

HIV and diabetes in Africa

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Introduction

Over 22.9 million people in sub-Saharan Africa are infected with HIV, representing nearly 70% of the world's total population of people living with HIV and AIDS (PLWHA).¹ Substantial funding from governments and non-government groups has led to a dramatic scale-up in provision of highly active antiretroviral treatment (HAART) across the continent in the last decade. There are now over 5 million Africans on HAART.¹ This is a remarkable feat given the challenges of providing HIV care in resource-limited settings. Indeed, HAART has significantly altered the natural history of this life-threatening condition.² However, as children and adults are living longer on HAART, there is increasing concern about rising incidence of insulin resistance, glucose intolerance, type 2 diabetes, and dyslipidaemia among PLWHA.³

This review describes how HIV infection and exposure to antiretroviral therapy can affect glycaemic control and onset of diabetic complications. We also review diabetes among HIV-infected children and diabetes management in patients on HAART, with particular focus on which anti-diabetic drugs are safe and effective.

Epidemiology

Since the advent of HAART, diabetes has become a leading cause of morbidity for patients with HIV in North America and Europe.^{4,5} Emerging data from across Africa also indicate that the prevalence of diabetes and dyslipidaemia is increasing as people are living longer on HAART.^{6,7} However, the rising prevalence of diabetes among PLWHA in Africa is only partly explained by the scale-up of HAART. Societal factors including increasing urbanisation are having a significant impact on the epidemiology of diabetes across the continent.⁸

Risk factors for diabetes

There are many factors that predispose people living with HIV to developing diabetes. Some of these are HIV-specific. However, many diabetes risk factors are the same regardless of whether the patient is HIV positive or not.

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1. **Age.** Age is a consistent risk factor, regardless of HIV status. Older people (>65 years) with HIV are up to four times more likely to develop diabetes compared with those under the age of 50 years.⁹
2. **Sex.** Several studies from high-income countries suggest that HIV-infected women on HAART have a lower risk of developing diabetes compared with men.¹⁰ One large multinational cohort analysis, found that male sex was associated with a 60% higher risk of diabetes.¹¹
3. **Obesity.** In a large multinational cohort analysis of HIV-infected individuals, diabetes rates were two-fold higher in obese participants, compared with those with normal body mass index (BMI).¹⁰ Fat distribution is more predictive than BMI for incidence of diabetes: patients with HIV and higher sex-appropriate waist-hip ratios are also far more likely to develop diabetes.¹¹
4. **Race.** While there has been a great deal of research into how race affects the development of diabetes in westernised nations, very little is known about the complex interplay of race and other societal factors on the development of diabetes among PLWHA in Africa.¹²

HIV-specific diabetes risk factors

In addition to the standard risk factors for diabetes, it is necessary to consider HIV-specific factors that have been associated with an increased risk of diabetes.

1. **HIV infection.** HIV itself and especially fluctuating viral load levels may lead to diabetes by inducing a chronic inflammatory state, which in turn leads to a decrease in adiponectin levels and an increase in insulin resistance. Unfortunately, data supporting this theory are sparse. Large cohort studies from Western countries have not demonstrated a significant association between duration of HIV infection and diabetes pathogenesis.^{11,13}
2. **CD4 count.** There does not seem to be a direct association between the CD4 count or the duration of infection and the risk of developing diabetes.^{11,13} There is also conflicting evidence as to whether CD4 nadir is associated with an increased risk of diabetes. In one recent analysis, HIV-infected men with a lower nadir CD4 count had an increased risk of incident glucose abnormalities compared with those with higher nadir CD4 counts.^{14,15} However, in another French cohort study of HIV-infected patients followed for 10 years,

there was no association between CD4 nadir and the onset of diabetes.¹³

3. **'Return to health' phenomenon.** With the introduction of anti-retrovirals, most HIV-infected patients experience an improvement in their general health. This return to health is associated with weight gain, improved appetite, and increased caloric intake. This in turn can lead to insulin resistance and diabetes.

Anti-retroviral therapy

The most important risk factor for the development of diabetes in PLWHA is exposure to antiretroviral drugs. Multiple studies have demonstrated that the initiation of HAART is associated with an increased risk of diabetes. There are several different mechanisms proposed. Many of these mechanisms are drug class-specific (see Table 1).

1. Nucleoside reverse transcriptase inhibitors (NRTIs).

This class of drugs is strongly linked to the development of diabetes.¹⁶ In the 'D:A:D' cohort, exposure to stavudine was associated with 19% relative risk of developing diabetes. Exposure to zidovudine and didanosine also increased the risk.¹¹ These drugs predispose to diabetes development as a consequence of the following mechanisms:

(a) *Mitochondrial toxicity.* Several NRTIs directly affect mitochondrial function.¹⁵ In turn, mitochondrial dysfunction has been implicated in the pathogenesis of insulin resistance. Short-term exposure to stavudine, for example, can reduce insulin sensitivity in healthy volunteers.¹⁷ As treatment guidelines are being updated the NRTIs most commonly associated with these side effects are being phased out.¹⁸

(b) *Lipodystrophy.* Several NRTIs, including stavudine and zidovudine, are associated with development of lipodystrophy, which itself is associated with acceler-

ated onset and increased prevalence of diabetes.^{19,20} In a large cohort study, the 'Lipodystrophy Case Definition Study', the prevalence of diabetes was 7% in those with lipodystrophy and 3% in those without.²⁰ Factors associated with lipodystrophy include CD4 count at ART initiation and ART duration.

(c) *Pancreatitis.* Rarely, certain NRTIs can cause pancreatitis. This in turn can lead to the development of diabetes.

2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs).

In most African countries, first-line regimens include one of the NNRTIs, either efavirenz or nevirapine. Studies have demonstrated that this class of drug is occasionally associated with development of dyslipidaemia.²¹ Nevirapine is linked to increases in low-density lipoprotein (LDL) concentrations²² whereas long-term use of efavirenz may lead to increases in total cholesterol and triglycerides.²³ Research has not demonstrated an association between this class of drug and diabetes.

3. Protease inhibitors (PIs).

This class of drugs (e.g. ritonavir, lopinavir) were the first HIV medications to be implicated in the pathogenesis of glucose abnormalities among HIV-infected patients.² Subsequent research has demonstrated that individual PIs have different capacities to induce insulin resistance and that risk of diabetes is dose-²⁴ and duration-¹³ dependent. Hyperglycaemia resolves in almost all patients where PIs are discontinued.²⁵ Evidence suggests that these drugs exert their effect by a number of mechanisms.

(a) *Down regulation of GLUT-4,*²⁶ the transporter responsible for movement of glucose into fat cells and cardiac and skeletal muscle, has been identified as one possible mechanism for diabetes in patients on certain PIs, such as ritonavir.

(b) *Inhibition of peroxisome proliferator-activated receptor γ activity,* leading to reduced adipocyte differentiation is another proposed mechanism.²⁵

(c) There is evidence that certain PIs, including saquinavir and ritonavir, lead to a reduction in beta cell function of between 25% and 50%.²⁷ The exact mechanism for this remains unclear. However, the therapeutic implication is that patients receiving these drugs who develop diabetes will benefit more from insulin therapy than from insulin-sensitiser therapy.²⁸

Table 1 Antiretroviral drugs commonly available in Africa

| Drug class | Examples |
|--|---|
| Nucleoside reverse transcriptase inhibitors (NRTIs) | Stavudine, zidovudine, lamivudine, abacavir, tenofovir, emtricitabine, didanosine |
| Non-nucleoside reverse transcriptase inhibitors (NNRTIs) | Efavirenz, nevirapine, etravirine |
| Protease inhibitors (PIs) | Indinavir, ritonavir, lopinavir, saquinavir, atazanavir, darunavir |
| Fusion inhibitors | Enfuvirtide |
| Integrase inhibitors | Raltegravir |
| CCR5 receptor inhibitors | Maraviroc |

Diabetic complications in HIV infection

While there is a great deal of research describing how HIV and HAART predispose to diabetes, there is far less research investigating the prevalence or severity of diabetes complications in PLWHA.

Nephropathy. Kidney damage can occur as a consequence of both diabetes and HIV itself. Recent research

suggests that HIV-infected patients with diabetes have rates of albuminuria that are twice that in HIV-uninfected patients.²⁸ Low-level albuminuria is itself associated with increased mortality for patients with diabetes and HIV. Therefore patients with albuminuria should be initiated if possible on treatment with angiotensin converting enzyme inhibitors (ACE inhibitors) unless there are other contraindications.

Retinopathy. Little data exist for diabetic retinopathy in HIV-infected individuals. One sub-Saharan African study of diabetic retinopathy prevalence found that sight-threatening diabetic retinopathy was not associated with HIV infection.²⁹

Neuropathy. Peripheral neuropathy is relatively common in HIV infection, often related to HAART toxicity. However, little is known about whether diabetes alters the natural history of HAART-related neuropathy, or whether HIV infection is associated with higher rates of diabetic neuropathy.

Cardiovascular disease. Existing data suggest that patients with HIV and diabetes have significantly increased risk of developing coronary artery disease compared with HIV-infected patients without diabetes.³⁰

Co-management of diabetes and HIV in Africa

Screening. Regular screening for diabetes is essential for all patients with HIV, especially those who are on HAART.³¹ South African guidelines suggest screening HIV-positive patients with risk factors every 6 months.³² In countries where there are no current guidelines for screening HIV-infected patients for diabetes, we recommend annual fasting blood glucose for all patients on HAART, where resources are available. More frequent monitoring may be reasonable for patients who are at highest risk because of their family history, and/or lipodystrophy.

Diagnosis. The same diagnostic criteria for diabetes apply for HIV-positive as for HIV-negative patients. However, glycated haemoglobin (HbA_{1c}) is not a recommended diagnostic test in HIV-positive patients because of the effects of the virus on haemoglobin, and the effects of some antiretroviral drugs, such as zidovudine. Although the precise mechanisms are not clear, HbA_{1c} appears to underestimate exposure by 10% to 15% in HIV-infected patients.³³ For this reason, we recommend using a fasting glucose or 2-hour plasma glucose value derived from an oral glucose tolerance test (OGTT) to diagnose diabetes in HIV-infected patients.

Treatment. The same general diabetes measures apply in HIV-positive and HIV-negative patients. Individuals should be encouraged to adopt healthy lifestyles and,

as appropriate, be encouraged to lose weight and stop smoking. As part of every assessment it is also important to exclude opportunistic infections, particularly tuberculosis. Given the numerous psychosocial challenges for patients living with diabetes and HIV, it is essential to foster a family-focused approach to patient care.

Treatment of HIV: switching HAART. The role of antiretroviral switching in the management of HIV-infected patients with diabetes is not clear. If a temporal relationship exists between the initiation of an antiretroviral agent and deterioration in glucose metabolism, and other HIV treatment options are available, antiretroviral substitution should be considered. Where possible, drugs that increase risk of diabetes and dyslipidaemia, such as stavudine, didanosine, lopinavir and indinavir, should be avoided.

Treatment of diabetes

In almost all situations, the same treatments for treating patients who are HIV-negative should be considered in patients that are HIV-positive. Where available, insulin should be considered first-line therapy for newly diagnosed patients with severe hyperglycaemia or for patients with contraindications to oral anti-diabetic drugs. However, for the majority of newly diagnosed patients oral anti-diabetic drug therapy with one or more drugs is appropriate in conjunction with lifestyle modifications.

Metformin. For most PLWHA diagnosed with diabetes, metformin is considered the first-line therapy. Its primary mechanism of action is to reduce hepatic glucose production. The gastrointestinal side-effects of metformin are increased in those with HIV enteropathy. For this reason it is important to start at a very low dose and titrate up gradually. The most serious side-effect of metformin therapy is lactic acidosis. The risk of lactic acidosis is increased when metformin is co-prescribed with stavudine and didanosine. The risk of lactic acidosis is also increased in renal dysfunction. It is important to exclude HIV-associated nephropathy (HIVAN) before initiating metformin, since the risk of lactic acidosis is increased when renal function is significantly reduced.³² If serum creatinine cannot be measured, a urine protein level by dipstick may be helpful (as long as other reasons for proteinuria can be excluded as far as possible). The risk of lactic acidosis may also be increased in severely ill patients with comorbid infections such as tuberculosis and in patients with cachexia;³³ such patients need to be monitored closely on metformin therapy.

Sulphonylureas. Sulphonylureas, such as glyburide and glibenclamide, are inexpensive and widely used second-line drugs in the general population. Despite limited data, it is likely that these drugs have safety and efficacy profiles among HIV-infected patients that are similar to those without HIV infection. The major adverse effects

of sulphonylurea therapy are weight gain and hypoglycaemia. Because of the increased risk of hypoglycaemia, liver disease is a relative contraindication for this class of drugs, as is significant renal dysfunction. There are no interactions between any of the commonly used HIV medications and sulphonylureas.

Thiazolidinediones (glitazones). Thiazolidinediones (TZDs) are considered third-line initial therapy for diabetes in the general population. They work by improving insulin sensitivity through direct action on skeletal muscle and indirect effects mediated through adipocyte function. They can cause a slight increase in subcutaneous fat deposition and for this reason they may be preferred in patients with lipodystrophy. However, the primary adverse effect of TZDs is weight gain and fluid retention. As a result of the fluid retention, these medications are associated with an increased risk of congestive heart failure. There is also a potential risk of impaired cardiovascular outcome, and for this reason rosiglitazone has been withdrawn in Europe and North America.

Insulin. Insulin is the most effective hypoglycaemia agent available and one of the most cost-effective. It does not have any interactions with antiretrovirals, is not contraindicated with renal or hepatic dysfunction, does not cause gastrointestinal side-effects, can correct both insulin deficiency and resistance when given in appropriate doses and does not increase the risk of cardiovascular disease.³³ Insulin is also safe to use in pregnancy. For these reasons, insulin is an important option for the management of diabetes for most patients with HIV infection. Unfortunately, insulin can be difficult to access in many African settings for reasons of cost and supply logistics.¹⁰ Also, as few patients have access to glucose self-monitoring resources, hypoglycaemia is also a side-effect of concern.

Diabetes in HIV-positive children

Worldwide, paediatric diabetes is primarily type 1 diabetes and represents 5–10% of all cases of diabetes. In sub-Saharan Africa, approximately 10% of diabetes cases are type 1.^{34,35} Available data suggest that the prevalence of childhood diabetes in Africa is low, with later age of onset than in the Western world.³⁶ The role of HIV infection in the pathogenesis of type 1 diabetes is unclear.

Perinatally, HIV-infected children are at risk for developing metabolic complications secondary to HAART, including lipodystrophy and abnormal lipid and glucose metabolism.³⁷ Recent studies estimate that the prevalence of metabolic disorders is 25–30% in children on HAART,³⁷ with fat redistribution and abnormal lipid metabolism being seen more frequently in children than insulin resistance.³⁸ The mechanism of development of metabolic side-effects is similar, and, as in adults, is associated with certain NRTIs and PIs.^{37,39,40} Older age (post-puberty) and duration of HAART are also risk factors for chil-

dren.^{37,39,40} The long-term effects of life-long HAART are unknown, including lifetime risk of diabetes. The effect of long-standing HIV and its pro-inflammatory state on diabetes, atherosclerosis, and cardiovascular disease among children with HIV is also unknown.

Treatment of type 1 diabetes in HIV-infected children is the same as treatment in their HIV-negative counterparts, i.e. insulin replacement.⁴¹ The treatment of metabolic complications in HIV-positive children is extrapolated from adult studies and includes change of HAART regimen, insulin-sensitising drugs, such as metformin and rosiglitazone, lipid-lowering agents in older children, diet, and exercise.^{37,41}

Conclusions

There is optimism across Africa as PLWHA have increased access to HAART. However, as adults are living longer on HAART and children are surviving on life-long antiretroviral therapy, they are also at increased risk of adverse metabolic side-effects, including diabetes and dyslipidaemia. It is therefore essential that clinicians managing patients with HIV are aware of these risks, screen regularly and treat promptly all patients with these metabolic sequelae.

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