OPINION

WHY SHOULD WE STILL CARE ABOUT THE STAVUDINE DOSE?

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Current recommendations advise that stavudine be phased out of use. The logistics and cost of switching are significant, and the World Health Organization has forecast that 1.55 million people will still be on stavudine-based antiretroviral therapy by the end of 2012. Stavudine is co-formulated in many countries, is very cheap and effective, and is well tolerated in initial therapy. However, the 40 mg BD dose was associated with considerable long-term toxicity. Several studies suggest that half the original recommended dose has excellent antiviral efficacy with significantly reduced metabolic side-effects. Despite generic tenofovir now being cheaper than zidovudine, tenofovir consumes the majority of adult antiretroviral programme medication budgets in programmes in Africa, where it is used in first-line therapy. Abacavir is far more expensive than zidovudine or tenofovir, and is a major cost driver in paediatric programmes with access to abacavir-based first-line treatment. Low-dose stavudine may offer the only cheaper (and possibly as effective and safe) alternative to programmes grappling with limited financial resources.

The UNAIDS 2010 global report estimated that 20 million adults and 2.3 million children in sub-Saharan Africa are HIV-infected,¹ of whom 6.7 million and 518 000, respectively, are currently on antiretroviral therapy (ART).²³ In the late 1990s stavudine was selected as the first-line antiretroviral of choice for adults and children in the developed world because it is extremely safe in the short term, in contrast to the toxicity and intolerance associated with zidovudine. In fact, stavudine was regarded as so safe that the original recommended dose for adults was 40 mg twice daily (BD), even though a number of randomised clinical trials had shown that it was equally effective at a dose of 20 mg BD.⁴⁻⁷ Forty milligrams BD was chosen fairly arbitrarily over 20 mg BD after the Stavudine 019 trial⁸ chose to test 40 mg twice daily rather than a lower dose, and found that stavudine had minimal short-term toxicity at that dose. The children’s dose was extrapolated from the adult dose using data from paediatric pharmacokinetic studies that showed that an oral dose of 1 mg/kg/dose twice daily in children weighing under 30 kg results in plasma exposure similar to that of an adult over 60 kg taking 40 mg twice daily, and that an oral dose of 0.5 mg/kg/ dose twice daily in children results in plasma exposure similar to that of an adult over 60 kg taking 20 mg twice daily.⁹⁻¹⁰ No virological outcomes were reported in those paediatric pharmacokinetic studies.

ART-associated lipoatrophy was first described in 1998,¹¹ 4 years after the introduction of stavudine as an antiretroviral agent. By 2002, lipoatrophy was recognised as a frequent delayed adverse effect of stavudine.¹² A large number of studies have since shown a causal link with nucleoside reverse transcriptase inhibitor exposure, particularly didanosine, stavudine and zidovudine, of which stavudine shows the strongest link. The effect of stavudine in causing lipoatrophy appears to be strongly dose-related, and in 2007 the World Health Organization advised that the recommended adult dose be lowered from 40 to 30 mg BD.¹³⁻¹⁴ The children’s dose was not lowered, however, because lipoatrophy was believed to be uncommon in children (although this assumption is currently being refuted). The lipoatrophy caused by stavudine typically does not manifest until 18 - 24 months of therapy, and even then may go unnoticed or may not be taken seriously by the health care provider for months or years as it slowly progresses. The typically long delay between drug initiation and manifestation of toxicity may have contributed to the delay in the global response in reducing the recommended dose from 40 to 30 mg BD. In the meantime, stavudine has gained a bad reputation due to the stigmatising effect of lipoatrophy, which resolves slowly and poorly. However, evidence accumulated over the last 15 years suggests that stavudine given at the equivalent of 20 mg BD leads to a significantly lower rate of lipoatrophy and of other mitochondrial adverse effects.¹³⁻¹⁵⁻¹⁷

The logistics and cost of switching all antiretroviral-treated individuals to non-stavudine therapy is significant. Generic tenofovir costs 6 times more per month than stavudine, while tenofovir co-formulated with emtricitibine costs 4 times more than a month’s supply of stavudine and lamivudine combined.¹⁸ In
addition, the use of tenofovir, which requires additional renal function monitoring, substantially increases the programme costs of safety monitoring. Taking the costs of toxicity management into account, the cost-effectiveness ratio (measured in cost per year of life saved) of tenofovir is double that of stavudine (when ART is initiated at 350 CD4 cells/μl in a one-line setting) with similar 5-year survival (89% v. 87%) when using the incidence of stavudine toxicity associated with 40 mg BD. Since the incidence of late adverse events due to stavudine is likely to be substantially reduced by using a more appropriate dose (20 mg BD), the advantages of tenofovir over stavudine may begin to dwindle. Given the escalating number of people being initiated on ART and the stress this places on existing ART programmes, it is unlikely that switching stable patients from stavudine to an alternative will be a high priority. In addition, for those initiated on alternative ART regimens, stavudine will probably remain an important second-line agent, especially in patients unable to tolerate or have affordable access to zidovudine or abacavir. Using stavudine in first-line therapy further preserves tenofovir over stavudine (2',3'-didehydro-3'-deoxythymidine) in children with human immunodeficiency virus infection. Antimicrob Agents Chemother 2001;45(3):756-763.

REFERENCES