Correspondence

High mortality in subjects with both diabetes and HIV in sub-Saharan Africa

Smit et al. [1] report that the mean age of people living with HIV in sub-Saharan Africa is increasing; the proportion suffering from at least one noncommunicable disease is predicted to rise. The authors are correct to highlight this important demographic change. There is a scarcity of data on the interaction between HIV and noncommunicable diseases. We performed the first prospective cohort study of diabetic retinopathy in sub-Saharan Africa [2,3]. In patients with both diabetes and HIV infection, we found a very high mortality rate but no increase in the rate of diabetic microvascular complications. Participants were systematically sampled from two hospital-based, primary care diabetes clinics. Glycaemic control, SBP, HIV status, urine albumin–creatinine ratio, and haemoglobin and serum lipid levels were assessed at baseline, 12 and 24 months. Retinopathy was graded at an accredited reading centre. Mortality was confirmed systematically either by death certificate or by key informants.

Of 357 people with diabetes included in the study, 50 were HIV positive (48 at baseline and two new diagnoses during the study). At baseline, HIV-positive participants demonstrated lower mean age (48.2 vs. 53.3 years; $P = 0.015$) and shorter duration of diabetes (2.8 vs. 4.4 years; $P = 0.002$) than HIV-negative individuals; a higher proportion of HIV-positive participants demonstrated raised urine albumin–creatinine ratio (50.0 vs. 31.6%; $P = 0.015$). Of 41 HIV-positive participants who underwent annual $CD4^+$ cell count testing, 32 (78%), 25 (61%) and 14 (34%) individuals had a $CD4^+$ cell count below 500, 350 and 200 cells/μl at any visit, respectively. At 24 months, 38 participants were assessed and nine had died (94% follow-up). Cumulative incidence of death amongst HIV-positive participants with diabetes at 12 and 24 months was 10% (1.7–18.3) and 18.1% (7.4–28.8), respectively ($n = 50$), compared with 5.4% at 24 months [2.8–8.0, 95% confidence interval (CI); $n = 294$] in HIV-negative participants with diabetes. In comparison, Malawi National HIV Programme data indicate a mortality rate of 5.1% 24 months after commencement of antiretroviral therapy [4]. In univariate analysis, death during the study was associated with proliferative diabetic retinopathy [odds ratio (OR) 6.47; 2.51–16.7; $P = 0.0001$], moderate visual impairment (OR 8.21; 2.48–27.1; $P = 0.001$) and HIV (OR 3.72; 1.54–9.00; $P = 0.003$).

At 24 months, two-step (or greater) progression of diabetic retinopathy was observed in 2/38 HIV-positive participants (5.3%) compared with 55/251 (21.9%) HIV-negative participants ($P < 0.015$ Fisher's exact). In multivariate logistic analysis, two-step progression of diabetic retinopathy was associated with HbA1c (OR 1.27, 95% CI 1.12–1.45), baseline grade of retinopathy (OR 1.39, 95% CI 1.02–1.91) and HIV infection (OR 0.16, 95% CI 0.03–0.78). The negative association between retinopathy progression and HIV infection may have been strongly influenced by the high mortality rate in people with HIV (people whose retinopathy would have otherwise progressed). No trend towards worsening renal function was identified at 24 months. Our data suggest that mortality in patients with both diabetes and HIV infection in Southern Malawi is very high. Previous studies have indicated that both HIV infection and antiretroviral therapies are associated with a vasculopathy which manifests as increased cardiovascular and cerebrovascular risk [5,6]. We did not find an increased rate of diabetic microvascular complications in persons with HIV in our cohort. Our results add to the growing literature on interaction between HIV and noncommunicable disease and highlight the urgent need for provision of integrated services for patients with diabetes and HIV infection.

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Conflicts of interest

There are no conflicts of interest.

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First reported use of zidovudine for prevention of perinatal HIV transmission in a premature neonate on extra corporal membrane oxygenation

The effects of extra corporal membrane oxygenation (ECMO) on pharmacokinetics of drugs is difficult to predict. Generally, an increased volume of distribution, decreased drug elimination, and sequestration of the drug to the ECMO circuit are factors potentially influencing the pharmacokinetics of drugs during ECMO [1,2]. Zidovudine is the only antiretroviral agent suitable for intravenous (IV) use in newborns for the prevention of perinatal HIV transmission. No reported cases of the influence of ECMO on the pharmacokinetics of zidovudine in prematures were found. We describe the first pharmacokinetics data in a premature neonate requiring IV zidovudine while on ECMO.

A premature child (gestational age 32 weeks) born from a virologically suppressed HIV-infected mother required ECMO to undergo the resection of an intrathoracic lesion compromising the lungs. IV zidovudine was administered for the prevention of HIV transmission as per standard guidelines. To cope with the anticipated increased volume of distribution (V_d) and to avoid the risks caused by under treatment, IV zidovudine was dosed 9 mg/kg/day (150% of the dose normally used in premature infants) for the duration of ECMO. Plasma samples were taken before, during and after ECMO. Samples were analysed using liquid chromatography-tandem mass spectrometry technology. Therapeutic drug monitoring (TDM) was used to observe treatment and pharmacokinetics parameters were calculated using noncompartmental analysis in Phoenix WinNonlin (Certara USA, Inc., Princeton, New Jersey, USA). Parents consented to the presentation of these data.

With clearance 0.62 l/h, V_d 3.3 l, and $t_{1/2}$ of 3.6 h, zidovudine concentrations remained above 0.8 mg/l during ECMO (Fig. 1). While pharmacokinetic reports on prematures are highly variable with no C_{trough} or area under the curve values being reported, these pharmacokinetics parameters suggest slow clearance of zidovudine, leading to a degree of exposure that has been correlated to increased safety risks in earlier studies [3]. No adverse events were reported in this case and zidovudine levels returned to normal on standard doses after ECMO cessation [4,5]. The HIV proviral DNA PCR in the child was negative at 3 months of age.

It might be difficult to tease out the influence of ECMO versus the premature age on the pharmacokinetics of zidovudine in this particular child. However, the fact that, after ECMO pharmacokinetics parameters of zidovudine were normal after administering normal doses while they were higher during ECMO at a higher dose of
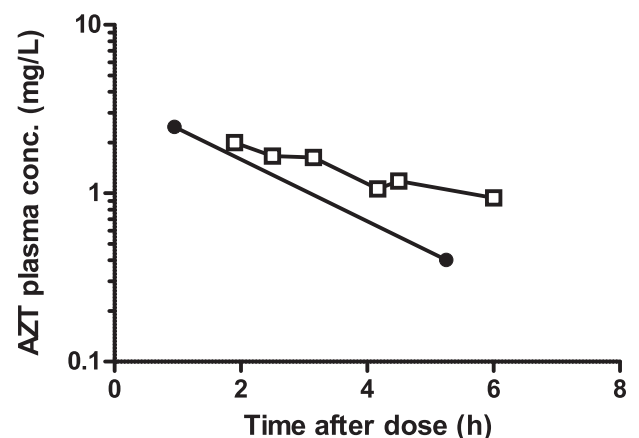

Fig. 1. Zidovudine levels post dosing. ● Zidovudine levels with intravenous medication, no extra corporal membrane oxygenation. □ Zidovudine levels with IV medication on extra corporal membrane oxygenation. AZT, zidovudine.