Genitourinary medicine

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HIV and cardiovascular risk

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The introduction of effective antiretroviral therapy (ART) has dramatically improved the morbidity and mortality associated with HIV disease and accompanying opportunistic diseases. Where HIV-positive individuals are able to access antiretroviral therapy HIV is now considered a chronic disease. Currently available ARTs are listed in Table 1.

In 2006 there were an estimated 73,000 persons of all ages living with HIV in the UK; approximately 21,600 (range 17,000–27,800) were unaware of their infection. Over 52,000 HIV-infected persons accessed care in the UK during 2006, a number that has more than doubled since 1997. Almost 4,000 people with HIV were aged 55 years or over in 2006, accounting for over one in every 13 persons accessing HIV-related care.[1]

As patients are living longer, chronic prevalent diseases of ageing including cardiovascular disease (CVD) are likely to contribute more substantially to morbidity and mortality in persons with HIV infection. This article will consider whether HIV or ART is an independent risk factor for CVD or whether any association with CVD is mediated exclusively through traditional risk factors. It remains unclear if standard risk evaluation algorithms such as the Framingham calculator are sufficiently accurate for decision making for HIV-positive patients.

A number of primary or traditional risk factors for CVD are well established, including age, smoking, hypertension, elevated total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol levels, diabetes mellitus, obesity and physical inactivity. Significant differences in established (especially smoking) and not traditional (such as inflammatory and clotting markers, cocaine and amphetamine use, specific coinfections) risk factors for CVD may exist between HIV-negative and HIV-positive populations.

Furthermore, changes in ART over time and the lag time between the onset of risk factors and CVD events pose challenges to determine whether HIV, ART or particular drug classes are associated with an increased CVD risk. A large prospective study with specific CVD end-points in HIV has not been undertaken and represents a considerable challenge to design and execute.

Impact of HIV on cardiovascular risk

HIV infection *per se* is associated with lipid abnormalities, typically raised triglycerides, reduced TC, high density lipoprotein (HDL) cholesterol and LDL cholesterol. Untreated HIV infection may also reduce peripheral glucose disposal. Commencing ART typically results in rises in TC, LDL and triglycerides and a more modest favourable impact on HDL.[2–4]

Compelling evidence that HIV is itself an important contributor to cardiovascular pathology emerged from the Strategies for Management of Antiretroviral Therapy Study Group. They investigated whether stopping and restarting ART above and below CD4 thresholds, respectively (drug conservation (DC) arm), could be used as a strategy for managing HIV, with the hope of minimising treatment related adverse events and medication costs.

Patients with CD4 counts above 350 cells/mm^3 and with optimum viral suppression (VS) were randomised to the DC arm or continuous ART, VS arm. ART was stopped in the DC arm until CD4 count dropped below 250 cells/mm^3 and continued until it reached over 350 cells/mm^3. The hazard ratio for death from any cause and the development of opportunistic infections was 2.6 (95% confidence interval 1.9–3.7, $p<0.001$) for the DC arm versus the VS arm.

Key Points

- **Primary risk factors remain the most important driver of cardiovascular risk**
- **HIV itself increases cardiovascular risk**
- **Antiretroviral therapy may increase the risk of cardiovascular disease**
- **Traditional prognostic tools need to be used with caution**
- **Despite potential side effects, antiretroviral therapy has vastly improved the prognosis of HIV**

KEY WORDS: antiretroviral therapy/HAART, cardiovasuclar risk, HIV, hypercholesterolaemia, metabolic side effects

Interestingly, not only was there an increase in opportunistic infections but also a significant increase in major CVD, renal or hepatic disease, with a hazard ratio of 1.6 for fatal or non-fatal CVD in the DC arm.[5] More recent data demonstrate significant increases in interleukin-6 and D-dimer following ART interruption.[6]

Impact of antiretroviral therapy on cardiovascular risk

Metabolic complications including dyslipidaemia, insulin resistance, lipodystrophy (peripheral fat loss and relative visceral fat accumulation) are well described in HIV patients receiving ART.[3,4,7]

Differences in the impact on lipids levels between ARTs within each drug class have been observed in clinical trials.[8] Although statistical significance has been shown, the practical significance is less clear. Studies of several protease inhibitors (PI) and stavudine in HIV-negative volunteers have suggested some PIs and stavudine may trigger insulin resistance.[9,10]

Sterne *et al* used a prognostic model specifically designed to incorporate cardiovascular risk factors that may be influenced by ART to gauge the impact of commencing treatment on the risk of coronary heart disease (CHD) in men. They found increases in the risk factors TC, glucose, body mass index (BMI) and triglycerides in patients after starting ART, more dramatic in the first three months of treatment and more pronounced in patients receiving PIs. Although these changes occurred in most patients commencing ART they appear to be relatively modest.[11]

The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group conducted a prospective, observational study to examine the risk of myocardial infarction (MI) in HIV-infected patients receiving highly active antiviral therapy (HAART).[3] Data were collected on more than 23,000 patients (median age 39 years) who were enrolled in 11 previously established cohorts in Europe, the USA and Australia. The patient population had a high baseline prevalence of traditional cardiovascular risk factors, including dyslipidaemia (42%), current smoker (47%), former smoker (16%), hypertension (5.6%), BMI above 30 kg/m^2 (4.7%) and diabetes mellitus (3.5%). Follow-up to February 2004 showed that 277 patients experienced an MI. The authors observed an increased incidence of MI with longer exposure to ART during the first seven years of use. After adjusting for potential confounding factors, there was a 17% relative increase in the rate of MI per year of exposure to ART. In addition to ART exposure, other independent predictors of MI included older age, current or former smoker, male gender and previous CVD. Elevated TC and triglyceride levels and diabetes mellitus at baseline were also associated with increased MI risk.

More recently, analyses of the effect of different classes of antiretrovirals on the rate of MI demonstrated an association between increased exposure to PIs and increased rate of MI (relative rate of MI per year of PI exposure 1.16). This was only partly explained by dyslipidaemia. No association was found between non-nucleoside reverse transcriptase inhibitors (NNRTIs) and MI risk.[4]

Table 1. Currently available antiretroviral therapy.

Nucleoside/tide reverse transcriptase inhibitors	
	Fixed dose combinations
Abacavir	Combivir (zidovudine and lamivudine)
Didanosine	Kivexa (abacavir and lamivudine)
Emtricitabine	Trizivir (zidovudine, abacavir and lamivudine)
Lamivudine	Truvada (tenofovir and emtricitabine)
Tenofovir disoproxil	
Stavudine (thymidine analogue)	
Zidovudine (thymidine analogue)	
Non-nucleoside reverse transcriptase inhibitors	
	Fixed dose combination
Efavirenz (sustiva)	Atripla (efavirenz, tenofovir and emtricitabine)
Nevirapine (viramune)	
Etravirine	
Protease inhibitors	**Entry/chemokine inhibitors**
Atazanavir (reyataz)	Enfurvitide (T-20)
Darunavir	Maraviroc (CCR5 inhibitor)
Fosamprenavir	
Indinavir	**Integrase inhibitor**
Kaletra	
Ritonavir	Raltegravir
Saquinavir	
Tipranavir	

Monitoring cardiovascular risk

Numerous tools are available to estimate cardiovascular risk among different populations, but they have not been evaluated in HIV-positive populations. The Framingham equation has been used to estimate cardiovascular risk in HIV-infected patients in a study comparing the predicted number of MI with the number of events observed in the DAD study. The results suggest that use of this equation for HIV-infected individuals overestimates absolute cardiovascular risk in those not on ART but underestimates the risk of MI in those on ART.[12]

Following this, the D:A:D CHD risk equation was developed to include the duration of PI exposure in addition to conventional risk factors of age, sex, family history of CHD, systolic blood pressure, smoking status, TC/HDL ratio, diabetes, weight and exercise. It accurately predicted CHD outcomes in the study

cohort but requires independent validation using other data sets prior to introduction into routine clinical practice.[13]

Management

It is clear that CVD risk reduction needs to be actively addressed in persons with HIV infection. The impact of any CVD intervention has a lag time because benefits accrue over several years. The earlier that CVD risk can be identified and interventions introduced, the sooner the risk can be managed. Risk reduction is relative rather than absolute. Thus, interventions implemented *now* in the HIV population will serve only to slow the trajectory of a potential CVD 'epidemic' among an ageing population of HIV-infected people and the benefits for any individual cannot be clearly measured.

Therapeutic lifestyle changes

Managing CVD risk involves assessing all potential CVD risk factors such as dyslipidaemia, insulin resistance, hypertension, lack of exercise and being overweight. In the setting of HIV infection, many of the interventions for reducing the CVD risk are comparable with those recommended for the general population. The basic initial intervention comprises therapeutic lifestyle changes such as smoking cessation, adherence to a 'Mediterranean diet' high in omega-3 fats, low in total and saturated fats and high in fibre, with fresh fruits and vegetables and regular exercise. A review of the available evidence shows that individuals with CHD who modify their diets reduce their risk of cardiovascular and 'all-cause' morbidity and mortality.

Pharmacological interventions

Pharmacological interventions with lipid-lowering drugs may be considered for patients with dyslipidaemia. More specifically, statins and newer agents (eg ezetimibe) that selectively inhibit the absorption of cholesterol in the small bowel are the most effective agents for treating hypercholesterolaemia, while fibric acid derivatives (fibrates) are more effective for treating hypertriglyceridaemia and raising HDL levels.[14] The National Cholesterol Education Programme (NCEP) Adult Treatment Panel III guidelines provide directions for managing dyslipidaemia, with targets adjusted according to risk.[15]

Patients taking statins should be monitored closely as the potential for drug interactions, particularly between PIs and statins, may increase the risk of toxicity, in particular rhabdomyolysis.[16]

Statins and fibrates appear to influence lipid levels similarly in HIV-infected individuals and in individuals within the general population. There is insufficient investigation of other effects of statins such as vascular tone to assess whether these effects are similarly preserved. Treatment with statins and fibrates rarely achieves NCEP-defined targets, so combinations of agents may be required.

Changing antiretroviral therapy. Although therapeutic lifestyle changes comprise the preferred initial approach to CVD risk management for individuals on established ART, treatment guidelines and some available clinical trials data suggest that switching certain antiretroviral drugs to agents with better lipid profiles, when feasible, can either meet lipid targets without the immediate need for further interventions or improve the chance of meeting target levels in conjunction with another intervention. For patients with available ART options, selecting an agent with a lower potential to induce metabolic abnormalities may be considered. For highly treatment-experienced patients with limited therapeutic options, the risk of virological or immunological failure must be weighed against the benefit of reducing an acute coronary event in the distant future.

Other drug classes. Most previous studies of dyslipidaemic individuals receiving a boosted or unboosted PI have focused on switching to an alternative drug class, such as an NNRTI or trizivir (a fixed dose combination of three nucleoside analogues). Replacement of a PI with an NNRTI or abacavir has been shown to help manage lipid abnormalities. These switches generally lead to a range of metabolic benefits, including decline in TC and LDL cholesterol and triglycerides and an increase in HDL cholesterol. The switch to an NNRTI may also improve the profile of lipid subfractions.

More recently switch studies within the PI class have indicated that atazanavir, both boosted and unboosted, as a replacement for another PI or boosted PI leads to improvements in lipids; this may be most evident in those with the greatest lipid abnormalities.[17,18] Other boosted PIs with more favourable reported lipid profiles may also be useful if a change of drug regimen is being considered.

Conclusions

It is clear that multiple factors contribute to cardiovascular risk in HIV-infected patients. It appears that both HIV itself, probably as a consequence of its pro-inflammatory and procoagulatory effects and unfavourable changes in HDL, and HAART, through its broad metabolic impact, increase the risk of CVD. Cardiovascular risk may vary modestly between different ART regimens. However, primary risk factors remain the key drivers of CVD risk. With the advent of newer classes of ART drugs with potentially less metabolic impact treatment paradigms, particularly related to CVD, will continually be reviewed.

Current prognostic risk algorithms have not been fully validated in the HIV setting and need to be used with caution. It is important to retain perspective: despite these potential side effects, ART has vastly improved the prognosis of HIV.

References

1 The UK Collaborative Group for HIV and STI Surveillance. *A complex picture. HIV and other sexually transmitted infections in the United Kingdom: 2006.* London: Health Protection Agency, Centre for Infections, 2006. www.hpa.org.uk/publications/2006/hiv_sti_2006/pdf/a_complex_Picture_2006_last.pdf

2 Riddler SA, Smit E, Cole SR *et al.* Impact of HIV infection and HAART on serum lipids in men. *JAMA* 2003;289:2978–82.

3 Friis-Møller N, Sabin CA, Weber R *et al.* Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003;349:1993–2003.

4 DAD Study Group, Friis-Møller N, Reiss P *et al.* Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 2007;356:1723–35.

5 Strategies for Management of Antiretroviral Therapy (SMART) Study Group, El-Sadr WM, Lundgren JD *et al.* CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006;355:2283–96.

6 Kuller L, SMART Study group. Elevated levels of Interleukin-6 and D-dimers are associated with an increased risk of death in patients with HIV. 15th Conference on Retroviruses and Opportunistic Infections Boston, February 3–6, 2008. Abstract 139.

7 Grinspoon S, Carr A, Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *N Engl J Med* 2005;352:48–62.

8 Fontas E, van Leth F, Sabin CA *et al.* D:A:D Study Group. Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: are different antiretroviral drugs associated with different lipid profiles? *J Infect Dis* 2004; 189:1056-74.

9 Fleischman A, Johnsen S, Systrom D *et al.* Effects of a nucleoside reverse transcriptase inhibitor, stavudine, on glucose disposal and mitochondrial function in muscle of healthy adults. *Am J Physiol Endocrinol Metab* 2007;292:E1666–73,.

10 Noor MA, Flint OP, Maa JF, Parker RA. Effects of Atazanavir/ritonavir and Lopinavir/ritonavir on Glucose Uptake and Insulin Sensitivity: Demonstrable Differences in Vitro and Clinically. *AIDS* 2006;20:1813–21.

11 Sterne JA, May M, Bucher HC *et al.* HAART and the heart: changes in coronary risk factors and implications for coronary risk in men starting antiretroviral therapy. *J Intern Med* 2007;261:255–67.

12 Law MG, Friis-Moller N, El-Sadr *et al.* The use of the Framingham Equation to predict Myocardial Infarctions in HIV-infected patients: Comparison with observed events in the D:A:D study. *HIV Med* 2006;7;218.

13 Friis-Møller N, Thiébaut R, Reiss P *et al.* Predicting the risk of coronary heart disease in HIV-infected patients: the D:A:D risk equation. CROI 2007.Poster 808.

14 Geraix J, Souza ME, Delatim FC, Pereira PC. Bezafibrate for the treatment of hypertriglyceridemia in HIV1-infected patients on highly active antiretroviral therapy. *Braz J Infect Dis* 2006;10:159–64.

15 Geletko SM, ZuWallack AR. Treatment of hyperlipidemia in HIV-infected patients. *Am J Health SystPharm* 58;7:607–14.

16 Fichtenbaum CJ, Gerber JG, Rosenkranz SL *et al.* NIAID AIDS Clinical Trials Group. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. *AIDS* 2002;16:569–77.

17 Colafigli M, Di Giambenedetto S, Bracciale L *et al.* Cardiovascular risk score change in HIV-1-infected patients switched to an atazanavir-based combination anti-retroviral regimen *HIV Medicine* 2008;9: 172–9.

18 Soriano V, García-Gasco P, Vispo E *et al.* Efficacy and safety of replacing lopinavir with atazanavir in HIV-infected patients with undetectable plasma viraemia: final results of the SLOAT trial. *J Antimicrob Chemother* 2008;61:200–5.