A Review: Human Immunodeficiency Virus Positive Adults on Antiretroviral Therapy and the Onset of Metabolic Complications

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Summary

Human immunodeficiency virus infection of adults on antiretroviral therapy is one of the major public health problems associated with considerable metabolic complications worldwide. The onset of these complications, present an obstacle to effective treatment. Genetic recombination and selection can over time result in the accumulation of various viral mutations and can thus multiply blood-viral load. One of the major indicators of these conditions may be human immunodeficiency virus associated distressing changes in the body such as diabetes mellitus and kidney disease. Although distinct mechanisms exist for each of these conditions, it has now become evident that interplay between two or more complications is frequently responsible for high levels of short-term and long-term therapeutic failures among these HIV infected adults. Even more distressing for these adults is that, clinical features such as lipohypertrophy and lipoatrophy may also be seen among some of some individuals.

Therefore, prevention and management of these complications pose an important challenge for the care of HIV-infected individuals. This is because uncontrolled replication of HIV, may contribute to the onset of metabolic complications such as cardiovascular disease. This is also complicated by the fact that other interventions have either not been sufficiently studied or are known to induce the onset of other metabolic complications. Perhaps a better use of antiretroviral therapy and understanding of the progression of HIV-infection, plus understanding of alternative therapy could manage these metabolic complications and help to avoid risk factors and negative effects associated with antiretroviral therapy.

The molecular basis of these entire cellular and body morphological processes remains to be determined. Therefore, in addition to improving the quality of life of adults infected with HIV and by identifying the role of antiretroviral therapy and/or alternative therapy in the development to metabolic complications; data on these could be used to elucidate these processes.

Introduction

Among HIV-infected adults on antiretroviral therapy (ART), there are serious side effects at molecular level due to cellular dysfunction. These may be characterized by impairment of oxidative phosphorylation that could lead to metabolic syndrome (MetS). Metabolic syndrome refers to a group of metabolic and vascular disorders that occur simultaneously and is frequently defined as having three or more of the following: high blood pressure, high glucose levels, large waist circumference, low high-density lipoprotein cholesterol (HDL-C) levels, and high triglyceride levels [1].

Over the past two decades in developed countries, implementation of highly active antiretroviral therapy (HAART) for patients infected with HIV has led to a dramatic reduction in AIDS-related mortality in both children and adults. At the same time, the prevalence of abnormalities of fat distribution and disorders of lipid and carbohydrate metabolism has significantly increased [2]. Clearly, the individual clinical features that make up these metabolic complications are predictive of clinical outcomes.

HIV-related metabolic alterations are associated with both the infection itself and the use of HAART. Some treatment regimens, especially those including nucleoside reverse transcriptase inhibitors (NRTIs) and/or protease inhibitors have been linked with insulin resistance, diabetes mellitus, dyslipidaemia, changes in body fat distribution and the risk of cardiovascular disease (CVD). The pathogenic mechanisms involved in these metabolic disorders are complex and include a direct effect of the drugs on lipid metabolism, adipocyte function, endothelial cells, mitochondria and proinflammatory cytokines; related host risk factors, such as race, age, sex and lifestyle habits, have also been described in HIV-infected patients. Insulin resistance is increasingly recognized as a chronic, low-level, inflammatory state. Hyperinsulinemia and the action of insulin have been proposed as common factors preceding hypertension, low HDL-C levels, hypertriglyceridemia, abdominal obesity and altered glucose tolerance, and all these abnormalities are linked to the development of coronary heart disease [2].

In addition to improving the quality of life in patients infected with HIV, and by identifying the role of HAART in the metabolic
complications development: the data on onset of these metabolic complications and accompanying drug toxicities that could be, in part, related to dysfunctional cellular processes that cause an increased electron “leakage” from the respiratory chain during oxidative phosphorylation with a consequent generation of reactive oxygen species (ROS), could be used to elucidate these processes.

World-wide, more than 35 million people are infected with HIV. The introduction of combination antiretroviral therapy (cART) has led to a decrease in morbidity and mortality in this population. As a result, life expectancy has increased, causing an epidemiological shift from AIDS-related to non-AIDS related disease such as CVD. Traditional and HIV-specific CVD risk factors combined with cART–related metabolic complications increase 1.5–2-fold in HIV-infected patients compared with HIV-uninfected patients [3].

**Metabolic Syndrome Before and after Initiation of HAART**

HIV positive adults need changes in their antiretroviral therapy because of their suppressed viral load in plasma. Thus, it is important to manage drug toxicity and intolerance, to improve poor adherence, and avoid drug interactions and pill burden. Long-term use due to the success of antiretroviral therapy (ART) [4], is complicated by the subsequent onset of different metabolic complications caused by either antiretroviral therapy interactions or increased viral load. The scenario is even more challenging because some HIV-positive adults across the world have actually never experienced viral suppression while receiving ART and have no evidence of drug resistance. Therefore, switching to any of the acceptable first-line therapies is expected to maintain virologic suppression [5]. Can this happen without the onset of key metabolic complications? Particularly, amongst these HIV positive adults, it may be also be difficult to know whether the discontinuation of one of the ARTs in a suppressive regimen constitute the removal of the onset of any one of the known metabolic complications.

Knowledge of the intracellular trafficking of viral proteins and the role of the polyprotein Gag of HIV-1 suggests that this process, once locked, would change the viral replication cycle by preventing formation of mature forms of the virus. The hypothesis is that the ART regimen will cause mitochondrial disturbances by inhibiting the mitochondrial DNA (mtDNA)-polymerase γ, leading to mitochondrial DNA depletion, respiratory chain dysfunction and reduced energy production by cells [5].

However, HIV has become a manageable (though incurable) entity since the introduction of HAART in the mid-1990s. As HIV infected patients live longer, non AIDS illnesses which were of secondary concern during the early days of HIV/AIDS epidemic are becoming increasingly important sources of morbidity and mortality in HIV-infected population [6]. The onset of these metabolic complications due to lipid and glucose metabolism, lead not only to cellular alterations but also to fat redistribution with lipoatrophy due to fat gain.

Therefore, of other metabolic complications such as liver disease accounts for an increasing proportion of non-AIDS death. While multiple mechanisms of liver disease exist in this population, viral hepatitis, particularly co-infection with hepatitis C virus (HCV), is common in patients with HIV infection. This HIV-HCV co-infected population represents a unique challenge to clinicians who must manage their patients’ HIV while remaining vigilant for progression of their coexistent liver [6].

This is also accompanied by body shape abnormalities and is named “HIV-associated lipodystrophy syndrome” [7]. These changes include cellular mitochondrial dysfunction. They are also associated with physiological, environmental and pathological insults such or endoplasmic reticulum (ER) stress, in which a collection of conserved intracellular signalling pathways, termed the unfolded protein response (UPR), are activated to maintain ER function for cell survival [8]. This is also to maintain homeostasis.

Ritonavir is one of the most representative therapeutic agents in this category of ART-associated metabolic complications. In combination with lopinavir it confers higher risks for cardiovascular disease (CVD) in HIV-1 patients. The kidney is also affected because of CVD. It is interesting that amprenavir and nelfinavir promote lower impacts compared to the therapy with lopinavir/ritonavir [8].

For HIV-infected adults, recent years have been marked by the introduction of ART representing a new perspective of improved life for these individuals. The use of these drugs has shown to effectively suppress the replication of HIV and dramatically reduce incidence of mortality and morbidity. This has led to a better and longer quality of life for these people. Apart from the substantial benefits that results from the use of different drug regimens, laboratory and clinical experience has shown in the past that ARVs can induce severe and considerable adverse effects related to metabolic complications of lipid metabolism. This is characterized by signs of lipodystrophy, insulin resistance, central adiposity, dyslipidaemia, increased risk of cardiovascular disease and even an increased risk of atherosclerosis [9]. In this article, I review a few of the onsets of metabolic complications in HIV positive adults on ART and develop strategies for modifying these therapies while maintaining long-term suppressed viral load.

**Potential Mechanisms**

The mechanisms that trigger the onset of metabolic complications in HIV positive adults on ART are the subject of on-going debate. The introduction of antiretroviral drugs for HIV-infected patients in the early nineties (1990) represented a new perspective on life for these people [9].

The proposed mechanism is that ART in HIV-infected adults affect the heart, leading to the development of cardiovascular disease or other metabolic complications. On the other hand, it is viral load and not ART that is responsible for the onset of these metabolic complications. Whatever reasons, advances in retroviral therapy are clear: HIV positive adults enjoy a better quality of life and a higher quality of life. Of course, the use of ART has shown to effectively suppress the replication of HIV-1 and dramatically reduce mortality and morbidity and a better and longer quality of life for HIV-1 patients [9]. New approaches for curing HIV-1
infection continue, and different challenges are the focus of many studies. Suppression of viral load could be monitored using nucleic acid tests to assess viral levels.

Perhaps, we could develop new ARV drugs that could mutate HIV attachment sites in the first place. The different ART regimens, all composed of at least three different antiretroviral drugs, are effective in reducing viral load (HIV-1-RNA) to undetectable levels after its inception. More recently, approaches that target the intracellular trafficking of viral proteins and post-translational modifications of viral proteins have been considered as promising new treatments [9]. If you mimic the amino acids responsible for the synthesis of HIV receptors you may solve the essential problem.

Therefore, inhibitors could block viral maturation by interrupting the final stage of processing the Gag protein or by inhibiting intermolecular bond to the capsid protein immature [9].

**Cellular Mechanisms**

Mitochondrial alterations could be induced by HIV infection because as the virus enters the host cell, its RNA is translated into DNA, and then inserted in the DNA of the cell. From here, the HIV is replicated and will remain within the cell even after it divides. This disruption in the mitochondrial respiratory process may cause the onset of metabolic complications in adipocytes, promote lipodystrophy syndrome and increase lipid levels in plasma. In particular, interference between protease inhibitors (PIs) and cellular proteases could also trigger the development of other metabolic alterations because some proteases are essential for mitochondrial biogenesis and metabolic function. Furthermore, functional changes of mitochondria in skeletal tissue promote insulin resistance and consequent dyslipidaemia [9].

**Hormonal Mechanisms**

Since the onset of HIV epidemic, HIV has been associated with a wide range of complex and interrelated hormonal, reproductive and metabolic abnormalities (endocrine abnormalities). These are often related to progressive HIV infection, opportunistic disease, immune reconstitution and combination antiretroviral therapy (cART) and affect every facet of the endocrine axis. Endocrine abnormalities associated with long-term HIV infection and therapy includes hypothyroidism, hyperthyroidism, adrenal insufficiency or excess insulin resistance and type 2 diabetes mellitus [10].

One of the limitations in clinical set ups is that to achieve maximal and durable suppression of HIV viral load. Practices must include the maximization of the patient’s adherence to ART, the rational use of ART, the preservation of future treatment options, and the use of viral load and drug resistance testing to guide changes in therapy that could be effective.

The development of endocrine abnormalities in HIV positive persons is believed to be multifactorial, with the precise pathogenesis of these disorders remaining unknown. Despite this, it appears that systemic inflammation is similarly associated with both the onset of endocrine/metabolic dysfunction and HIV positive status. Untreated HIV infection results in elevated cytokine levels, which decrease upon initiation of HIV therapy. However, despite viral suppression with cART, some inflammatory markers and cytokines such as interleukin (IL)-6, C reactive protein (CRP) and tumour necrosis factor alpha (TNF-α) remain elevated. These markers are also associated with altered sex steroid levels, onset of type 2 diabetes mellitus (T2DM) in HIV infection and have been shown to be associated with altered glucocorticoid secretion [10].

**Inflammation and Ageing Mechanisms**

The association between systemic inflammation and treated HIV infection parallel that of inflammation and ageing as they share similar mechanisms. HIV infection induces inflammation, causing oxidative stress that damages both telomeres and mitochondrial DNA (mt DNA). Telomeres are repetitive DNA sequence that cap and protect the ends of chromosomes and maintain chromosome stability. Telomere is the basis of a widely accepted theory of ageing [10].

Nonadherence to ART is associated with incomplete and non-contiguous HIV viral load suppression. This leads to ineffective control of viral load and an increased risk of viral mutations associated with drug resistance. In particular, to establish baseline profiles of metabolic complications from HIV-infected adults on ART, an adherence of greater than 95% for ART is needed by HIV-infected individuals, a percentage that may be difficult because ART are expensive, extremely intricate in terms of timing and dietary restrictions, and also considerable pill burden.

**Immunological Mechanisms**

HAART has transformed the HIV epidemic by not only dramatically reducing mortality and mobility, but also modifying the value of virological and immunological disease markers. Accordingly, several virologic and immunological markers have been reassessed in post-HAART era for their significance in predicting both the risk of progression to AIDS and death. Among such markers, IL-6 levels have become a highly valuable predictor of morbidity and mortality [11].

The high predictive value of IL-6 have been associated with increased risk of developing multiple infections, cardiovascular disease, diabetes and neuropsychological disorders.

ART improves the health of persons living with HIV by delaying disease progression through suppression of viral replication and facilitating CD4 cell count recovery, while also greatly reducing the risk of transmitting HIV to others. Recent evidence indicates that initiating ART as soon as possible after HIV diagnosis is optimal for improved health, increased lifespan and HIV prevention [12].

Total CD4 counts predict HIV disease progression but do not necessarily reflect normalization of immune function [13].

**Current Major Problem of HIV Management**

Cardiovascular diseases (CVDs) such as hypertension, atherosclerotic disease and heart failure may be increasing, as this could be exacerbated by the high number of HIV-infected adults. The HIV-infected adult population is ageing and, since age may
be one of a major non-modifiable risk factor for CVD, the risk for CVD may be expected to increase progressively amongst these HIV-infected adults.

These patients are still higher than in the general population and non-AIDS-related morbidity and mortality is increasing. CVD, particularly ischemic heart disease, is an important cause of morbidity and mortality among these HIV-infected individuals. Although traditional cardiovascular risk factors are highly prevalent and accepted to play a role in HIV-associated cardiovascular disease, the role of long-term cART and HIV infection itself remains controversial [14].

Compared to CVD, HIV infection amongst adults could also be associated with an increase in metabolic complications such as insulin resistance, dyslipidaemia, lipodystrophy, endothelial dysfunction, accelerated atherosclerosis and coagulation abnormalities. Lipid disorders, characterized by low high-density lipoprotein cholesterol (HDL-C) and high triglyceride (TG) levels form a large part of the risk for CVD in the HIV-infected adult population, and may be related to the HIV infection itself, ART or both [15].

It would be interesting to find out whether HIV-infected adults could under normal circumstances, have lower fasting TG and higher HDL-C levels than people who are ART naïve. In addition, for CVD risk factors seen in the general population, there are specific factors in people living with HIV that could increase risk, i.e. chronic inflammation, metabolic changes associated with the infection, its therapy and other metabolic complications such as chronic kidney disease [16].

Early identification and management of CVD complications is, therefore, necessary, but also difficult as resources may not always be readily available. The development of a non-invasive tool to help identify adults who are most likely to derive clinical benefit from CVD risk-reduction therapy is, therefore, very important. It would be interesting to identify the most important risk factors for the development of CVD in a cohort of HIV-infected adults.

Adherence to antiretroviral medication is a critical component of HIV treatment and management. The probability of the progression to AIDS and death decreases with consistent and proper adherence to antiretroviral therapy (ART), and poor adherence can result in negative health outcomes and treatment-resistant strains of the virus. Among adolescents and young adults living with HIV, rates of suboptimal adherence produce poorer outcomes than their adult counterparts. In the US and globally, adolescents living with HIV face unique barriers to maintaining high adherence levels because they progress through major milestones in cognitive and social development and transition to adult HIV care. Compared with adults, adolescents and young adults in the United States have poorer retention in care, a larger delay in the initiation of ART, and lower rates of virological suppression [17].

Underlying Mechanism Under Post-HAART Era

Initiation of ART during acute HIV infection (AHI) could offer particular benefits to patients by limiting the establishment of latent viral reservoirs, decreasing systemic inflammation, and improving immune reconstitution. The immediate goal of therapy initiated during AHI, as in chronic infection, is virologic suppression. However, the optimal strategies for virologic suppression and identifying virologic failure after initiation of ART during AHI have not been defined [18].

The search for different HAART strategies to reverse the onset of metabolic complications while maintaining long-term suppressed viral load has led to the use of less metabolically active antiretroviral drugs without compromising antiretroviral efficacy. This helps to maintain long term suppressed viral load. This also delays the onset of metabolic complications.

Current Progress in the Therapeutic Management of HIV-Associated Metabolic Complications

Although distinct mechanisms exist for the metabolic complications in HIV-infected adults, it has now become apparent that current highly active antiretroviral therapy (HAART) regimens do not produce the significant side effects and long-term toxicity that characterized many older ART regimens. It is often possible to identify a drug that causes side effects for a given patient. The one-pill, once-daily regimens substantially reduce pill burden, and the potency and barrier to viral resistance for any of the current preferred ART regimens are high [19].

Current Limitations and Future Direction

Although the association of CVD with early protease inhibitors has been well documented, still controversial is its relationship with nucleoside reverse transcriptase inhibitors, particularly abacavir. Several studies have demonstrated an increased risk of MI and overall CVD events among abacavir users, whereas others have found no association [20].

Because evidence of an increased CVD risk among abacavir users has been based on observational rather than randomized studies, concerns have been raised about bias. Specifically, patients with CVD risk factors such as renal dysfunction have been prescribed abacavir-containing ART to avoid the nephrotoxicity associated with tenofovir (ie, confounding by indication). Similarly, patients who develop nephrotoxicity on tenofovir-containing regimens may be more likely to switch onto abacavir and thus be censored in per-protocol analyses (ie, selection bias). Both of these scenarios could result in an apparent higher risk of CVD among abacavir users that is not caused by the medication. Thus, we evaluated the effect of abacavir on CVD in a large cohort study of HIV-infected individuals initiating ART, using inverse-probability weighting (IPW) estimation to account for confounding and time-varying selection bias introduced by renal dysfunction and other risk factors [20].

Switching away from thymidine NRTIs is the only recommended strategy to restore subcutaneous fat in patients with HIV-associated lipoatrophy, but improvement is slow and limited. Whether or not changes in antiretroviral drugs other than Thymidine NRTIs will have an additional body fat impact in HIV-infected patients with lipoatrophy who already had thymidine NRTIs discontinued in
Adherence to (or compliance with) a medication regimen is generally defined as the extent to which patients take medications as prescribed by their health care providers. One way to quantify adherence is to estimate the proportion of prescribed doses taken in a specific time period. Self-reported data collected in the concluded clinical trials indicate that the overall adherence to PrEP was high. However, measures of drug detected in biological specimens showed much lower adherence than self-reported, likely contributing to the failure of 2 clinical trials to demonstrate PrEP efficacy [22].

ART initiation, leading to viral suppression and CD4 count gain, often results in weight gain [23]. Possible mechanisms include a reduction in metabolic requirements as well as inflammation in those with suppressed viral load, a return to good health and resumption of “normal” lifestyles and, possibly, the effects of individual ART [23].

Sex steroid hormones [ ethinyl / estradiol (EE2) and progesterin] and certain antiretrovirals(ARVs), such as non-nucleoside reverse transcriptase inhibitors like nevirapine and EFV, and protease inhibitors like LPV / r have common metabolic pathways, mainly via the cytochrome P450 enzyme system, especially Cyp 3A4. As a result, the blood levels of both hormones and ARVs could be affected with concomitant use- a consequence which might compromise their effectiveness or enhance their toxicity [24].

HIV-dynamic studies have improved our understanding of the process of virus elimination after initiation of cART. During the first few weeks of treatment there is a rapid decline of viral load, primarily because of the decay of productively infected cells. The rate of decay becomes slower after the release of HIV viruses by macrophages and other long-lived cells of the lymph nodes [25].

Clinicians may be tempted to increase monitoring or switch drug therapy during the phase of slow viral load decline, even though this is predictable and the patient is likely to achieve viral suppression. Early treatment switching may be unnecessary and has disadvantages, including that the new regimen may be less effective than the current one, a reduction in the number of available future options, and the possibility of side effects associated with new regimen. Conversely, delays in switching regimen after virologic failure has occurred could result in accumulation of resistance mutations, immunological decline, and increased risk of clinical events. Guidelines recommend that a switch of cART -regimen should be considered if a patient viral load fails to fall to undetectable levels (< 50 copies/ml) after 24-36 weeks of treatment [25].

Development of Advanced Drug Delivery System

Maximal and durable suppression of HIV viral load is one of the goals of ART. Antiretroviral are known to cause significant, potentially fatal, drug interactions. Therefore, starting or modifying treatment for chronic conditions in HIV-infected individuals on combination antiretroviral therapy can result in potentially significant drug interactions, as shown by numerous case series published to date. Whether age-associated alterations in drug metabolism affect the outcome of drug interactions in this context remains to be determined, but they are a potential risk for increased toxicity in some individuals [26].

Combination antiretroviral therapy (cART) can provide durable viral suppression of HIV infection and dramatically improve Africa’s HIV-related mortality and morbidity. High levels of adherence to therapy are necessary to achieve optimal viral suppression and patients are counselled against late dosing of their antiretrovirals in order to prevent treatment failure and development of resistance. Air travel across time zones can therefore present challenges in the optimum timing of medication administration, not only to minimize the chance of developing resistant virus, but also to minimize the risk of medication-related toxicity [27].

Ongoing challenges HIV research is that reduced antiretroviral therapy (ART) exposure could be associated with end-organ morbidity. Subsequently, multiple observational studies identified prolonged exposure to viremia as a risk factor for morbidity and mortality, independent of either CD4 count or a current undetectable viral load [28]. However, continuing success of ART has, on the other hand, resulted in dramatic reductions in human immunodeficiency virus (HIV)-associated morbidity and mortality [29].

An increase in viral load levels may be accompanied by a decrease in CD4 cell counts. This may be due to a single factor or the following combination of factors: the development of drug resistance, reduced potency of ART, adverse pharmacological parameters, patient nonadherence, interpatient variability, and progressive decline of the immune system including pharmacologic failure because of diminished drug concentration at the site of action. These include pharmacokinetics (i.e. reduced bioavailability, decreased/inefficient absorption, accelerated metabolism, and drug interactions) or drug failure secondary to other causes [30].

Failure of ART commonly may be linked with the emergence and selection of drug-resistant variants. Drug-resistant strains may emerge with a lack of medication adherence and alterations in the antiretroviral pharmacokinetic parameters, resulting in a limitation of drug availability to the site of replication [30].

70% of therapeutic failures are attributed to drug-resistant strains of HIV, and insufficient delivery of drug to the site of replication. Drug resistant strains are usually members of the quasi species that arise from the strain of HIV initially infecting the individual (wild type), and drug resistant strains emerge under selective pressure of drug therapy [30].

Once ART is discontinued, viral load levels rise, indicating that at least some degree of replication was being suppressed by ART. The rebounding of viral replication without drug suppression provides evidence that it may be beneficial for patients with persistent viremia to continue combination therapy, especially with regimens containing protease inhibitors, to maintain a lower viral replication rate and to have an improved prognosis.
References


