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AN OVERVIEW ON HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) ADVERSE EFFECTS 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 (HAART) 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 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.*

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INTRODUCTION:

The use of 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 (ADRs) [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 1st year of therapy [3]. HAART 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, antiretroviral 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 reactions, 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 NRTIs 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 ADRs and its management.

Significant Adverse effects of HAART Therapy: ART 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 antiretroviral 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.

1. Nucleotide Reverse Transcriptase Inhibitors (NRTI'S): NRTIs are nucleoside analogues that prevent DNA elongation and viral reproduction. This class of ARV agents 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:

A. ZIDOVUDINE (AZT):

1. ANEMIA & BONE MARROW TOXICITY: AZT can be toxic to the bone marrow the soft tissue inside bones where blood cells are made, can cause anemia (lowered red blood cell levels) and neutropenia (lowered neutrophil or white blood cell counts).

2. LACTIC ACIDOSIS & HEPATIC STEATOSIS: 2 related conditions are, lactic acidosis (a buildup of lactic acid in the blood) and hepatic steatosis (excess fat in the liver), have occurred in some people who have used nucleoside analogues. These conditions can be serious or fatal. They have mostly been seen in women and people who are overweight or who have been on nucleosides a long time. Lactic acidosis is rare (less than 1 case per year for every thousand patients), and has mostly been seen with nucleoside analogues other than AZT.

- increased levels of sugar (glucose)
- increased levels of the hormone insulin
- decreased sensitivity to insulin (insulin resistance)
- decreased levels of HDL-cholesterol (high density lipoprotein) or "good" cholesterol.

3. Common effects: Anemia, neutropenia, headache, fatigue, nausea and myalgia are the most common toxicities.

B. DIDANOSINE: May cause life threatening damage to the liver and a potentially life threatening condition called lactic acidosis. The risk that will develop lactic acidosis may be higher in woman, if overweight or if have been treated with medications for HIV for a long time. If have or have ever had liver disease.

Common effects: shortness of breath, fast breathing, changes in heartbeat, nausea, vomiting, loss of appetite, weight loss, diarrhea, pain in the upper right part of your stomach, unusual bleeding or bruising, yellowing of the skin or eyes, dark colored urine, light colored bowel movements, extreme tiredness, cold or blue colored hands and feet or muscle pain.

C. STAVUDINE:

1. Lactic Acidosis/Severe Hepatomegaly with Steatosis/Hepatic Failure: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and other antiretroviral. Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and Didanosine with other antiretroviral agents. The combination of stavudine and Didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.

2. NEUROLOGIC SYMPTOMS: Peripheral neuropathy, manifested by numbness, tingling or pain in the hands or feet has been reported in patients receiving HAART. Peripheral neuropathy has occurred more frequently in patients with advanced HIV disease, a history of neuropathy or concurrent neurotoxic drug therapy.

3. PANCREATITIS: Fatal and nonfatal pancreatitis has occurred during therapy when HAART was part of a combination regimen that included Didanosine with or without hydroxyurea, in both treatment naive and treatment experienced patients, regardless of degree of immunosuppression. The combination of HAART and Didanosine (with or without hydroxyurea) and any other agents that are toxic to the pancreas should be suspended in patients with suspected pancreatitis. Reinstitution of HAART after a confirmed diagnosis of pancreatitis should be undertaken with particular caution and close patient monitoring. The new regimen should contain neither Didanosine nor hydroxyurea.

4. Other side effects: In addition to peripheral neuropathy, the most frequent side effects observed in studies of adults taking the recommended dose of HAART were headache, diarrhea, rash and nausea and vomiting. Other side effects may include abdominal pain, muscle pain, insomnia, loss of appetite, chills or fever, allergic reactions and blood disorders

D. LAMIVUDINE: Very rarely, lamivudine can cause a decrease in certain types of blood counts. Anemia (a reduced number of red blood cells that can make you feel tired or short of breath), leucopenia (a decrease in the number of white blood cells so that you have a higher risk of bacterial infection) or thrombocytopenia (a decrease in the number of platelets that can increase your risk of bleeding or bruising) may occur. These adverse effects usually occur after you have been on the drug for a long period of time. Blood tests will be done regularly to check for any changes in these values.
Common effect: Fever, Chills, Shortness of Breath, Racing Heartbeat, Fatigue, Bleeding or Bruising.

E. ABACAVIR: The most serious side effect of Abacavir is a hypersensitivity reaction that has the symptoms of a flu-like illness. This happens in about 3 % of people who take Abacavir and can be fatal. Symptoms can include fever and chills, muscle and joint pain, fatigue and feeling rundown, nausea and vomiting, skin rash or shortness of breath.
Other common side effects of Abacavir can include: Skin Rash, Fatigue, Headache, Insomnia, Diarrhea, Nausea, Vomiting, and Muscle Pain.

F. ENTECAVIR: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with antiretrovirals. Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued antihepatitis B therapy, including entecavir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue antihepatitis B therapy.

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 1st 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, has been associated with lipodystrophy.[16] Stavudine associated lipodystrophy has prevailed 50 - 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 CD^{4+} 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 lipodystrophy 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 ART. Its reported incidence rates vary from 1.3 to 10 per 1000 person [27]. The prevalence of hyperlactatemia 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 (NRTIs). Drugs such as stavudine, didanosine and zalcitabine induce more messenger transfer DNA (MT DNA) inhibition than others [29,30]. During the Monotherapy 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 monotherapy 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 and Lamivudine with 12 (86 %) on efavirenz and 2 on nevirapine as the 3rd (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 1 of the most frequent side effect that occurs during therapy with some nucleoside reverse transcriptase inhibitors, mainly zalcitabine, didanosine and stavudine.[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-year [44]. Moreover a study from Malawian cohort reported that 56 % of patients have developed peripheral neuropathy while receiving stavudine therapy [45].

ANEMIA (MYELOSUPPRESSION):

Studies have consistently shown that the prevalence of anemia is high in the HIV infected population, particularly among those with AIDS.[46] Although HAART has been shown to reduce anemia by rendering the advancement of disease, zidovudine and 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 CD^{4+} cell count and preexisting anemia.[51] Studies from 8 Nigeria 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 S M 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].

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

NNRTIs are potent antiretroviral agents recommended for use in the treatment of HIV infection [56]. The NNRTIs 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.

A. EFAVIRENZ:

PSYCHIATRIC SYMPTOMS: Serious psychiatric adverse experiences have been reported in patients treated with EFAVIRENZ. The frequency of specific serious psychiatric events among patients who received SUSTIVA or control regimens, respectively, were severe depression (1.6 %, 0.6 %), suicidal ideation (0.6 %, 0.3 %), nonfatal suicide attempts (0.4 %, 0 %), aggressive behavior (0.4 %, 0.3 %), paranoid reactions (0.4 %, 0.3 %) and manic reactions (0.1 %, 0 %). Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse experiences, with the frequency of each of the above events ranging from 0.3 % for manic reactions to 2.0 % for both severe depression and suicidal ideation and determine whether the risks of continued therapy outweigh the benefits.

NERVOUS SYSTEM SYMPTOMS: These symptoms included, but were not limited to, dizziness (28.1 %), insomnia (16.3 %), impaired concentration (8.3 %), somnolence (7.0 %), abnormal dreams (6.2 %) and hallucinations (1.2 %). These symptoms were severe in 2.0 % of patients and 2.1 % of patients discontinued therapy as a result. These symptoms usually begin during the 1st or 2nd day of therapy and generally resolve after the 1st 2 - 4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5 - 9 %. Patients who experience central nervous system symptoms such as dizziness, impaired concentration, and/or drowsiness should avoid potentially hazardous tasks such as driving or operating machinery.

CONVULSIONS: Convulsions have been observed infrequently in patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medications primarily metabolized by the liver such as phenytoin, carbamazepine, and phenobarbital, may require periodic monitoring of plasma levels. Caution must be taken in any patient with a history of seizures.

FAT REDISTRIBUTION:

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long term consequences of these events are currently unknown.

B. DELAVIRDINE: Delavirdine may inhibit the metabolism of many different drugs (e.g., antiarrhythmics, calcium channel blockers, sedative hypnotics and others), serious and/or life-threatening drug Delavirdine. Delavirdine is metabolized primarily by the liver. Therefore, caution should be exercised when administering RESCRIPTOR Tablets to patients with impaired hepatic function.

IMMUNE RECONSTITUTION SYNDROME: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy During the initial phase of the combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia) Autoimmune disorders (such as Graves' disease, polymyositis and Guillain - Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however the time to onset is more variable and can occur many months after initiation of treatment**.**

SKIN RASH: Severe rash, including rare cases of erythema multiforme and Stevens Johnson syndrome, has been reported in patients. Erythema multiforme and Stevens Johnson Syndrome (SJS) were rarely seen in clinical trials and resolved after withdrawal of DELAVIRDINE. Any patient experiencing severe rash or rash accompanied by symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling and muscle or joint aches should discontinue.

C. ETRAVIRINE:

SEVERE SKIN AND HYPERSENSITIVITY REACTIONS: Severe, potentially life threatening and fatal skin reactions have been reported. These include cases of SJS, toxic epidermal necrolysis and erythema multiforme. Hypersensitivity reactions have

also been reported and were characterized by rash, constitutional findings and sometimes organ dysfunction, including hepatic failure. Discontinue etravirine immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia).

FAT REDISTRIBUTION:
Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long term consequences of these events are currently unknown.

IMMUNE RECONSTITUTION SYNDROME:
It has been reported in patients treated with combination ART. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jiroveci* pneumonia and tuberculosis), which may necessitate further evaluation and treatment.

D. NEVIRAPINE:
The most serious adverse reactions associated with nevirapine are hepatitis/hepatic failure, SJS, toxic epidermal necrolysis and hypersensitivity reactions. Hepatitis/hepatic failure may be associated with signs of hypersensitivity which can include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy or renal dysfunction.

SKIN REACTIONS*:*
Severe and life threatening skin reactions, including fatal cases, have been reported, occurring most frequently during the 1st 6 - weeks of therapy. These have included cases of SJS, toxic epidermal necrolysis and hypersensitivity reactions characterized by rash, constitutional findings and organ dysfunction including hepatic failure.

HEPATIC EVENTS:
Severe life threatening and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure. In some cases, patients presented with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. Fever and flu-like symptoms accompanied some of these hepatic events. Some events, particularly those with rash and other symptoms, have progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, hepatic encephalopathy, prolonged partial thromboplastin time or eosinophilia. Patients with signs or symptoms of hepatitis must be advised to discontinue Nevirapine and immediately seek medical evaluation, which should include liver function tests.

E. RILPIVIRINE:
HEPATOTOXICITY:
Patients with underlying hepatitis B or C virus infection or marked elevations in transaminases prior to treatment may be at increased risk for worsening or development of transaminase elevations. A few cases of hepatic toxicity have been reported in adult patients receiving a rilpivirine containing regimen who had no preexisting hepatic disease or other identifiable risk factors. The patients with underlying hepatic disease such as hepatitis B or C virus infection, or in patients with marked elevations in transaminases prior to treatment initiation. Liver enzyme monitoring should also be considered for patients without preexisting hepatic dysfunction or other risk factors.

DEPRESSIVE DISORDERS:
The adverse reaction depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation).

SKIN & HYPERSENSITIVITY REACTIONS:
Severe skin and hypersensitivity reactions have been reported during the postmarketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with rilpivirine containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries, if signs or symptoms of severe skin or hypersensitivity reactions develop, including but not limited to, severe rash or rash accompanied by fever, blisters, mucosal involvement, conjunctivitis, facial edema, angioedema, hepatitis or eosinophilia.

FAT REDISTRIBUTION:
Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement

(buffalo hump), peripheral wasting, facial wasting, breast enlargement and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy.

HYPERSENSITIVITY RASH:

It 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 % - 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 % incidence 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 co-infected 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 Cote divoire 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 effect [83].

3. 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].

A. AMPRENAVIR: Rifampin should not be used in combination with amprenavir because it reduces plasma concentrations and AUC of amprenavir by about 90 %. A drug interaction study in healthy subjects has shown that ritonavir significantly increases plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasal administered fluticasone propionate. Therefore, coadministration of fluticasone propionate and AGENERASE/ritonavir is not recommended unless the potential benefit to the patient outweighs

the risk of systemic corticosteroid side effects acute hemolytic anemia. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases [89].

B. ATAZANAVIR:

HYPERBILIRUBINEMIA: Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies. No long term safety data are available for patients experiencing persistent elevations in total bilirubin > 5 times ULN. Alternative antiretroviral therapy to this may be considered if jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for patients. Dose reduction of atazanavir is not recommended since long-term efficacy of reduced doses has not been established.

RASH: Rashes were generally mild to moderate maculopapular skin eruptions. Dosing with this drug was often continued without interruption in patients who developed rash. The discontinuation rate for rash in clinical trials was 0.4 %. It should be discontinued if severe rash develops.

HEPATIC IMPAIRMENT & TOXICITY: It is principally metabolized by the liver, caution should be exercised when administering this drug to patients with hepatic impairment because atazanavir concentrations may be increased. Patients with underlying hepatitis B or C viral infections or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. There are no clinical trial data on the use of this/ritonavir in patients with any degree of hepatic impairment.

HEMOPHILIA: There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established

C. NELFINAVIR:

DIABETES MELLITUS/HYPERGLYCEMIA: New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported during post marketing surveillance in HIV infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.[90]

Hemophilia: There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has not been established.

D. INDINAVIR:

HEMOLYTIC ANEMIA: Acute hemolytic anemia, including cases resulting in death, has been reported in patients treated with indinavir. Once a diagnosis is apparent, appropriate measures for the treatment of hemolytic anemia should be instituted, including discontinuation of indinavir.

HEPATITIS: Hepatitis including cases resulting in hepatic failure and death has been reported in patients treated with indinavir. Because the majority of these patients had confounding medical conditions and/or was receiving concomitant therapy (ies), a causal relationship between indinavir and these events has not been established.

4. NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NtRTI):

A. ADEFOVIR:

HEPATIC IMPAIRMENT: The pharmacokinetics of adefovir following a 10 mg single dose of has been studied in non-chronic hepatitis B patients with hepatic impairment. There were no substantial alterations in adefovir pharmacokinetics in patients with moderate and severe hepatic impairment compared to unimpaired patients. No change in adefovir dosing is required in patients with hepatic impairment.

NEPHROTOXICITY: Nephrotoxicity characterized by a delayed onset of gradual increases in serum creatinine and decreases in serum phosphorus was historically shown to be the treatment limiting toxicity of adefovir therapy at substantially higher doses in HIV infected patients (60 and 120 mg daily) and in chronic hepatitis B patients (30 mg daily). Chronic administration of adefovir (10 mg once daily) may result in delayed nephrotoxicity. The overall risk of nephrotoxicity in patients with

adequate renal function is low. However, this is of special importance in patients at risk of or having underlying renal dysfunction and patients taking concomitant nephrotoxic agents such as cyclosporine, tacrolimus, aminoglycosides, vancomycin and non-steroidal antiinflammatory drugs.

LACTIC ACIDOSIS/SEVERE
HEPATOMEGALY WITH STEATOSIS: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors

B. TENOFOVIR:
RENAL IMPAIRMENT: Tenofovir is principally eliminated by the kidney. Dosing interval adjustment is recommended in all patients with creatinine clearance < 50 mL/min. No safety data are available in patients with renal dysfunction who received tenofovir using these dosing guidelines. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia). The majority of these cases occurred in patients with underlying systemic or renal disease or in patients taking nephrotoxic agents, however, some cases occurred in patients without identified risk factors.

LACTIC ACIDOSIS/SEVERE
HEPATOMEGALY WITH STEATOSIS:
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors.

5. FUSION INHIBITOR: Enfuvirtide is the only available agent in this class of antiretroviral drugs. It inhibits fusion of the virus to the cell membrane of the CD^{4+} T cell, thereby preventing HIV from entering the cell.

A. DOLUTEGRAVIR:
HYPERSENSITIVITY REACTIONS:
Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing).

FAT REDISTRIBUTION:
Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

B. ELVITEGRAVIR:
LACTIC ACIDOSIS/SEVERE
HEPATOMEGALY WITH STEATOSIS:
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir DF and emtricitabine, components of stribild, alone or in combination with other antiretrovirals. Treatment with stribild should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

IMMUNE RECONSTITUTION SYNDROME:
Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including stribild. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections. Autoimmune disorders (such as Graves' disease, polymyositis and Guillain - Barré syndrome) [91].

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.

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