Cardiovascular, renal and liver events associated with human immunodeficiency virus type 1 infection and antiretroviral therapy

Eric S Daar

Address: Division of HIV Medicine, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Los Angeles, CA 90502, USA
Email: edaar@labiomed.org

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Abstract

The first 15 years of the human immunodeficiency virus type 1 epidemic was characterized by patients progressing to clinical acquired immunodeficiency syndrome and death. The availability of potent antiretrovirals led to the recognition of unique adverse events associated with select drugs. More recent data suggest that end-organ damage may be associated with ongoing viremia. Further understanding of the potential role different drugs and the virus itself has on various organs can enhance the clinician’s ability to manage patients in the clinic.

Introduction and context

Prior to the availability of potent antiretroviral (ARV) therapy, human immunodeficiency virus type 1 (HIV-1) infection was notable for the inevitable progression to acquired immunodeficiency syndrome (AIDS)-defining events and death. With the advent of mono- and dual-nucleoside reverse transcriptase inhibitor (NRTI) therapy, there was recognition of diverse drug-related adverse events. The introduction of combination ARV therapy with dual NRTIs plus protease inhibitors (PIs) was associated with a dramatic decline in AIDS and mortality, along with an increased appreciation for the development of diverse metabolic complications, such as insulin resistance and dyslipidemia, as well as more recent reports actually showing evidence of premature cardiovascular disease [1]. In addition, co-morbid conditions such as renal and hepatic disease increasingly influenced the quality of the lives of HIV-1-infected individuals. Over the ensuing years research has attempted to define the potential role that select ARV agents and HIV-1 infection itself have on hepatic, renal, and cardiovascular disease.

Recent advances

Cardiovascular disease

Numerous factors are known to be associated with increased risk of atherosclerotic disease, such as diabetes mellitus, hypertension, smoking, family history and dyslipidemia, all of which occur with variable frequency in those with HIV-1 infection. As combination ARV therapy allowed HIV-1-infected individuals to live longer, these common causes of mortality have become an increasing problem in the HIV clinic. Moreover, concerns are enhanced by the association between select ARV agents and insulin resistance, dyslipidemia and fat maldistribution, along with case reports of premature cardiovascular disease [1]. While there is little evidence clearly demonstrating an association between any specific drug and visceral adiposity, lipodystrophy does appear to be a HIV-1-specific condition primarily linked to the use of thymidine analogues such as zidovudine and stavudine [2]. Similarly, it is now clear that lipid abnormalities have been seen with select NRTIs, non-NRTIs, and PIs. In fact, there are specific guidelines for the management of dyslipidemia in HIV-1-infected individuals [3,4].

While several studies have reported a relationship between ARV use and cardiovascular events, the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) cohort is the largest longitudinal study specifically designed to address this question. This study has provided the best evidence that there is an independent
higher levels of CD4+ T cells could minimize some of the toxic drugs [20].

Renal disease
Renal disease is common amongst those with HIV-1 infection and is often multifactorial; possible factors include HIV-1-associated nephropathy and co-morbid conditions such as diabetes mellitus and hypertension, as well as co-infection with hepatitis B and C [19]. Certain ARV drugs have also been associated with nephrotoxicity, such as indinavir, a drug rarely used in the current era that frequently caused nephrolithiasis and occasionally interstitial nephritis. In addition, tenofovir DF has been linked to the development of proximal renal tubular dysfunction. It is clearly recommended that routine monitoring of renal function should occur in all HIV-1-infected patients, with particular attention given to those with co-morbid conditions or taking nephrotoxic drugs [20].

One recent study attempted to define the relationship between renal function, tenofovir DF use, and the degree of plasma HIV-1 RNA suppression. This was a relatively small cohort study showing that those with complete viral suppression on a tenofovir DF-containing regimen actually experienced an increase in glomerular filtration rate. In contrast, there was a small but significant decline in renal function amongst those on tenofovir DF that did not achieve full virologic suppression. The authors hypothesize that ongoing viremia, and perhaps the associated increase in inflammation, could be contributing to these adverse outcomes [21]. Other studies have shown a similar relationship between HIV-1 replication and progression of renal disease [22,23].

Intriguing data have recently emerged to suggest a relationship between ongoing viremia and cardiovascular disease [12]. Data from the SMART study, designed to assess whether treatment interruption in those with ongoing viremia, and perhaps the associated increase in inflammation, could be contributing to these adverse outcomes [21]. Other studies have shown a similar relationship between HIV-1 replication and progression of renal disease [22,23].
**Hepatic disease**

The overwhelming burden of hepatic disease in HIV-1-infected individuals is related to co-infection with hepatitis B and C [24]. HIV-1 and hepatitis co-infection treatment guidelines provide detailed information about relevant interactions between these chronic viral infections and how co-infection influences the management of each pathogen [25]. There is also an increased risk of hepatic steatosis that may be associated with hyperlipidemia, insulin resistance and select ARV agents [26]. Several ARVs have also been shown to result in hepatotoxicity, the strongest links being with high-dose ritonavir, rarely used in the current treatment era, and tipranavir and nevirapine, the latter being in association with immunologic reactions that can be optimized by avoiding use in men with >400 CD4+ T-cells/μL and women with >250 CD4+ T cells/μL [27]. There have been a few case reports of significant hepatotoxicity with the CCR5 antagonist maraviroc, but this has not been clearly seen in the pivotal randomized controlled trials [28]. While there was some increased risk of hepatotoxicity associated with treatment interruption in the SMART study [13], there are currently much fewer data linking ongoing HIV-1 replication to liver abnormalities than what has been described for cardiovascular and renal disease.

**Implications for clinical practice**

There are currently many ARV options available to patients living with HIV-1 disease. A thorough understanding of the relationship between different drugs and various adverse events is critical to the optimal management of such patients. The first step towards safely using any medication is to know what conditions any given individual is predisposed to, to understand the safety profile of each drug, and to monitor for adverse events. In the case of cardiovascular disease it is important to emphasize efforts to modify known risk factors and to monitor and manage dyslipidemia [4]. When lipid abnormalities are present, clinicians should be aware of how different medications may be contributing to these problems and should consider changes in therapy when appropriate. The emerging data linking select drugs to cardiovascular disease, while not definitive, should also be considered when making any clinical decision, particularly in those with other risk factors. Similar considerations apply to underlying renal disease, where control of traditional risk factors such as diabetes mellitus and hypertension should be prioritized along with careful monitoring and avoidance of nephrotoxic drugs in those at greatest risk. With regards to liver disease, the best strategy is to diligently screen for hepatitis B and C co-infection, minimize use of hepatotoxic agents and to provide immunization against viral hepatitis when appropriate. In addition, all patients should be carefully monitored for liver disease, with a particular focus on those taking hepatotoxic agents and who are hepatitis B and/or C co-infected.

The recent data linking ongoing HIV-1 replication with cardiovascular disease, and possibly renal disease, are provocative, and the association remains an area of increasing investigation. Clinicians should be aware of these studies, their potential implications with regards to the use of ARV therapy, and how these findings might support the earlier initiation of treatment in a given individual. However, this needs to be balanced by the fact that the studies remain preliminary and the results thus far have been mostly hypothesis generating. Furthermore, decisions regarding the timing of treatment must be made in the context of the specific patient to be treated as well as the overall costs and known risks associated with the use of ARV therapy.

**Abbreviations**

AIDS, acquired immunodeficiency syndrome; ANRS, Agence Nationale de Recherches sur le Sida et les Hépatites Virales (National Agency for AIDS Research); ARV, antiretroviral; D:A:D, Data Collection on Adverse Events of Anti-HIV Drugs; HIV-1, human immunodeficiency virus type 1; IL, interleukin; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SMART, Strategies for Management of Anti-Retroviral Therapy; tenofovir DF, tenofovir disoproxil fumarate.

**Competing interests**

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