

# The future of HIV vasculopathy when our patients are on antiretroviral therapy

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## Summary

South Africa was one of the last countries in Africa to be affected by the HIV epidemic, but currently has one of the highest prevalences in the world. Antiretroviral therapy (ART) was recently introduced in South Africa, and as of December 2007 antiretroviral treatment coverage in this country was about 25% (UNAIDS, 2008). There is a well-documented relationship between vascular disease and HIV infection. This HIV vasculopathy may manifest as arterial aneurysms, occlusive disease or complications of hypercoagulability. The question to be asked is 'What is the future of HIV vasculopathy when our patients are on antiretroviral therapy?'

## The HIV epidemic

The global percentage of people living with HIV has stabilised since 2000.<sup>1</sup> However, the overall number of people living with HIV has increased as a result of the ongoing number of new infections each year and the beneficial effects of more widely available ART. Sub-Saharan Africa remains the part of the world most heavily affected by HIV, accounting for 67% of all people living with HIV and for 72% of AIDS deaths in 2007.<sup>1</sup> In South Africa the prevalence of HIV infection is about 30% among pregnant women attending antenatal clinics.<sup>1</sup> The epidemic stabilised in South Africa between 2004 and 2007, but at an unacceptably high level.<sup>1</sup>

## Antiretroviral therapy

Currently available antiretroviral drugs inhibit enzymes of the human immunodeficiency virus. The antiretroviral drug classes are the nucleoside analogues, such as zidovudine (AZT), the non-nucleoside reverse transcriptase inhibitors, such as nevirapine, and the protease inhibitors, such as indinavir and atazanavir. Antiretrovirals may be used to prevent infection (following exposure or to prevent transmission from mother to child) or to treat established HIV infection. Current South African public sector guidelines recommend that ART in adults be commenced at a CD4 count below 200 cells/ $\mu$ l or in World Health Organization (WHO) stage 4 disease. However, international consensus guidelines support the strategy of offering ART to anyone with HIV-related symptoms or signs, while asymptomatic persons with CD4 cell counts of more than 350/ $\mu$ l can generally be observed without therapy.<sup>2,3</sup> Combination ART should suppress the plasma HIV-1 RNA titre to less than 50 copies per ml. This target correlates with durability

of viral suppression, prevention of the emergence of drug resistance, and immunological and clinical benefit. Since the HIV mutates rapidly and there is a high viral turnover, inappropriate drug prescribing or poor adherence may cause rapid development of drug resistance.

Treatment of most major opportunistic infections in patients with AIDS consists of acute treatment, followed by suppressive therapy (or secondary prophylaxis) to prevent recurrences. Primary prophylaxis with co-trimoxazole is indicated for all patients with clinical evidence of significant immune suppression (WHO clinical stage 3 or 4 or CD4 count below 200 cells/ $\mu$ l). Randomised trials indicate that the risk of opportunistic infections can be reduced by 50 - 80% or more with appropriate prophylaxis.<sup>4,5</sup>

The treatment of HIV infection in South Africa has recently undergone considerable change with the availability of ART. Multiple clinical trials have shown the virological and immunological efficacy of the new highly active antiretroviral drug combinations by measuring the plasma load of HIV RNA and CD4 cell counts.<sup>6,7</sup> Data from the HIV Outpatient Study in the USA showed a dramatic reduction in morbidity and mortality among HIV patients on antiretroviral drugs.<sup>8</sup> In this study, reductions in death and disease (opportunistic infections) were clearly linked to the increasing use of combination ART, with the most dramatic reductions coinciding with increased use of protease inhibitors.

## Early vascular consequences of HIV infection

HIV-associated vasculitis may affect small-, medium- or large-sized arteries. The patient with large-vessel involvement may present with false aneurysms or thrombotic occlusion. The pathogenic mechanisms of this disease are not completely understood. HIV replication or opportunistic infection may induce direct injury of the vessel wall, or an immune mechanism may cause vascular damage.

The treatment of HIV vasculopathy has the triple objective of controlling the HIV infection, curing the vasculitis and managing the aneurysms and occlusive disease. Suppressing HIV replication is best done using three or more antiretroviral agents. Deciding how to treat the vasculitis is not easy, because its pathogenesis is not completely understood. However, opportunistic infections should be treated. Some success has been reported with plasmapheresis.<sup>9</sup> The rationale behind plasma exchange is the presence of circulating immune complexes in patients with HIV vasculitis. Treatment with steroids and cytotoxic agents (mainly cyclophosphamide) is controversial. It may



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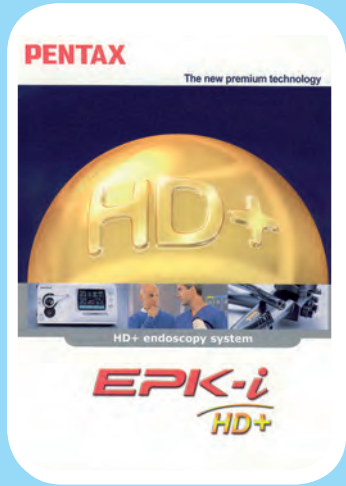
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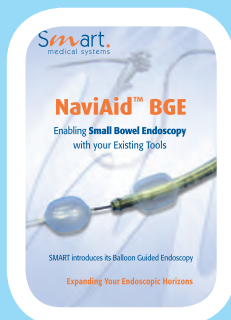
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be helpful in the short term, but in the long term can lead to relapses and complications due to virus persistence.

The preventive effects of antiretroviral drugs and prophylactic antibiotics with regard to the development of HIV vasculopathy are not known. However, since HIV vasculopathy is probably due to HIV replication, opportunistic infections and/or immune mechanisms, antiretroviral drugs and antibiotics should decrease its incidence.

### Late metabolic and atherogenic consequences of HIV infection

HIV infection causes metabolic changes that may accelerate atherosclerosis. The metabolic changes of concern include raised triglycerides, decreased HDL, raised C-reactive protein, raised fibrinogen and increased plasminogen-activating inhibitor activity.<sup>10</sup> Also, a number of studies in Western populations showed a higher prevalence of smoking in HIV-infected people when compared with the general population.<sup>11</sup> The metabolic changes associated with HIV infection have been shown to increase coronary artery disease complications.<sup>12</sup>

### Late metabolic and atherogenic consequences of antiretroviral drugs

Protease inhibitors have been associated with a range of metabolic side-effects, including the metabolic syndrome (hyperlipidaemia, central fat accumulation and insulin resistance), that have been implicated in the pathogenesis of atherosclerosis. The nucleoside analogues can cause lipotrophy and damage to mitochondria. These metabolic derangements caused by the protease inhibitors and nucleoside analogues have contributed to the rationale that the start of ART should be deferred until it is clearly necessary and that protease inhibitors should be avoided as long as possible. Cardiovascular risk is a concern. In a large, multicohort study, combination ART was associated with a 26% increase in the risk of myocardial infarction per year of regimen exposure.<sup>13</sup> Atazanavir, a new protease inhibitor, has the advantage of not inducing lipid elevations, but further study is needed to assess whether this advantage translates into reduced cardiovascular risk with this drug compared with the other protease inhibitors.<sup>14</sup>

### Future of HIV vasculopathy when our patients are on antiretroviral drugs

Treatment of patients with antiretroviral drugs will reduce their viral load and improve their immunity, which should result in less arterial damage and fewer patients with acute HIV-related vasculopathy. Control of their disease should also improve the metabolic derangements seen in HIV

patients. However, the antiretroviral drugs, and especially the older protease inhibitors with their metabolic side-effects, can result in vascular damage and accelerated long-term atherosclerotic cardiovascular disease. This problem is best managed by treating the modifiable risk factors of atherosclerosis (particularly smoking and hypertension), and it is hoped that new protease inhibitors with a more favourable risk profile for metabolic derangements will be developed.

The author has attempted to show the various factors involved in changing the cardiovascular status of patients infected with HIV. It is difficult to predict the end result. However, treatment with potent combination ART has transformed HIV infection from a rapidly fatal disease into a chronic illness that some patients can live with for more than two decades. In future, when most of our patients are on antiretrovirals and the percentage of our people living with HIV has stabilised, South African vascular surgeons will probably manage fewer acute HIV-related aneurysms and thrombotic occlusions but perhaps more chronic peripheral arterial disease.

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