Research Article

Adverse Effect of Highly Active Anti-Retroviral Therapy (HAART) In HIV/AIDS Patients

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ABSTRACT

HIV/AIDS remains the greatest public health concern in the world. With current scenario, HIV-AIDS is considered as a chronic disease due to the advent of highly active antiretroviral therapy that has significantly improved the status of 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. 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. A better understanding of the adverse effects of antiretroviral agents is of interest not only for HIV specialists as they try to optimize therapy, but also for other physicians who care for HIV positive patients. Current article reviews a note on demerits of the therapy, major complications and metabolic abnormalities that occur as a consequence of highly active anti-retroviral therapy (HAART). **Conclusion:** It is critical that all health care providers and patients be trained to recognize the symptoms and signs of most of the adverse drug reactions early on. Proper protocols for management of the condition should be readily available. Adverse event surveillance at facilities offering HAART need to be formalized. Proper surveillance of side-effects will enable evidence-based decisions to be taken to avoid potentially fatal complications.

Keywords: Lactic Acidosis, hypersensitivity rash, neuropsychiatric disorders, hepatotoxicity, co-morbid condition.

INTRODUCTION

The use of highly active anti-retroviral therapy (HAART) has an increasing effect on the quality of life and also has an important impact on the course and treatment of disease and disease-related morbidities in HIV-infected patients.[1] Despite of its high potential for disease management its use is also associated with a number of adverse drug reactions.[2] These adverse reactions and treatment failure are the chief reasons which often results in discontinuation of HAART among HIV-infected patients. The adverse reactions are experienced by 80% of HIV infected patients within the first year of therapy.[3] Highly Active Anti-retroviral Therapy has played the role of a corner stone in management of patients with HIV/AIDS infection.[4] However, many patients discontinue therapy or will require a withdrawal due to the adverse reactions associated with it, resulting in treatment failure.[5] Moreover, antiretro virus therapy (ART) drugs are highly toxic and many drug induced toxicities are associated with its use such as fat redistribution, dyslipidemia, sexual dysfunction, insulin resistance and diabetes, leading to non-compliance and may sometime to discontinuation of the HAART treatment.[6,7] For instance the use of Nucleoside reverse transcriptase inhibitors (NRTI's) has been associated with hypersensitivity reac-

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tions, anemia and neutropenia.[8] Non-nucleoside reverse transcriptase inhibitors (NNRTI's) were linked with rash and hepatotoxicity.[9] Protease Inhibitors (PI's) have also been associated with hyperglycemia, dyslipidemia and gastrointestinal symptoms.[10,11]

In this article we have reviewed the adverse effects of HAART therapy, giving specific attention to the metabolic abnormalities associated with HIV treatment, including dyslipidemias, lipodystrophy syndrome and lactic acidosis associated with NRTI mitochondrial toxicity. Our ultimate goal is to improve and make effective HIV treatment by providing physicians a thorough knowledge of the adverse reactions associated with its use which will help them out in promoting early recognition, reducing potential of developing adverse drug reactions and its management.

Significant Adverse effects of HAART Therapy:

Anti-retroviral therapy can have a wide range of adverse effects on the human body of which there is a mild but common one which occur early in most anti retroviral regimens leading to gastrointestinal effects such as bloating, nausea and diarrhea, which may be time dependent or may persist throughout therapy.[5] Other common adverse effects are like nightmares associated with Efavirenz of NNRTI's and headache and fatigue caused by the use of Zidovudine of NRTI's. Moreover several severe and uncommon adverse effects of HAART therapy also occur like NRTI's associated peripheral neuropathy, anemia, lactic acidosis, hepatic steatosis and hyperlactatemia. Pruritus, nephrolithiasis, ingrown toenails due to the use of Protease inhibitors (PI's) and NNRTI's associated hypersensitivity reactions like rashes and central nervous system toxicity.

Nucleotide Reverse Transcriptase Inhibitors (NRTI'S):

NRTIs are nucleoside analogues that prevent DNA elongation and viral reproduction. This class of ARV drugs consists of several drugs like Zidovudine, Lamivudine, Didanosine, Zalcitabine, Stavudine, Tenofovir, and Abacavir mainly. These drugs are triphosphorylated intracellularly to become nucleotides and are then incorporated into the viral DNA chain by the viral reverse transcription enzyme; their presence in the DNA halts transcription. However recent work has described disruption of mitochondrial function through NRTI-mediated inhibition of human DNA polymerase γ, with subsequent adverse events ranging from nucleoside-associated lactic acidosis to hepatic

Steatosis.[12,13] Some of the important and severe adverse events associated with the use of NRTI's are discussed below.

Lipodystrophy:

Lipodystrophy is part of a metabolic syndrome, characterized by degenerative condition of the body that includes insulin resistance, accelerated bone loss and dyslipidemias. Lipodystrophy affecting HIV-positive patients was first described in 1998.[14] The main clinical features are peripheral fat loss (lipoatrophy) in the face, limbs and buttocks, accompanied by central fat accumulation in the abdomen, breasts, over the dorsocervical spine (the "buffalo hump") and lipomas.[15] NRTIs, especially Stavudine (d4T), has been associated with lipodystrophy.[16] Stavudine-associated lipodystrophy has prevailed 50 to 63% in western studies.[17] Patients who received protease inhibitors (PIs), which independently cause lipodystrophy, were also included in this study, however the risk has been shown to be greater for those initiating HAART with a low CD4 cell count.[18,19] A small South Korean cohort and multiple subsequent east Asian cohorts have shown a 3.5% rate of lipodystrophy.[20-22] In a study carried out at general hospital of Douala (Cameroon), consisting of 339 patients, lipodystrophy accounted for 5.3% of all ADRs.[23] In a study consisting of 410 patients from Chinese ethnicity in Singapore it was found that lipodystrophy affected mood for 36% and social relations for 23% of the patients.[21] The prevalence of lipodystropy in developed countries, associated with stavudine was 50%-63%.[24] In a recent study in Nigeria on HIV/AIDS patients carried out on patients of 38 hospitals lipodystrophy was reported to be 49.9% which is higher than 24.8% in a Rawandan Cohort.[25,26]

Lactic Acidosis:

Lactic acidosis is a serious and uncommon complication of antiretroviral therapy (ART). Its reported incidence rates vary from 1.3 to 10 per 1000 person.[27] The prevalence of hyperlactataemia in outpatients on ART is around 9–16%.[28] Previous studies show that lactic acidosis is caused due to mitochondrial toxicity and the toxicity is developed through the inhibition of mitochondrial DNA polymerase gamma (mt DNA polymerase gama) by nucleotide reverse transcriptase inhibitors (NRTI). Drugs such as stavudine (d4T), didanosine (ddI), and zalcitabine (ddC) induce more messenger transfer DNA (mt DNA) inhibition than others.[29,30] During the Mono therapy era lactic acidosis events reported were mainly Zidovudine associated.[31] A study of University college of London reported that 90% of cases on ZDV therapy at the time of the LA episode were taking it as mono-therapy and the cases of LA associated with ZDV therapy had more advanced disease compared with patients exposed to NRTI other than ZDV. Additionally, the case fatality rate (CFR) among ZDV treated

patients was 68%, compared with 37% for patients not exposed to ZDV.[32] Another study carried out in HIV-infected patients on HAART treatment reported that incidence rate of lactic acidosis ranges from 1.3 to 3.9 cases per 1000 person-years.[33] One more south African study reported that 14 cases of lactic acidosis were diagnosed in 737 persons in which the incidence rate was 19 cases per 1000 person-years of Treatment and all patients were on 2 NRTIs, Stavudine(d4T) and Lamivudine (3TC), with 12 (86%) on efavirenz (EFV) and 2 on nevirapine as the third (non-NRTI) drug.[34] Didanosine and stavudine have higher capacities to inhibit the activity of DNA g-polymerase in vitro than do other NRTIs and have been associated in clinical studies with a higher risk for lactic acidosis in HIV-infected patients.[35,36] Multiple cohort studies and case reports from developing countries which is although relatively infrequent, highlight concerns about timely diagnosis of life-threatening stavudine-induced lactic acidosis, for which women may be at a higher risk.[37-42]

Peripheral Neuropathy:

Peripheral neuropathy is a well-known adverse effect associated with nucleoside reverse transcriptase inhibitors (NRTIs). Peripheral neuropathy is one of the most frequent side effect that occurs during therapy with some nucleoside reverse transcriptase inhibitors, mainly zalcitabine (ddC), didanosine (ddI) and stavudine (d4T).[43] The study of Gordana Dragovic and Djordje Jevtovic reported that out of 112 patients, Peripheral neuropathy developed in 32 patients, who complained of neurological symptoms with manifestation of nerve conduction abnormalities, electric abnormalities, pain, and paresthesia with or without clinical abnormality with the lowest incidence rate (IR) for peripheral neuropathy of 0.13 per 100 person-years was found in the didanosine group while the highest IR was in the didanosine+stavudine group that was 0.18 per 100 person-years.[44] Moreover a study from Malawian cohort reported that 56% of patients have developed peripheral neuropathy while receiving stavudine Therapy.[45]

Anemia (Myelo-suppression):

Studies have consistently shown that the prevalence of anemia is high in the HIV-infected population, particularly among those with AIDS.[46] Although highly active antiretroviral therapy (HAART) has been shown to reduce anemia by rendering the advancement of disease, zidovudine (ZDV), an element of some HAART regimens, has been associated with hematological toxicity.[47-49] After the therapy initiation, Zidovudine-related anemia usually occurs within 3 months.[50] Risk factors include high zidovudine dosage, increased treatment duration, low CD4 cell count, and preexisting anemia.[51] Studies from 8 Nigeria, Co te d'Ivoire, Haiti, and India have found rates of zidovudine- related anemia of 3%–12%.[50-53] A study by Sharma et al from Gujarat has reported 20% of anemia by observing 71% incidence of side effects in their patients who were on HAART.[54] Another study from South India reported a 5.4% incidence of anemia.[50] In SM Curkendall et al, it was reported that 13.0% of patients initiating a ZDV-containing regimen and 8.7% of those initiating another NRTI containing regimen had anemia's.[55]

Non-Nucleotide Reverse Transcriptase Inhibitors (NNRTI'S):

The non-nucleoside reverse transcriptase inhibitors (NNRTI) are potent antiretroviral agents recommended for use in the treatment of HIV infection.[56] The NNRTI bind to a hydrophobic pocket on the reverse transcriptase (RT) enzyme close to the active site and these drugs inhibit HIV-1 allosterically by displacing the catalytic aspartate residues relative to the polymerase binding site.[57] This class of antiretroviral drugs mainly contains nevirapine (NVP), delavirdine (DLV), and efavirenz (EFV). Nevirapine is the most commonly used NNRTI in developing countries because of its lower cost, compared with efavirenz.[58,59] Some of the important and severe adverse effects of NNRTI's are Hypersensitivity rash, hepatotoxicity and Neuro toxicity.

Hypersensitivity Rash:

Hypersensitivity rash is common in patients living with HIV infection. Hypersensitivity rash occurred in 16%–20% of patients in studies reported from developed countries.[5,60] The NRTIs and PIs were not associated with an increase in allergic drug reaction on their introduction; however rashes were diagnosed in 10% to 20% of patients following approval of the NNRTIs.[5] The data for the incidence of NNRTI-associated rashes reported in the literature are highly variable. Only a few studies have directly compared efavirenz and nevirapine.[61] Female patients may be at an increased risk for nevirapine-associated rash.[62,63] Because of little evidence of rash cross-toxicity between the nevirapine and efavirenz, nevirapine therapy can safely be replaced with efavirenz therapy for those who experience adverse reactions.[62,64] Drug rashes usually develop on the tenth day after starting therapy, while in hypersensitivity reactions the symptoms appear after each tablet taken.[61]

Hepatotoxicity:

Hepatotoxicity, liver enzyme elevation and drug interactions are significant complications in HIV patients on HAART. [65] In patients commencing antiretroviral therapy, 14%-20% will experience elevation of liver enzymes.[66] A South African study reported 17% inci-

dence of serious hepatotoxicity among 385 patients receiving nevirapine-based regimens.[67] Another study from Thailand found that 17 (18.6%) of 91 patients receiving nevirapine therapy developed serious hepatitis.[68] Moreover some studies also found that there are high hepatotoxicity rates in HBV and HCV infected HIV patients that are 57.4% and 72.2% respectively while conversely there is increase in the rate of progression to cirrhosis in HBV-HCV co-infected patients on long-term nevirapine use.[69,70] Several studies have found that HCV- and/or HBV-coinfected patients are at increased risk to develop severe hepatotoxicity following initiation of antiretroviral therapy containing HIV-1 protease inhibitors (PIs), particularly ritonavir[71,72] however more recent studies revealed that HIV infected patients in which ARV drugs are increasingly prescribed shows greater effectiveness and tolerability which include HIV-1–specific non-nucleoside analog reverse transcriptase inhibitors (NNRTIs), such as nevirapine (NVP) and efavirenz (EFV), instead of PIs.[73–75]

Neuropsychiatric Disorders:

HIV infection increases the patient's risk for various psychiatric disorders, including depression, mania, psychosis, and substance abuse.[76] Antiretroviral therapy may precipitate or worsen psychiatric disorders.[77,78] With regard to tolerability and adherence, neuropsychiatric disorders are the most concerning adverse effects associated with efavirenz therapy. In western cohorts, one-half of patients have these symptoms at initiation of efavirenz therapy but these symptoms usually resolve within 1 month.[79] A study from Haiti found that 46 (10%) of 452 patients discontinued efavirenz therapy because of persistent neurotoxicity.[52] A study from Coˆte d'Ivoire also found a high neurotoxicity rate (69%) after initiation of efavirenz therapy.[80] CNS side-effects observed with efavirenz include dizziness, headache, confusion, stupor, impaired concentration, agitation, amnesia, depersonalization, hallucinations, insomnia, and abnormal or vivid dreams.[81,82] These side-effects usually resolve within 6–10 weeks after starting treatment for most patients, but for some patients, symptoms seem to wax and wane for long term. In pivotal clinical trials, few patients discontinued treatment as a result while more than 50% of patients taking efavirenz experienced some CNS effects.[83]

Protease Inhibitors:

Prolonged use of highly active antiretroviral therapy (HAART), including protease inhibitors (PIs), is necessary to control HIV infection. PIs are usually indicated in advanced HIV infection, whereas HIV-infected subjects with no sign of disease progression are usually kept PI-naïve.[84] Eight different PIs are presently available according to FDA, saquinavir, ritonavir, indinavir, nelfinavir, atazanavir, darunavir, fosamprenavir and tipranavir.[85] Hyperlipidemia, lipodystrophy, and hyperglycemia are increasingly described adverse side-effects of Protease inhibitors.[86-88]

Dyslipidemia:

Use of HIV PIs has been associated with hyperlipidemia that is more common and more severe than what was observed before the advent of HAART.[88] Sixty-two (47%) of 133 PI recipients at one clinic had lipid abnormalities that met the 1994 NCEP intervention Criteria.[20,89] The dyslipidemia associated with use of HIV PIs often includes hypercholesterolemia. Much of the increase is in the level of very-low density lipoproteins (VLDLs) and, to a lesser extent, intermediate-density lipoproteins (IDLs).[90,91] Increased rates of myocardial infarction are arising as a result of dyslipidemia in HIV-infected patients on antiretroviral (ARV) that have been confirmed by studies such as the D:A:D study which showed associations between exposure to antiretroviral therapy and an increased risk of myocardial infarction.[92-94]

CONCLUSION

The recent development of HAART has highly improved the life expectancy of HIV AIDS patients but the long-term use of novel, potent antiviral agents has led to new problems and complications. Current therapies require lifelong treatment which can be associated with significant toxicities. Antiretroviral therapy is becoming increasingly effective but also gradually complex. The many adverse effects of therapy may cause symptoms affecting a variety of organ systems. Although current antiretroviral regimens are potent from an antiviral perspective, they often fail because of patient non-adherence. To optimize adherence, and hence efficacy, clinicians must focus on preventing adverse effects, and distinguishing ones that are self-limited from those that are potentially serious. There is a need for simple and uncomplicated treatment options which could provide sustained potency and limited toxicity.

CONFLICTS OF INTEREST

The author has no conflict of interest to declare.

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