Commentary

Antiretroviral therapy in resource-limited settings: is there still a role for stavudine?

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Phanuphak et al. compared three strategies for first-line antiretroviral therapy in 150 Thai patients: initiating therapy with zidovudine (AZT), tenofovir disoproxil fumarate (TDF), or a 24-week lead-in phase with stavudine (d4T) followed by a switch to AZT. Those taking d4T had higher haemoglobin levels and CD4+ T-cell counts without an increase in neuropathic symptoms, peripheral neuropathy or lipoatrophy compared with those on AZT. Because AZT is associated with more short-term side effects and toxicity than d4T, and because most d4T toxicity occurs only after long-term use, this approach may have advantages over initial use of AZT. However, TDF-based regimens, while more expensive, are more effective, better tolerated, less toxic, less likely to lead to cross-resistance, and possibly more cost-effective. The goal in resource-limited settings should be to move away from use of thymidine analogues in first-line regimens.

The long-term toxicity of stavudine (d4T) has been recognized for years, and it is slowly being replaced with safer antiretroviral agents. This has been successful in resource-rich countries, where d4T is now rarely prescribed. However, even after d4T was replaced on the list of WHO-recommended agents by zidovudine (AZT) and tenofovir disoproxil fumarate (TDF) [1], it remains widely used in many resource-limited settings because of its low cost.

The toxicities of d4T, some mediated by mitochondrial toxicity, are well-characterized. The most common are peripheral sensory neuropathy and lipoatrophy. Pancreatitis, lactic acidosis and hepatic steatosis are less common but can be severe and even fatal. Based on its toxicity, the once popular nucleoside ‘backbone’ of d4T plus lamivudine (3TC) is now categorized as ‘not recommended’ in the treatment guidelines from the US Department of Health and Human Services (DHHS) [2].

Thus it was with some trepidation that I approached the task of commenting on a study evaluating a novel way to use this old nemesis in contemporary HIV therapy. At a time when d4T is disappearing from most treatment guidelines and is being phased out of clinical practice, Phanuphak et al. [3] suggest that it can be safely incorporated into initial therapy as a short-term alternative to AZT and TDF.

The investigators took advantage of the short-term safety and tolerability of d4T: its toxicities typically appear only after long-term administration. They randomized 150 treatment-naive Thai participants to start antiretroviral therapy (ART) with a standard AZT-based regimen, a TDF-based regimen or a 24-week lead-in with d4T followed by a switch to AZT, each in combination with 3TC and nevirapine (NVP). The results were intriguing, but perhaps not surprising. After 24 weeks, those taking the d4T lead-in had higher haemoglobin levels and CD4+ T-cell counts, without an increase in neuropathic symptoms or peripheral neuropathy, compared with those on AZT. At 72 weeks there was a non-significant trend toward lower fat mass in the d4T lead-in arm, but the difference was only about 500 g, and no lipoatrophy was observed. The trial was not powered to compare virological or immunological responses to ART, but there were no obvious differences among the arms. The study did not specifically assess more subjective side effects, such as nausea, fatigue and headache, but one would assume that they would be less common in patients taking either d4T or TDF than AZT.

The implication of this small study is that d4T, given at the reduced doses now in widespread use, might still have a role in the treatment of HIV infection in resource-limited settings. If the choice of initial therapy is between a d4T- versus an AZT-based regimen, a lead-in phase with d4T might result in better short-term outcomes, since drug toxicity does not usually occur within the first 6 months, and there are clear advantages of d4T over AZT initially. Patients diagnosed with...
advanced HIV infection, especially in countries where malaria and intestinal helminth infections are endemic, may have symptomatic anaemia, which may be exacerbated by AZT. AZT-related bone marrow suppression blunts CD4+ T-cell response to ART, which may have clinical consequences in people starting therapy with advanced disease. Finally, AZT is more likely to cause nausea, headache and fatigue than d4T, side effects that may discourage patients from adhering to and continuing ART. In the Thai study, four participants switched from AZT to TDF, three due to anaemia and one due to lipoatrophy.

The authors note that their study is too small to capture the less common but more serious side effects of d4T, such as hepatic steatosis and lactic acidosis, which can occur with short-term administration, nor can they address the relative efficacy of the regimens they studied. Of the four initial ART regimens recommended by the WHO, only one, TDF, 3TC and efa-virenz, is a preferred regimen according to current DHHS [2] and IAS–USA guidelines [4], and there are remaining concerns about the efficacy of the widely used combination of TDF, 3TC and NVP [5].

What are the clinical and policy implications of this study? There are countries in which d4T is still prescribed as first-line therapy, with switching occurring only after toxicity becomes clinically apparent. In other countries AZT or TDF are prescribed to patients starting ART, but those already taking d4T without evidence of toxicity remain on that drug. There is often an economic incentive to use up existing supplies of d4T rather than switching to AZT or TDF, even after country guidelines have changed. The Thai study suggests a safer way to use supplies of d4T: by using it in a short-term lead-in phase, then switching to safer drugs after 6 months. Even without a larger, more definitive study, it is hard to imagine that this would not be a safer approach than leaving people on d4T until they develop toxicity.

But before we get too excited about the d4T lead-in approach, let’s remember that this strategy applies to settings where the choice of initial therapy is between d4T and AZT, not to countries where TDF has already replaced thymidine analogues. The advantages of a d4T lead-in phase in this study were mostly advantages over AZT, which, like d4T, has fallen out of favour in resource-rich settings. AZT, given as a component of initial therapy, is less effective than tenofovir [6], is dosed twice a day, causes nausea, headache, fatigue, anaemia, leukopenia and a blunted CD4+ T-cell response to ART. It is also a cause of lipoatrophy, which, though slower to occur than with d4T, may be less reversible [7]. A short-term lead-in with d4T is less likely to have advantages over immediate use of TDF, except in patients who may present with acute illnesses that affect renal function or that require the use of nephrotoxic agents.

There are also important advantages of TDF over both d4T and AZT with respect to drug resistance and nucleoside reverse transcriptase inhibitor (NRTI) sequencing. When patients fail therapy with a thymidine-analogue-containing regimen, they typically begin to accumulate thymidine analogue mutations (TAMs), which result in progressive cross-resistance within the NRTI class. In settings where treatment failure is diagnosed based on CD4+ T-cell decline or infrequent viral load monitoring, a patient failing ART may have extensive TAM-mediated NRTI resistance, including resistance to TDF, by the time second-line ART is started [8]. By contrast, patients failing regimens containing TDF with either 3TC or emtricitabine typically have the M184V mutation with or without K65R, leaving AZT as a fully active NRTI for second-line therapy regardless of the duration of failure. The implication is that use of AZT in second-line therapy is reliable after failure of TDF in first-line therapy, whereas the efficacy of TDF after failure of AZT is unpredictable and dependent on the availability of viral load monitoring and resistance testing. While second-line therapy may be effective regardless of NRTI susceptibility because of the high resistance barrier of ritonavir-boosted protease inhibitors, the use of NRTIs in patients with high-level NRTI resistance incurs an unnecessary cost and subjects them to the risk of unnecessary toxicity.

Finally, TDF-based regimens may be more cost-effective than those containing thymidine analogues [9,10]. The higher cost of generic TDF can be offset by the reduced need for monitoring and treatment of drug-related toxicities, greater efficacy with reduced need for switch to more expensive second-line therapy, and the ability to reliably sequence within the NRTI class when TDF is used first.

In summary, the paper by Phanuphak et al. [3] offers an intriguing and potentially viable option for settings in which thymidine analogues are still prescribed for first-line therapy. When resources are constrained, such creative and innovative approaches to safely expanding ART are critical. However, for reasons of efficacy, toxicity, resistance and cost-effectiveness, our goal should ultimately be to move away from the use of thymidine analogues in initial therapy, eliminating d4T entirely and reserving AZT for second-line therapy, where its activity can be assumed without the need for resistance testing.

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References


