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Some Toxic Effects of Antiretroviral Therapy

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ABSTRACT

Antiretroviral therapy (ART) has significantly improved the heath conditions of those living with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). This has encouraged more HIV-positive patients to be enrolled into care. Problem of side effects exists. Some of these side effects are mild and transient; few are serious and life-threatening. There are short term and long term adverse effects. Some short term effects include headache, nausea, diarrhea, mild central nervous system syndrome of lethargy or confusion. Long term toxicities include; myositis, peripheral neuropathy, pancreatitis, and hepatic steatosis. Severe adverse effects have contributed to non-adherence and have caused some patients to delay therapy. Physicians need information on toxicities of ART in order to appropriately weigh the option of second line drugs. HIV- positive patients should be well informed in order to allay anxiety and fear, thereby helping them to adjust to a more tolerable regimen. In conclusion, the numerous benefits of antiretroviral therapy such as decreased risk of progression to AIDS and improvement in physical and mental health far outweigh some adverse effects that may occur.

Keywords: HIV/AIDS, Antiretroviral Therapy and Toxicity.

INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) for the treatment of human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS) has remarkably improved the general condition of those infected with this virus. This led to a significant reduction in AIDS-related morbidity and mortality *(*Palella *et al.,* 1998; Detels *et al.,* 1998; Hogg *et al.,* 1999). This has prompted most HIV-positive patients to embrace therapy. Unfortunately, some

patients may discontinue their initial HAART regimen because of adverse effects, in addition to other factors (Lucas *et al.,* 1999). Adverse effects, therefore, may create intentional non-adherence (Nachega *et al.,* 2011).

ANTIRETROVIRAL THERAPY

Combination antiretroviral therapy or HAART is the cornerstone of management of patients with HIV infection. The clinical effectiveness of antiretroviral therapy has improved markedly over the past few years. Adverse effects associated with these drugs have been documented. These side effects are, however, less with some of the newer recommended treatments (Vogel *et al.,* 2010).

Currently licensed drugs for the treatment of HIV infection fall into two main categories:

- Those that inhibit the viral reverse transcriptase enzyme.
- Those that inhibit the viral protease enzyme.

The reverse transcriptase inhibitors include the nucleoside analogues: Zidovudine (AZT); Lamivudine (ZTC), Emtricitabine (FTC), Stavudine (d4T), Abacavir (ABC), Didanosine (ddI), Tenofovir (TDF), Zalcitabine.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) include: efavirenz (EFV), nevirapine (NVP), delavirdine.

The reverse transcriptase inhibitors block HIV replication cycle at the point of RNA dependent DNA synthesis, the reverse transcription step. While the non- nucleoside reverse transcriptase inhibitors are quite selective for the HIV-1 reverse transcriptase, the nucleoside analogues inhibit a variety of DNA polymerization reactions in addition to those of the HIV-1 reverse transcriptase. For these reason, serious side effects are more common with the nucleoside analogues and include mitochondrial damage that can lead to hepatic steatosis and lactic acidosis as well as peripheral neuropathy and pancreatitis.

Protease inhibitors (PIs) include: Lopinavir/r (LPV/r), Indinavir (IDV), Saquinavir (SQV), Ritonavir (RTV). They bind competitively to the substrate site of the viral protease enzyme. This enzyme is responsible for the post-translational processing and cleavage of large structural core protein during budding from the infected cell. Inhibition results in the production of immature virus particles.

Adverse effects refer to unwanted effects of a drug or class of drugs on a patient. While some affects are relatively specific to one of the HIV

drug classes (e.g. rash with NNTIs or gastrointestinal complaints with protease inhibitors), each drug has its own set of side effects or may cause problems in particular circumstances. There is the host (patient) factor. Thus side effects may vary widely among patients (Volberding, 2003).

Antiretrovival therapy (ART) can have a wide range of adverse effects on the human body. These effects are generally categorized into two: short-term and long-term HIV drug toxicities. Short-term HIV drug toxicity is common and can contribute to early drug discontinuation and non-adherence. The symptoms include gastrointestinal effects such as bloating, nausea, and diarrhea which may be transient or may persist through out therapy (Carr and Cooper, 2000). Zidovudine, for example, is known to cause headache, nausea, and a mild central nervous system syndrome of lethargy or confusion. Similarly, nevirapine causes an early rash in up to 20% of patients, and many treated with nelfinavir experience diarrhea (Volberding, 2003). Nightmares are associated with efavirenz (EFV). Some early side effects are treatable, many are transient and few are serious.

Long-term antiretroviral toxicities are more problematic. Cases of myositis, peripheral neuropathy, pancreatitis, and hepatic steatosis were recognized as associated with nucleoside analogue therapy when that was the only available drug class. Such cases now also occasionally associated with moderate to severe lactic acidemia, continue to be seen and are speculated to be due to drug-associated mitochondrial toxicity (Lonergan *et al.,* 2000; Masur, 2001). Furthermore, fat atrophy (most noticeable on the face) is believed to be a consequence of nucleoside analogue-induced mitochondrial damage (Bogner *et al.,* 2001; Dube *et al.,* 2000).

There is increasing reports of metabolic abnormalities such as impaired glucose metabolism and insulin resistance, lactic acidosis, osteopenia and dyslipidemia. Distressing morphologic changes in body habitus associated with these metabolic abnormalities are characterized by accumulation of fats in the abdomen (visceral fat compartment) and in the dorsocervical area of the neck, as well as by the depletion of fat in the face, buttocks, and extremities (Chow *et al.,* 2006). Metabolic toxicities may manifest as osteopenia and avascular necrosis of

the femoral head (Monier *et al.,* 2000). As with other side effects, the metabolic toxicities are not possible to predict or to avoid and, once established are at best partially reversible (Dube *et al.,* 2000).The causes of the metabolic disturbances and morphologic changes related to ART are not well elucidated. The aetiology is likely to involve the effect of HIV itself as well as the direct and indirect effects of ART, super-imposed on individual characteristics such as genetic predisposition, gander, and age (Chow *et al.,* 2006).

SKIN RASH

Rash is a common adverse effect of the NNRTIs, particularly nevirapine. Approximately 16% of patients taking this agent experience a mild to moderate maculopapular rash, with or without pruritus, on the trunk, face and extremities, within the first 6 weeks on therapy (Fagot *et al.,* 2001). Severe rashes occur in about 6.5% of nevirapine-treated patients, mainly during the first 4 weeks of treatment, including Stevens-Johnson syndrome and toxic epidermal necrolysis in less than 1% of all patients treated with nevirapine (Fagot *et al.,* 2001). Although most rashes are self-limiting, nevirapine should be permanently discontinued if the rash is severe or accompanied by constitutional symptoms (Dybul *et al.,* 2002).

While the nucleoside analogue abacavir is generally well tolerated, it causes a hypersensitivity syndrome in 3% to 5% of patients (Clay, 2002; Hewitt, 2002), who present with non-specific symptoms (including malaise and fever with or without rash) starting during the first 6 weeks of treatment. However, the true basal incidence is difficult to establish as inter-study variability is high due to the influence of certain patient characteristics, in particular ethnicity, with rates being significantly higher in Caucasians than in patients of African descent (Hetherington *et al.,* 2002; Symonds *et al.,* 2002).Symptoms usually develop early on in therapy. Some case-cohort studies identified a genetic risk factor for abacavir hypersensitivity (Rockstroh *et al.,* 2007). Re-challenge with abacavir after hypersensitivity reaction should not be attempted as severe symptoms may occur rapidly, including life-threatening hypotension and death (Montessori *et al.,* 2004).

DYSLIPIDEMIA

Dyslipidemia refers to abnormality of lipid metabolism. The level of this disorder associated with increased risk of cardiovascular disease occurs in about 70% of HIV-1 infected patients receiving antiretroviral therapy (Lucas *et al.,* 1999; Friis-Moller *et al.,* 2003). Features of

dyslipidemia in this syndrome include severe hypertriglyceridemia, low levels of high density lipoprotein (HDL) cholesterol and elevation of low-density lipoprotein (LDL) cholesterol. The dyslipidemia is more profound among those receiving PIs and in those with fat redistribution (lipoaccumulation or lipoatrophy) (Lucas, 1999).

NRTIs appear to have less of a tendency than PIs to cause dyslipidemia, particularly on a short-term basis. The combination of ZDV/ZTC/ABC given as a first-time antiretroviral regimen to antiretroviral-naïve subjects caused little or no changes in triglyceride and cholesterol levels over the first 24-week period of administration (Shikuma *et al.,* 2006). However, d4T has been demonstrated to cause dyslipidemia (Domingo *et al.,* 2004).

BONE DISEASE (OSTEONECROSIS)

Osteonecrosis or avascular necrosis is defined as bone tissue death as a result of compromised blood flow to bone. Osteonecrosis has been reported in the setting of HIV infection even prior to the availability of potent ART (Blacksin *et al.,* 1999; Goorney *et al.,* 1990; Gerster *et al.,* 1991). Affected bones included the femoral head and condyle, humeral head, proximal tibia, and bones of the hand and wrist. Interruption of the vascular supply to bone results in a stepwise progression through ischemia, hyperemia, an increase in intraosseous pressure and eventually death of osteocytes. Osteonecrosis usually affects bone closest to the joint space. It occurs rarely in HIV Patients.

Magnetic Resonance Imaging (MRI) studies reveal subchondral luceny followed by the collapse of bone and narrowing of the joint space. Although rare, osteonecrosis has been seen in patients with advanced HIV disease and in males between the ages of 20 and 50 years, with majority of affected patients having at least one risk factor previously associated with osteonecrosis on the HIV- uninfected population (Glesby *et al.,* 2001, Gutierrez *et al.,* 2002).

Osteoporosis and Osteopenia are associated with HAART. The diagnosis of osteoporosis is based on measurement of bone mineral density, which can be accomplished by a variety of techniques. The current standard of care and the most widely accepted method is dual-energy X-ray absorptiometry (DEXA) at the spine and hip (Khan *et al.,* 2002). After the introduction of HAART, Tebas *et al.,* (2000) reported a cross-sectional DEXA analysis of whole body, lumbar spine

and proximal femur bone mineral density in 112 male subjects: 50% of the HIV- positive patients receiving PIs, but only 23% of HIV-positive patients not receiving PIs and 29% of healthy seronegative controls had osteoporosis or osteopenia.

FAT MALDISTRIBUTION

Body fat abnormalities have been reported to include, singularly or in combination, central fat accumulation, evidenced by increased abdominal girth (due to increase in visceral fat), development of dorsocervical fat pad ("buffalo lump"), and breast enlargement, as well as loss of peripheral subcutaneous fat (lipoatrophy).The latter designation includes subcutaneous fat loss of the extremities, buttocks, and face. The combination of these morphologic changes and antiretroviral-associated metabolic derangements has been referred to as the lipodystrophy syndrome. The lipodystrophy syndrome can be distressing to HIV- positive patients on ART and has been linked with both short-term and long-term failure to comply with antiretroviral regimens (Duran *et al.,* 2001). PI therapy has been most strongly linked to the lipodystrophy syndrome, although NRTIs, especially d4T have also been associated with lipodystrophy (Saint-Marc *et al.,* 1999).

HYPERLACTATEMIA AND LACTIC ACIDOSIS

Lactic acidemia has been associated with NRTI use (Lewis and Dalakis 1995; Lai *et al.,* 1991; Bissuel *et al.,* 1994).Lactic acidemia refers to increased plasma lactate (Hyperlactatemia) that does not cause an abnormal blood pH, whereas lactic acidosis consists of a high lactate level accompanied by metabolic acidosis and decreased blood pH. The spectrum of disease within this syndrome ranges from fulminant decompensated multiorgan dysfunction characterized by severe acidosis and hemodynamic instability, to less severe symptomatic hyperlactatemia with hepatic steatosis (fatty liver), to intermittent chronic low-grade hyperlactatemia without acidosis, steatosis or symptoms. The clinical course is characterized by often vague complaints of malaise, nausea and vomiting, fatigue and tachypnea (Antoniou *et al.,* 2003), followed by liver failure, cardiac dysrhythmias and death (Montessori *et al.,* 2004).

There is no cause for alarm in a condition of asymptomatic low-level increase in lactate, as there is no conclusive evidence that asymptomatic lactate elevations are dangerous in the short-term or predictive of more severe lactic acidemia (McComsey and Yau, 2004). Because there is no way to predict who will develop lactic acidemia,

patients on NRTI therapy should be made aware of the signs and symptoms of the syndrome and of the need to seek medical care promptly should these occur.

HEPATOTOXICITY

Hepatotoxicity is associated with most of the antiretroviral agents, although initially most concern focused on the PIs. The hepatotoxicity of this drug class varies with the specific drug. In a prospective cohort study, 30% of patients who initiated treatment with ritonavir, but only 6% to7% of those who initiated therapy with squinavir, nelfinavir or indinavir experienced severe hepatotoxicity (defined as grade 3 or 4 change in the serum levels of alanine aminotransferase and aspartate aminotransferase) (Sulkowski *et al.,* 2000).The rate of severe hepatotoxicity associated with any PI among patients with hepatitis C infection was 12% twice as high as among patients without hepatitis C infection (Montessori *et al.,* 2004). The NNRTIs are also associated with hepatotoxicity. Reisler *et al.,* (2001) reported that the rate of hepatotoxicity was 8.9% and 10.8% respectively, among patients receiving nevirapine and efavirenz.

FOLLOW-UP

Routine laboratory monitoring should be done approximately every 3 months to determine whether the patient has asymptomatic abnormalities. Monitoring laboratory tests include complete and differential blood counts and measurements of creatinine, electrolyte, liver transaminase, bilirubin and amylase levels. Patients should also be monitored at regular intervals (approximately every 3 months) for dyslipidemia, diabetes and lipoaccumulation or lipoatrophy. This laboratory work should include determination of total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride and fasting blood glucose levels. Information should be elicited from patient and physical examination done for changes in fat distribution. Changes in therapy because of toxicity, non-adherence or non-tolerability do occur. If the regimen is otherwise successful, any single drug can be substituted ideally for another better tolerated one of at least equal potency.

CONCLUSION

Antiretroviral therapy has significantly improved the quality of life of those living with HIV/AIDS. The impact is so dramatic and substantial that many HIV- positive patients are beginning to lead normal lives: going back to business,

continuing with higher educational pursuits. This has prompted some people to regard HIV/AIDS as a chronic illness instead of a life-threatening disease.

Antiretroviral therapy is not without side effects. Some of these adverse effects are mild and transient, few are serious and may warrant switch to second- line drug. It is pertinent for treating physicians to recognize these side effects early and act accordingly. On the other hand patients need to be well informed so as to allay anxiety and prevent intentional non-adherence. The benefits of antiretroviral therapy far outweigh some of these adverse effects.

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