistic class of antiretroviral drug that target protease cleavage sites in Gag. Bevirimat is the first-in-class maturation inhibitor, which specifically inhibits cleavage of SP1 from the C-terminus of Capsid.20

**Side Effects and Adverse Reaction**

Adverse drug reaction is a response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function (WHO, 1972). Side effect is any unintended effect of a drug occurring at normal dosage which is related to the pharmacological properties of the drug.21

**Factors Associated with Side Effects**

Women have higher chances of acquiring Steven Johnsons syndrome, hepatotoxicity with nevirapine and higher toxicity rates of lactic acidosis from NRTIs.22

Other factors that can have an add on effect on ARTs are the simultaneous usage of medications that have an additive toxic effect, conditions that can exacerbate the side effects, e.g. viral hepatitis, alcoholism that have an added burden on the liver, drug interactions, drug related toxicities (use of ribavirin with didanosine) and genetic factors (patients sensitive to abacavir), history of psychiatric illness. The most common cause of nonadherence, mortality and discontinuing therapy are the adverse effects caused due to ART (Bersoff-Matcha et al 2001).22-24

**Some Common Adverse Effects**

**Effect on Fat, Lean and Bone Mass**

Lipodystrophy (Fig. 1), also called fat redistribution, is a disturbance in the way your body produces, uses, and stores fat. It is associated with side effects, such as peripheral fat wasting, central adiposity, dyslipidemia and insulin resistance. Monocyte CD36 levels are affected with the patient exposure to antiretroviral therapy, mainly protease inhibitors. The protease inhibitors act on the peroxisome proliferator activated receptor (PPAR) by impairing the production of 9 cis retinoic acid. PPAR is further, associated with the activation of CD36 which is a scavenger receptor present on macrophages. CD36 present on macrophages takes in lipoproteins and also acts as a high affinity transporter to adipose tissues. Fall in the PPAR dramatically increases the serum fatty acids, triglycerides and cholesterol levels (Abumrad NA et al 1993).25-28

Protease inhibitors adversely affect the differentiation of fat on transcription factors, such as sterol regulatory element binding protein-1 (SREBP- 1). In a study done by Yelmokas et al in 2001 in a cohort of 203 HIV-positive men and...
63 HIV-positive women, they observed that patients who had protease based HAART treatment had redistribution of fat mass from the legs to the trunk. They further also noted that HAART was associated with a significant reduction in bone mineral content suggesting osteoporosis.29

The pathogenesis of HIV associated lipodystrophy most likely involves mechanisms, such as inhibition of mitochondrial enzymes by NRTI’s which leads to mitochondrial dysfunction and abnormal fat accumulation. Carr et al (1998) expressed that the genetic sequence of the catalytic region of HIV-1 protease has 60% similarity to proteins that are involved in the lipid metabolism. They were cytoplasmic retinoic acid binding protein type 1 (CRABP-1) and low-density lipoprotein receptor-related protein (LRP).30-34

Studies on the effect of antiretroviral therapy on body composition by Mallon et al (2003), the limb fat, central abdominal fat and lean mass was calculated in HIV seropositive patients who were on antiretroviral therapy with stavudine as a compulsory regimen. Stavudine was the single independent factor associated with increased limb fat loss and increased central abdominal fat. The other factors associated were increase in HIV RNA. This prospective study observed that there was a progressive, selective loss of limb fat during the period.56

Nucleoside reverse transcriptase inhibitors particularly didanosine and stavudine was commonly associated with Pancreatitis. But studies have found that Tipranavir, a protease inhibitor can also induce pancreatitis via the induction of hypertriglyceridemia.35,36

Hepatotoxicity: Hepatotoxicity is defined as an increase of at least three-fold in serum alanine aminotransferase or aspartate aminotransferase levels compared with baseline values. Hepatotoxicity is most commonly associated with the administration of nevirapine. Though nevirapine was the first NNRTI introduced it was very soon associated with hepatotoxicity with more than 6 months of treatment with the drug. The risk of hepatotoxicity increased with associated risk factors, such as HCV infection and hepatotoxic agents such as alcohol, antitubercular drugs and abnormal baseline alanine aminotransferase were identified as patient risk factors.37,38

Blood Pressure and Antiretroviral Therapy
Crane et al (2006) suggested that antiretroviral therapy can cause raise systolic blood pressure (SBP), hence the baseline value of SBP should be noted before ART is initiated. Those patients who were initiated on protease inhibitors more specifically on lopinavir/ritonavir were found to be associated with the increase in SBP. Rosario et al (2007) further suggest that the increase in blood pressure could be a result in the overall improvement of the general health of the patient and the people with a lower SBP in the start of the treatment had a steady improvement in the blood pressure as the treatment continued.39,40

Atherosclerosis
Protease inhibitors have also been implicated in the pathogenesis of increased fibrinogen levels in patients with HIV infection. Madden et al (2008) in their study of 1131 HIV infected patients and 281 controls found and assessed the cardiovascular risk in these patients. The patients were on individual PIs like ritonavir and indinavir. They found that protease inhibitors had the single univariate association with the higher levels of fibrinogen in HIV infected patients compared to normal subjects.

Candidiasis also was one of the most prevalent groups in a study done in a Mexican HIV seropositive patients undergoing highly active antiretroviral therapy and the prevalence was found to be highest in the HAART/PI group. Among the other oral lesions were, Herpes labialis, HIV associated periodontitis, xerostomia, hairy leukoplakia and nonspecific oral ulcers. Among the fungal organisms, Candida albicans has been shown to be present at a higher frequency among patients with HIV undergoing antiretroviral therapy (indinavir/ritonavir/saquinavir + zidovudine [AZT] + lamivudine [3TC]).40,41

Antiretroviral Therapy and the Oral Cavity
Studies have shown that short term usage of HAART has a very good effect on the oral cavity by preventing oral lesion, however the long term usage of the same can result in side effects.42 HAART has a very good effect on the oral cavity as it reduces the number of HIV associated oral lesions like oral candidiasis and oral hairy leukoplakia. Studies have shown that long term usage can result in the development of other side effects such as pigmentation, salivary gland disorders being salivary gland enlargement sometimes being tender and painful (Ranganathan 2007).43-44 Protease inhibitor based antiretroviral therapy has resulted in the decrease in the incidence of oral candidiasis and studies have proven the same. However, some studies proved otherwise, PI usage and oral lesions had no significant relation (Cauda R et al, 1999).45

Gingival Epithelium
On a study, on the gingival epithelium it was found that protease inhibitors (Amprenavir) severely affected the proliferation and differentiation of gingival keratinocytes by affecting cytoerkatin PCNA and cyclin A. IRIS and the oral cavity: there has been an increase in the incidence of salivary
gland diseases in the era of HAART which has been linked to immune reconstitution syndrome. In a study done by Ortega et al, it was found that among the oral manifestations parotid enlargement was the most common (57.14%) with candidiasis among the most frequently seen lesion among the nonimmune reconstitution group. On the salivary gland: studies have shown that antiretroviral therapy has an effect on salivary gland. However, the pathogenesis is not clearly understood. In a study done on a cohort of 668 HIV seropositive women in Africa, Navazesh et al had concluded that protease inhibitors was a significant risk factor in the development of salivary gland disorders. Salivary gland manifestations were put in the category of unstimulated and stimulated flow rate changes, complaints of dry mouth, painful, tender or any enlargement of the salivary gland. The authors also pointed that salivary structure and composition could have been altered or the lipodystrophic changes induced by PI itself could lead to deposition of adipose layer on the gland thereby reducing salivary flow rate (Aguirre-Urizar et al 2004; Olive et al 1998; Ceballos-Salobrena et al 2000). These findings were in significant contrast to the study done by Ramirez-Amador et al 2003 were no changes were found to be present. Further still Nicolatou-Gatis et al (2004) also reported there was no change in the incidence of salivary gland diseases in their cohort of 95 HIV seropositive patients. 

Hyperpigmentation: A known complication of antiretroviral therapy is melanotic hyperpigmentation (p < 0.05) this type of pigmentation was most commonly associated with ART especially in those whom zidovudine was administered.

CONCLUSION

This article thus briefly summarizes the most commonly seen effects associated with antiretroviral therapy. Further, studies are needed to actually correlate ART and its intraoral effects and its true pathogenesis.

REFERENCES


