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# Adverse Effects of Highly Active Anti-Retroviral Therapy (HAART)

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## Abstract

HIV/AIDS remains the greatest public health concern in the world. Nowadays HIV-AIDS is considered as a chronic disease due to the advent of highly active antiretroviral therapy. This therapy has significantly improved the status of the infected population, making HIV a manageable illness. However, recent studies suggest that exposure to antiretroviral medications may have marked adverse effects, independent of HIV status. This review article gives a note on the demerits of the therapy, major complications and metabolic abnormalities that occur as a consequence of HAART. The effect of antiretroviral (ARV) therapies on the incidence of serious non-AIDS events (SNAEs) has also been considered.

**Keywords:** Human Immunodeficiency Virus; Acquired Immunodeficiency Syndrome; Highly Active Anti-Retroviral Therapy; Combination Anti-Retroviral Therapy; Nucleotide Reverse Transcriptase Inhibitors; Non-Nucleotide Reverse Transcriptase Inhibitors; Protease Inhibitors; Osteonecrosis; Osteopenia; Osteoporosis; Rhabdomyolysis; Cardiovascular complications; Distal symmetric polyneuropathy; Insulin Resistance; Hyperglycemia; Hyperlipidemia; Lipodystrophy

**Abbreviations:** HIV: Human Immunodeficiency Virus; AIDS: Acquired Immunodeficiency Syndrome; HAART: Highly Active Anti-Retroviral Therapy; ART: Anti-Retroviral Therapy; cART: Combination Anti-Retroviral Therapy; NRTIs: Nucleotide Reverse Transcriptase Inhibitors; NNRTIs: Non-Nucleotide Reverse Transcriptase Inhibitors; PIs: Protease Inhibitors; IN: Integrase; QOL: Quality of Life; VL: Viral Load; IRIS: Immune Recovery Inflammatory Syndrome; SNAEs: Serious Non-AIDS Events; BMD: Bone Mineral Density; DSP: Distal Symmetric Polyneuropathy; SVR: Sustained Virological Response

## Introduction

Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) remains a significant problem and the concern is not only a major public health issue, but also a socio-economic and developmental crisis that affects all sectors of the population [1]. HIV/AIDS remains the greatest public health crises in the world today and is the fourth leading cause of mortality in the world [2]. Nowadays HIV-AIDS is considered as a chronic disease because individuals have the potential to live upward of 20 years on highly active antiretroviral therapy [3]. Highly Active Anti-Retroviral Therapy (HAART), a combination therapy of three or more HIV-suppressing drugs, has significantly improved the immunological status of the infected population, making HIV a manageable illness [4].

Chronic human immunodeficiency viral infection is characterized by defects in the immune system including depletion of $CD^{4+}$ T-cells and impaired T-cell function. Successful antiretroviral therapy (ART) suppresses viral replication [5]. The $CD^{4+}$ T-cell lymphocyte count is one of the most important prognostic factors for progression of HIV infection, and forms the basis for recommendations in the development of antiretroviral treatment and prophylaxis [6]. The decision of ART depends upon the $CD^{4+}$ count of each individual [7]. Antiretroviral treatment was considered for the patient in view of high viral load, low CD4 count and elderly patient [8]. Recent success in defining the human immunodeficiency virus type 1 (HIV-1) – host cell protein interaction network has provided an opportunity for development of novel antiviral therapeutics targeted to host proteins required for virus infection [9]. $CD4^{+}$ T lymphocytes carrying proviral DNA provide a reservoir for human immunodeficiency virus–type 1 (HIV-1) in patients on highly active antiretroviral therapy (HAART) [10].

Antiretroviral therapy refers to the use of pharmacologic agents that have specific inhibitory effects on HIV replication. Antiretroviral agents belongs to six distinct classes of drugs, the nucleoside and nucleotide reverse transcriptase Inhibitors, The non nucleoside reverse transcriptase Inhibitors, The protease Inhibitors, The fusion inhibitors, The CRR 5 Co receptor antagonistic and The Integrase Inhibitors. Each of these classes of drugs inhibits HIV replication at different stages in HIV life cycle [11].

Use of combination antiretroviral therapy (cART) also referred to as highly active antiretroviral therapy (HAART), resulted in a marked improvement in the prognosis of HIV disease [12]. HAART includes the combination of three different types of highly effective anti-HIV-1 drugs, including nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleotide reverse transcriptase inhibitors (NNRTIs) and non-peptidic viral protease inhibitors (PIs) [13]. The goals of treatment are to suppress plasma viremia for as long as possible, to delay the selection of drug resistance mutations, and to preserve immune function. PIs, NRTIs and NNRTIs are associated with potent and durable viral suppression [14].

Human immunodeficiency virus type 1 (HIV-1) integrase (IN) is a key molecule for HIV genomic integration and is important in other steps of HIV-1 replication, including reverse transcription, nuclear import, chromatin targeting, virus release and maturation [15]. Non-nucleoside reverse transcriptase inhibitor (NNRTI) -based

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antiretroviral therapy (ART) regimens have been recommended and widely used in resource-limited settings because of their reliable efficacy, low pill burden, and low cost [16].

## Demerits of HAART

The introduction of the highly active antiretroviral therapy (HAART) in 1996 has drastically reduced the morbidity and mortality associated with the HIV infection [17]. However, recent studies suggest that exposure to antiretroviral medications may have marked adverse effects, independent of HIV status. Adverse events are common in patients receiving ARV therapy. Adverse events have been shown to compromise quality of life (QOL) and interfere with adherence to ARV regimens [14]. Nucleoside analogs and protease inhibitors have been linked to mitochondrial toxicity [18] and various metabolic and cardiovascular complications [4].

With combination antiretroviral therapy (cART) regimen, the durability of HIV control is limited by many factors (adherence to treatment, drug toxicity, bioavailability, among the most important) [19]. Emergence of HIV-1 drug resistance is an inevitable consequence of antiretroviral therapy (ART) failure [20,21]. The use of a combination of potent antiviral drugs leads to a reconstitution of the immune system, which in the short- and in the mid-term is sufficient to radically increase the life expectancy and to markedly reduce the incidence of opportunistic events. Incomplete immune reconstitution and persistent immune system hyperactivation in spite of highly active antiretroviral therapy continue to be a challenge [22].

Accurate quantification of HIV-1 Viral Load (VL) in plasma compartment is an important criterion for disease monitoring and management and has now become a standard method for monitoring HIV-infected patients on antiretroviral therapy [23].

## Consequences of HAART

Each drug class has side effects: nucleoside/nucleotide reverse transcriptase inhibitors are associated with lactic acidosis, lipodystrophy, and hyperlipidemia; non-nucleoside reverse transcriptase inhibitors are associated with neuropsychiatric symptoms, rash, liver toxicity, and lipid abnormalities; and protease inhibitors are associated with gastrointestinal intolerance and glucose and lipid abnormalities [24]. Drug safety is likely to be the most important factor to distinguish one antiretroviral regimen from another [25].

As the elimination of mother-to-child transmission of HIV becomes a reality, more patients are becoming exposed to antiretrovirals *in utero*. With the advent of antiretroviral therapy (ART), the incidence of perinatal HIV-1 transmission has decreased. Antiretroviral therapy is effective in preventing perinatal HIV transmission but may be associated with adverse long-term side effects in exposed infants. Though mothers on HAART regimens may have optimal health, they expose their children to potent drugs and possible toxicity [4].

### Major complications

Antiretroviral toxicity is an increasingly important issue in the management of HIV-infected patients [26]. The effect of antiretroviral (ARV) therapies on the incidence of serious non-AIDS events (SNAEs) has been considered. SNAEs were defined as cardiovascular events (myocardial infarction, ischaemic stroke, peripheral vascular disease, cardiac revascularisation procedure), non-AIDS defining cancer, end stage liver disease, non-traumatic fractures of long torso-bones [27]. It is also associated with long-term complications of peripheral nervous system and the central nervous system [28], has a profound effect on the skeleton and can lead to osteoporosis [29]. Longer time spent receiving HAART and higher CD4 cell counts at HAART initiation were associated with death from non-AIDS causes [30].

**Bone disorders:** *Osteonecrosis* means "bone death." Bone can die if its blood supply is cut off and it can't get nutrients; this is called avascular necrosis. Osteonecrosis occurs in the hip bones of some people with HIV. The bone mineral density is decreases and hip fracture risk increases [29]. *Osteopenia* is a condition in which the bones lose calcium and phosphate minerals and become less dense. This makes the bones weaker. When bone loss becomes more severe, the condition is referred to as *Osteoporosis*. Osteoporosis can be reliably detected by measurement of bone mineral density (BMD) [31]. Continuous ART is associated with decline in BMD [32]. Increased risk of these bone disorders are observed in patients with high intake of HIV protease inhibitors (PIs) [33]. Fracture prevention efforts should be an important consideration in the treatment [34]. Many factors may affect the prevalence of osteopenia and osteoporosis such as age of diagnosis, duration of disease etc [35].

**Muscular disorders:** HIV-infected patients may develop a variety of muscular disorders such as polymyositis, inclusion- body myositis, myopathy secondary to HIV therapy, HIV wasting syndrome, and rhabdomyolysis [36]. HAART therapy increases the risk of their occurrence.

**Cardiovascular disorders:** Recent advances in medicine have led to a significant decline in mortality associated with HIV infection and hence increased life expectancy in HIV-infected individuals. Antiretroviral drugs are associated with higher cardiovascular risk [37]. Cardiovascular complications have become an important health concern in HIV-infected population especially after the introduction of anti-retroviral therapy. HAART regimen and the increased life span of infected individuals on HAART have led to an increased incidence of cardiovascular complications [38]. Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes mellitus and increased incidence is seen in patients with HIV [39]. HAART itself causes in a high proportion of patients a metabolic syndrome, characterized by lipodystrophy/lipoatrophy, dyslipidemia and insulin resistance that may be associated with an increase in peripheral artery and coronary artery diseases [40].

**Neurological disorders:** The prevalence of the most frequent HIV associated neurological disorders and their incidence decreased since the introduction of HAART [41]. Current highly active antiretroviral therapy (HAART) for the treatment of HIV infection is associated with long term side effects. Nucleoside reverse transcriptase inhibitors (NRTIs) are currently an essential part of highly active antiretroviral therapy (HAART) for the treatment of HIV. The use of some dideoxynucleotide analogues may be limited by mitochondrial toxicity leading to distal symmetric polyneuropathy (DSP). Nearly one-third of patients treated with nucleoside reverse transcriptase inhibitors (NRTIs) experience peripheral neuropathic side effects [42]. Alterations in cardiac innervations have been described in HIV infection and AIDS due to autonomic neuropathy [43].

**Liver Disorders:** The liver is the largest organ in the human body, the second to brain in organ complexity. Liver is the main metabolizing organ in the body [44]. It is mainly responsible for the immunologic equilibrium hence any disturbance in its function will compromise the immune state [45]. Treatment of HIV infection with

highly antiretroviral therapy (HAART) may be limited by liver toxicity [46]. Liver disease is a major cause of morbidity and mortality in HIV-infected persons [47]. Abnormalities in liver function are common and may be caused by HIV itself. Coinfection with hepatitis viruses increases the risk of liver toxicity while taking antiretroviral therapy. Hepatotoxicity is a serious complication in patients taking HAART [48]. All antiretroviral drugs classes, NRTIs, NNRTIs and PIs may cause hepatotoxicity but in different pathways [49]. Drug-induced hepatotoxicity is an important cause of acute liver failure [50].

These drugs influence the rate of sustained virological response (SVR) in HIV/HCV-coinfected individuals [51]. Patients who receive protease inhibitors (PIs)-based antiretroviral therapy (ART) show a higher Hepatitis C viremia than those treated with other regimens, mainly those including nonnucleoside reverse transcriptase inhibitors (NNRTI) [52]. Some nucleoside retrotranscriptase inhibitors (NRTI) may decrease the tolerability of HCV therapy due to different interactions and toxicities, reducing the rate of success of such a therapy [51]. Liver disease caused by HIV-1/HCV co-infection is characterized by the inflammation and cell-death. Liver diseases constitute a high proportion of mortalities among HIV-1 patients [53].

**Immune Disorders:** After initiation of Anti-Retroviral Therapy (ART) despite improved immune function, Immune Recovery Inflammatory Syndrome (IRIS) has been observed that is characterized by a paradoxical deterioration of clinical status. It is caused by inflammatory response against the infectious antigen [54]. Suppression of HIV replication by highly active antiretroviral therapy (HAART) often restores protective pathogen-specific immune responses, but in some patients the restored immune response is immunopathological and causes disease immune restoration disease (IRD) [55].

### Metabolic abnormalities

Inspite of the remarkable improvements in the survival and quality of life style in HIV patients with the use of highly active antiretroviral therapy (HAART), various complications such as hyperlipidemia, lipodystrophy, impaired glucose metabolism etc have been observed. Highly active antiretroviral therapy (HAART) was recently associated with disturbance of lipid metabolism, fat mass distribution and insulin resistance [56].

**Glucose abnormalities:** Alterations in the normal glucose levels in blood will lead to abnormal physiological states causing either hypoglycemia (low glucose levels) or hyperglycemia (high glucose levels) [57]. It is also associated with long-term complications of peripheral nervous system and the central nervous system [28], has a profound effect on the skeleton and can lead to osteoporosis [29]. Cardiovascular disease (CVD) is a major complication and a leading cause of early death among persons with diabetes [58]. *Insulin Resistance* is a condition in which the body cannot use insulin effectively and higher concentrations of insulin are required to exert normal effects. Insulin is needed to help control the amount of sugar in the body and is one of the most extensively studied proteins in many fields [59]. The coexistence of obesity, glucose intolerance, dyslipidemia, and hypertension, is termed as insulin resistance syndrome [60]. PIs are mainly responsible for insulin resistance. Diabetes mellitus is a disease of abnormal glucose metabolism resulting in hyperglycemia due to either a deficiency of insulin secretion or insulin resistance or both [61].

Diabetes is a chronic disorder characterized by high levels of glucose in the blood and is a common disorder affecting individuals of all ages. *Hyperglycemia* is a symptom of Diabetes [62]. Increased risk of diabetes mellitus is observed in people taking HAART, specifically protease inhibitors (PIs). Hyperglycemia, new-onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis has been reported in HIV-infected patients taking PIs. Diabetes mellitus, one of the most prevalent diseases in developing world, is a metabolic disorder characterized by hyperglycemia and other metabolic alterations due to relative or absolute insulin deficiency [63]. Treatment with HIV protease inhibitors (PIs) and infection with hepatitis C virus increase the risk of hyperglycemia and diabetes in people with HIV. The risk of developing hyperglycemia is the same with all PIs. People who are older, obese [64], family history with diabetes are also at greater risk for developing hyperglycemia. Hyperglycemia is also associated with excessive free radical generation and oxidant stress [65]. Diabetic patients also have increased risk of fractures [66].

**Lipid abnormalities:** *Hyperlipidemia* is an increase in the amount of fat in the blood. These increases can lead to heart disease and pancreatitis. Some protease inhibitors (PIs) can raise blood lipid (fat) levels. *Lipodystrophy* also called fat redistribution is a disturbance in the way your body produces, uses, and stores fat. It is mainly caused by the high use of protease inhibitors (PIs) and Nucleoside Reverse Transcriptase Inhibitors (NRTIs). There are two different kinds of lipodystrophy. In fat wasting, also known as lipoatrophy, fat is lost from particular areas of the body, especially the arms, legs, face, and buttocks. The second kind of lipodystrophy is fat accumulation, also known as hyperadiposity [33]. Diabetic dyslipidemia is associated with increased risk of cardiovascular disease [67].

## Conclusion

The recent development of HAART has drastically improved the life expectancy of AIDS patients but the long-term use of novel, potent antiviral agents has lead to new problems and complications. Current therapies require lifelong treatment which can be associated with significant toxicity and economic cost. In some instances, the use of cART may be restricted by contraindications, drug resistance, or limited access. There is a need for simple treatment options which provide sustained potency, limited toxicity, a high genetic barrier to development of resistance and also reduced cost.

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