**Introduction**

With advances in antiretroviral therapy (ART), the life-expectancy of people living with human immunodeficiency virus (HIV) has increased. With this, however, comes the burden of comorbidity related to advancing age, the disease process and ART itself. Zidovudine (AZT) is a nucleoside reverse transcriptase inhibitor (NRTI) sometimes used as part of ART regimens, although it is now less frequently used due to potential adverse effects and its twice-daily dosing schedule. It is a thymidine analogue which inhibits viral reverse transcriptase, one of the enzymes involved in HIV replication. It has been available as treatment for HIV since its Food and Drug Administration licensure in 1987.  

**Pharmacology**

Zidovudine is used in the treatment of HIV and is a synthetic analogue of the nucleoside thymidine. It is ordinarily combined with other antiretroviral agents and selectively inhibits reverse transcriptase, the enzyme required to convert viral RNA to DNA, during the virus’ life cycle. Zidovudine is first intracellularly phosphorylated to its active form zidovudine triphosphate (AZT-TP). It can then competitively insert into the DNA chain that is forming by reverse transcription from the viral RNA template. Since AZT-TP does not have the 3’-OH group needed for elongation of the DNA chain, it acts as a chain terminator (see Figure 1). Administration is ordinarily by the oral route, often co-formulated with lamivudine, another NRTI. It may be administered intravenously when the oral route is compromised, and sometimes in the peri-partum period as part of preventative measures aiming to reduce mother to child HIV transmission. There is good absorption from the gastrointestinal tract with an approximate serum bioavailability of 60–70%. It is inactivated by glucuronidation in the liver.

**Trials of efficacy and safety**

The earliest antiretroviral trials of zidovudine examined its effects as a monotherapy. These were later followed by trials assessing its effects in combination with other drugs, with combination ART now being standard. A double-blind, randomised controlled trial (published in 1990) followed on from the initial Phase II
trials that led to licensing. It compared placebo to both a total 500mg per day dose and a total 1500mg per day dose. It used pathologically verified progression to acquired immunodeficiency syndrome (AIDS) as an endpoint. The study showed that zidovudine was effective at treating HIV (in terms of improving or maintaining CD4 count) with minimal evidence of toxicity when administered at the lower dose. The main side effects attributed to zidovudine in the study were nausea and vomiting. Haematological toxicity also occurred (anaemia and neutropenia most commonly), but the incidence was greater in the higher dose group, with comparable incidence between the lower dose group and the group receiving placebo. Thus, from this study, lower doses of the drug were recommended, with the hypothesised benefit of a more tolerable toxicity profile.\textsuperscript{2,3}

Zidovudine is used less frequently nowadays in part due to its metabolic effects, namely dyslipidaemia, lipodystrophy, hyperlactataemia and hyperglycaemia. European AIDS Clinical Society (EACS) guidelines suggest that lipodystrophy may be prevented by avoiding the use of drugs like zidovudine, and indeed suggest its discontinuation when lipodystrophy is present. Additionally, in the situation of hyperlactataemia greater than $5\text{mmol/L}$, zidovudine discontinuation is advised.\textsuperscript{1} A recent small study showed decreased insulin-mediated peripheral glucose uptake and reduced peripheral insulin sensitivity in HIV positive persons treated with an AZT containing combination of ART (specifically, zidovudine/lamivudine/lopinavir/ritonavir) compared with an NRTI sparing regimen (nevirapine/lopinavir/ritonavir). The exact cause of this is not clear. A potential mechanism for this was identified as AZT-induced mitochondrial dysfunction. The likelihood, however, is that insulin resistance in zidovudine use is multifactorial.\textsuperscript{4}

**Specific evidence for use in diabetes**

There is a scarcity of data concerning the specific use of zidovudine in diabetes. The EACS have produced guidelines for addressing metabolic diseases in the context of HIV. They provide no specific recommendation as to the frequency of screening tests for metabolic conditions, other than that they should be regular. Diagnostic criteria for diabetes mellitus are no different from those used in the general population and an abnormal result should always be repeated before a diagnosis is made. The first management approach produced by the guideline for zidovudine is that hyperglycaemia, as with HIV-negative patients, should be non-pharmacological, i.e. diet, physical exercise and smoking cessation. For type 2 diabetes mellitus, metformin is usually cited as the first choice of oral hypoglycaemic, followed by a combination with a further oral agent if HbA\textsubscript{1c} is persistently $>6.5–7\%$ (48–53 mmol/mol). If combination oral hypoglycaemic therapy fails to improve HbA\textsubscript{1c} then insulin (in addition to metformin) is recommended. Treatment of type 1 diabetes mellitus should be as for HIV-negative individuals.\textsuperscript{1}

**Discussion**

An association between zidovudine and hyperglycaemia has been shown. In addition, co-prescribing in HIV and diabetes patients is complex and should involve experienced physicians from both specialties. Patients taking this medication should therefore have frequent assessment of blood glucose, to assess glycaemic control, regardless of whether they are known to have established diabetes mellitus or not. In addition, there should also be screening for other metabolic diseases.

Management of type 1 diabetes mellitus is as for HIV negative patients. For type 2 diabetes mellitus, lifestyle changes are recommended initially, although, if the improvement in HbA\textsubscript{1c} is inadequate, oral agents followed by insulin may be required. Ultimately, the approach used should be based on individual patient needs and circumstances.\textsuperscript{1}

**Declarations of interests**

GlaxoSmithKline, co-owner of ViiV Healthcare UK Ltd (manufacturer of zidovudine), has previously provided Dr C McGoldrick with sponsorship for conference attendance.

**References**


**Key points**

- AZT has the potential to worsen several metabolic conditions including glycaemic control in patients with or without established diabetes mellitus
- Regular monitoring of metabolic diseases is recommended
- Management in comorbid patients should ideally be a collaborative effort between specialties

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- Methyldopa
- Metoprolol
- Metoprolamide
- Omacor
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