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Review article

d4T: keep it or abandon it?

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Stavudine is a nucleoside analogue used widely for first-line treatment of HIV in developing and middle-income countries. The World Health Organization recommended that all patients should switch to stavudine (30mg BID). However, there is evidence from the dose-ranging trials that patients with body weight below 60kg should use a dose of 20mg BID. For patients who show adverse events on stavudine, a switch to other nucleoside analogues can be considered. This article reviews d4T to study if it should be kept or abandoned.

Keywords: Dose reduction, resource limited setting, stavudine

Stavudine is a nucleoside analogue used widely for first-line treatment of HIV in developing and middle-income countries [1, 2]. Stavudine is mainly used in low-cost fixed dose combinations (e.g. stavudine/lamvudine/nevirapine). Stavudine is rarely used in North America and Europe because of an excess risk of lipodystrophy first seen at the 40 mg BID dose [3]. The original dose was 40 mg BID for people with body weight above 60 kg, and 30 mg BID for body weight below 60 kg [4]. In a meta-analysis of the dose-ranging trials, there were equivalent rates of HIV RNA suppression for a lower dose of stavudine (30 mg BID, with 20 mg BID if body weight is below 60 kg), compared with the original dose [5]. Patients taking the lower doses of stavudine had a reduced risk of peripheral neuropathy, with some evidence for lower elevations in lipids and a reduced risk of lipodystrophy [5].

In 2007, the World Health Organization recommended that all patients should switch to stavudine 30mg BID [6]. However, there is evidence from the dose-ranging trials that patients with body weight below 60kg should use a dose of 20 mg BID [7-9]. For patients who show adverse events on stavudine, a switch to other nucleoside analogues (tenofovir or zidovudine) can be considered.

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There is strong pressure to increase the number of people on antiretrovirals worldwide, from five million to 17 million [10, 11]. However, there may be little additional funding from PEPFAR and the Global Fund to achieve this. Where funding is limited, there is a moral dilemma over whether to treat more patients with stavudine-based HAART, despite the risk of lipodystrophy, versus treating fewer patients with better-tolerated drugs such as tenofovir.

Weight adjusted dosing of stavudine

The dose of stavudine has normally been adjusted for body weight. The first dose-ranging trials used mg per kg dosing. Then, later trials used d4T 40 mg BID for people with body weight above 60 kg, and 30 mg BID for those with body weight below 60 kg [4]. In this article, we label this dosing as 40(30) mg BID - so the dose for people with higher body weight will be first, and the dose for people with lower body weight will be shown in brackets. The other dose commonly studied has been 30(20) mg BID: i.e. stavudine 30 mg for patients with weight above 60 kg and 20 mg BID for those with body weight below 60 kg.

1990-1995: the initial development of stavudine

The clinical trials program leading to marketing approval of stavudine left regulators with a dilemma. Phase 2 trials had shown similar antiretroviral efficacy for stavudine doses of 20-40 mg BID, but there were

dose-related rises in the incidence of peripheral neuropathy within this dosing range [12, 13]. In the d4T 019 trial [14], NRTI pre-treated patients were randomized to continue zidovudine or switch to stavudine. This was the pivotal trial for approval of stavudine – used only the 40(30) mg BID dose, and showed efficacy versus continued zidovudine in an NRTI pre-treated population.

The stavudine parallel track program [15], which randomized over 10,000 NRTI pre-treated patients to either 40(30) mg or 20(15) mg BID of stavudine, was stopped by the Data Safety Monitoring Board owing to excessive rates of peripheral neuropathy on the 40(30) mg BID arm, and all patients were switched to the 20(15) mg BID dose. In this trial, the percentage of patients with neuropathy was 21% in the d4T 40(30) arm, versus 15% in the 20(15) mg BID arm, which was highly statistically significant; there was no difference in survival between the two arms.

In 1995, the FDA and European regulators approved the 40(30)mg BID dose of stavudine, since efficacy had only been shown at this dose, in the d4T 019 trial. However, stavudine tablets with strengths of 40, 30, 20, and 15 mg were made commercially available [4]. This allowed studies of lower stavudine doses to be conducted.

The Gilead 903 trial

In this trial [3], 611 treatment naïve patients were randomized to receive lamivudine plus efavirenz, with either stavudine 40(30) mg BID, or tenofovir. After 144 weeks of randomized treatment, the Gilead 903 trial showed equivalent efficacy (measured as HIV RNA suppression below 50 copies/mL or rises in CD4 count) for standard dose stavudine versus tenofovir over three years of treatment. The incidence of drug resistance at failure was also similar between the arms. The number of Grade 3 or 4 adverse events and deaths were very similar between the arms. However, the percentage of patients with investigator-defined lipoatrophy was higher in the stavudine arm (19%) versus the tenofovir arm (3%). Concerns over the excess risk of lipoatrophy, in this and other trials, have led most developed countries to stop using stavudine in routine clinical practice. Even so, stavudine has remained a very widely used drug in developing and middle-income countries, owing to its low cost and availability in fixed dose combinations. **Table 1** shows summary results from the Gilead 903 trial.

1995-2007: Clinical trials of lower doses of stavudine

The question of dose-optimization for stavudine has been continually evaluated in the 15 years since the initial approval, with a series of investigator led clinical trials and cohort analyses assessing the efficacy and safety of stavudine, mainly at the dose of 30(20) mg BID. The design of the key randomized trials and cohort studies is shown in **Table 2**. Three of the randomized trials and two of the non-randomized studies included weight adjusted dosing. The mean body weight at baseline in the first three studies (HIVNAT 002 [7], ARV065 [8] and ETOX [9]) was close to 60 kg, suggesting that 50% of the patients in these trials were receiving either stavudine 30mg BID in the control arm, or 20 mg BID in the low dose arm. In the ARV065 trial, a very low dose of d4T was used: 20mg BID for body weight above 60 kg and 15 mg BID for body weight below 60kg. Two Spanish trials [16, 17] and the French Phoenix trial [18] recruited patients with high body weight, taking the 40 mg BID dose, and then evaluated the 30 mg BID dose in the experimental arms.

Table 1. Efficacy and safety of d4T/3TC/EFV versus TDF/3TC/EFV in the Gilead 903 trial (Week 144 results)

Efficacy and safety parameters	Week 144 results	
	d4T/3TC/EFV n=306	TDF/3TC/EFV n=305
Mean rise in CD4 counts (cells/mL)	+283	+263
HIV RNA <50 copies/mL (%)	69%	73%
NNRTI resistance (%)	9%	9%
3TC resistance (%)	6%	6%
Grade 3 or 4 adverse events	27%	25%
Deaths	5	6
Lipodystrophy	19%	3%

Table 2. Summary of key post-approval randomized trials evaluating lower doses of stavudine

Study, n [reference]	Inclusion	Mean weight	Treatment arms
Randomized trials			
HIVNAT 002, n=63 [7]	Naïve	58 kg	d4T 40(30) *vs*. 30(20) mg BID (with ddI)
ARV065, n=229 [8]	Naïve	54 kg	d4T 40(30) *vs*. 20(15) mg BID (with ddI)
ETOX, n=54 [9]	Naïve	62 kg	d4T 40(30) *vs*. 30(20) mg BID (+ NRTI/EFV)
Madrid trial, n=75 [16]	HIV RNA <50	>60 kg	d4T kept at 40 *vs*. switched to 30 mg BID as part of HAART
Barcelona trial, n=41 [17]	HIV RNA < 200	>60 kg	d4T kept at 40 *vs*. switched to 30 mg BID as part of HAART
Non-randomised studies:			
Phoenix trial, n=57 [18]	HIV RNA <400	>60 kg	d4T 40 switched to 30 mg BID
Munich cohort, n=508 [20]	starting stavudine	< or >60 kg	d4T 40(30) *vs*. 30(20) mg BID as part of HAART
Bangkok cohort, n=80 [21]	taking stavudine	57 kg	d4T 40(30) switched to 30(20) mg BID

A meta-analysis of the efficacy in these trials showed equivalent rates of HIV RNA suppression for the 30(20) mg BID dose, relative to the 40(30) mg BID dose [5]. In addition, there were several safety benefits observed for the lower doses of stavudine, shown in **Table 3** (**a**: randomized trials and **b**: non-randomized studies). The results from these safety analyses are from a wide range of trials and cohorts, with data not collected or reported in a systematic way. Where the data has been reported, there was strong evidence that lower doses of stavudine reduced the risk of peripheral neuropathy. There was weaker evidence for a correlation between stavudine dosing and the risk of lipid elevations, lactic acidosis, and lipodystrophy. A new randomized trial would be required to better define the safety profile of the 30(20) mg BID dose of stavudine.

2007: Reduction in the dose of stavudine

The World Health Organization recommended a reduction in the dose of the stavudine, from 40mg to 30mg BID, after the meta-analysis of dose-ranging studies showed the same efficacy at the lower dose, but with an improved safety profile [6]. Patients who took the 30mg BID dose of stavudine had a lower risk of peripheral neuropathy and were less likely to discontinue treatment. The World Health Organization now recommends the 30 mg BID dose of stavudine for all patients [6]. However, this advice did not include weight-adjusted doses. The evidence from the dose-ranging trials supports the use of stavudine at a dose of 20 mg BID for patients with body weight below 60kg.

Economics of stavudine versus other antiretrovirals

Of the 33 million people currently infected with HIV/AIDS, around 90% live in low-income countries [10]. An estimated 33 million people are infected with HIV worldwide. Approximately five million people have been started on antiretroviral treatment in low and middle-income countries. However, an additional 11 million people will be in need of treatment, if guidelines are updated to recommend antiretrovirals for all patients with CD4 counts below 350 cells/μL. Of the remaining people infected with HIV but with high CD4 counts, most will need to start antiretrovirals as their disease progresses. Funding for access programs, through PEPFAR, the Global Fund, and national governments is already being restricted, partly because of the Global Financial Crisis. Antiretroviral treatment programs have to lower overall costs, so that the maximum number of people with HIV can be treated for limited budgets. Antiretroviral treatment can account for the majority of the total cost of access programs.

The G8 financial promises (HIV/AIDS funds in proportion to GDP) have not been met by France, Germany, UK, Canada, Russia or Japan. The budget shortfall has led to PEFPAR-funded programs being more cautious with large increase of new patients, with the exception of countries with partnership framework in place such as Malawi or Swaziland. The Global Fund is now short of three billion dollars in 2010, with the risk of jeopardizing future proposals for continuing scale up in 2010 and further.

If we are to achieve Universal access to HIV treatment within current treatment budgets, there will have to be cuts in the unit costs of HIV treatment and care. These might be possible through lowering the diagnostic tests performed, simplifying systems of patient care, or lowering the costs of the antiretroviral drugs treatment. The key advantage of using stavudine is its low cost, but this needs to be set against the

Table 3. Summary of safety findings from randomized clinical trials (**a**) and non-randomised studies evaluating lower doses of stavudine (**b**)

(**a**) Randomized clinical trials

Study [reference]	Main safety results	
Phase 1 trial [12]	Dose related rises in peripheral neuropathy	
Phase 2 trial [13]	Dose related rises in peripheral neuropathy	
Parallel track [15]	Dose related rises in peripheral neuropathy	
HIVNAT 002 [7]	No clear safety findings reported	
ARV065 [8]	3 cases of lactic acidosis in high dose d4T arm, none in d4T low dose arm	
ETOX [9]	Dose related effects	- treatment discontinuation
		- lactate elevations
		- mtDNA reductions in PBMC
		- reductions in malar fat thickness
		- reductions in body fat mass
Barcelona trial [17]	No dose effects	- triglycerides / cholesterol
		- mtDNA content
		- lactate elevations
		- measures of lipoatrophy
Madrid trial [16]	No dose effects	- triglycerides / cholesterol
		- lactate elevations

(**b**) Non-randomized studies evaluating lower doses of stavudine

Study [reference]	Main safety results	
Munich cohort [21]	Dose related effects	- treatment discontinuation
		- peripheral neuropathy
	No dose effects	- hyperlactataemia
Phoenix study [18]	Effects of stavudine dose reduction on:	
		- lowering triglycerides,
		- lowering cholesterol
		- lowering lactates
	Neuropathy evaluations inconclusive	
Bangkok cohort [22]		Effects of stavudine dose reduction on
		- resolution of lipoatrophy

excess risk of lipodystrophy, with the stigma and distress this can bring. In the Gilead 903 trial, the risk of lipodystrophy after three years of treatment was 19% for stavudine 40(30) mg BID, and 3% for tenofovir based HAART [3]. However, we do not know how much lower this would be if the 30(20) mg BID dose of stavudine was used. Clinical pharmacology trials have shown a significant correlation between stavudine plasma concentrations and the risk of lipoatrophy [19]. In the Bangkok cohort, there were improvements in lipoatrophy when patients were switched to lower doses of stavudine [Hanvanich 2005]. The only way to reliably answer this question would be with a new randomized trial of stavudine 30(20) mg BID versus tenofovir, as part of a standard NRTI/NNRTI based first-line HAART treatment.

Conclusions and implications

1) The 30 mg BID dose of stavudine, recently recommended by the World Heath Organization is better tolerated than the original 40 mg BID dose. Further, it is showing equivalent efficacy. There is evidence for a lower rate of peripheral neuropathy for the 30 mg BID dose, plus some evidence for improved lipids and a lower risk of lipodystrophy.

2) When evaluating safety data on stavudine versus other nucleoside analogues, it is important to use recent data, where patients have been given the new 30mg BID dose of stavudine.

3) The dosing of stavudine has been adjusted for weight in several randomised trials and cohort studies. The combined results from these studies support the use of stavudine at a dose of 20 mg BID for people with body weight below 60 kg.

4) Stavudine is still very widely used in Africa and Asia, owing to its low cost and availability in fixed dose combinations. In sub-Saharan Africa, the lowest cost of d4T/3TC/NVP is $89, compared with $210 for TDF/3TC/EFV [20]. However, tenofovir may be significantly more expensive in middle-income countries. In developed countries, stavudine is now rarely used, owing to the excess risk of peripheral neuropathy and lipodystrophy.

5) In countries where funding for treatment with HIV is severely limited and antiretroviral treatment costs account for a high percentage of total spending, the continued use of stavudine could be considered. However, there should be a system for switching patients who develop adverse events on stavudine to other nucleosides such as tenofovir, if they are locally available and affordable.

6) Where the price of tenofovir is affordable, the first-line use of tenofovir instead of stavudine would lower the risk of lipodystrophy: this can be very distressing and stigmatising to patients, and may take several years to reverse after stavudine treatment is stopped. However the use of tenofovir will not necessarily improve overall treatment efficacy, or lower the risk of drug resistance, relative to the use of stavudine.

7) A new randomised clinical trial, comparing first line use of stavudine 30(20) mg BID versus tenofovir, in combination with 3TC and an NNRTI, could establish whether the newly optimised dose of stavudine shows an acceptable safety profile.

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