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First-line treatment choices proving challenging for African ART programmes

Toxicity rates on d4T

Dr Moses Kamya highlighted surprising results from Uganda, where researchers at Mulago and Mbarara hospitals calculated the differences in treatment failure rates between patients who started treatment with d4T/3TC/nevirapine (usually a generic fixed dose triple combination tablet) and AZT/3TC/efavirenz (in the form of branded products in separate tablets).

The analysis included 776 patients (526 adults and 250 children). Overall, 75% of patients who started treatment had viral load below 400 copies/ml after one year – the remainder were either dead, lost to follow-up, had switched treatment due to side-effects or had changed to a second-line regimen due to virological or clinical failure of treatment.

Patients receiving the d4T-based combination were 2.59 times more likely to experience treatment failure when compared with the efavirenz-treated group, although the confidence intervals of this estimate were wide (1.20-5.59).

“Why did the d4T regimen perform less well?” asked Dr Kamya. “We really don’t know. We suspect it is tolerability but we did not document that enough.”

But he also speculated that the results might reflect a greater potency of efavirenz, although the results of the 2NN study showed no difference between a nevirapine and an efavirenz-based regimen in rates of virologic suppression.

There were also suggestions that the generic products might not be as effective as the branded products, although no evidence was supplied to support this view.

Replacing d4T: what can you afford?

The limitations of d4T-based treatment have already led some countries in Africa to dispense with it.

Alwyn Mwinga of Zambia told the conference that her country had already replaced d4T-based treatment with a first-line regimen of tenofovir, 3TC and efavirenz, using Aspen’s South African-manufactured version of *Atripla*, a fixed dose tablet containing all three drugs in one tablet.

Zambia has 100,000 patients already on treatment through 293 sites, with less than 300 patients currently requiring second-line treatment.

Although tenofovir-based treatment will prove more expensive than a d4T-based regimen, a lower frequency of adverse events can be expected, together with less potential for cross-resistance in second-line treatment.

However for most countries second-line treatment is a hypothetical exercise at present, due not to cost but to the very low rates of patients experiencing virologic failure of first-line treatment. The more pressing concern is the poor tolerability of d4T-based treatment.

In Namibia d4T-based treatment has also been phased out, in favour of an AZT-based regimen.

“Namibia cannot afford tenofovir,” said Dr Ndapewa Hamunime of the Namibian Ministry of Health, explaining why her country had chosen AZT as the basis for future treatment. Henceforth patients

will start treatment with AZT/3TC/nevirapine. Tenofovir is being reserved as first-line therapy for HIV-infected patients with active hepatitis B.

Meanwhile thousands continuing to do well on d4T will be switched over to AZT after two years; those with lipodystrophy, peripheral neuropathy or liver enzymes elevated more than three times above the upper limit of normal are being switched immediately.

“No patient is to be switched from d4T without good reason,” said Dr Hamunime, reminding the conference audience that for a treatment programme like Namibia, even stepping up to AZT-based therapy imposes a significant additional burden. Namibia has 2.5 million people, an estimated HIV prevalence of 19%, 80,000 needing treatment and 35,000 already on treatment. AZT-based treatment costs an additional \$48 a year per person.

Tenofovir in first-line treatment

Tenofovir is currently unaffordable for most countries, but that is set to change, according to Anil Soni of the Clinton HIV/AIDS Initiative, which has been working with generic manufacturers to bring down tenofovir costs in the past year. He said that four manufacturers will have submitted dossiers for WHO prequalification of generic versions of *Atripla* (tenofovir, 3TC and efavirenz) by the end of the year, and eight manufacturers will have submitted generic tenofovir tablets by the end of the year.

As more products become available the prices will be driven down, although tenofovir and efavirenz-based combinations will always remain more expensive because they contain a larger volume of chemicals and the raw materials required for their manufacture are more expensive than d4T and nevirapine.

But tenofovir also poses a practical difficulty for treatment programmes in Africa: safety monitoring. A rare side-effect of the drug is kidney toxicity, most likely to occur in people with pre-existing kidney problems or taking other drugs that are also toxic to the kidneys.

Zambia will carry out creatinine monitoring to detect impaired kidney function, but said Professor Charles Gilks of the World Health Organization, “the problem with putting a barrier of creatinine [monitoring] in front-line therapy is that it may exclude all those without access to creatinine or urea testing. CD4 counts are more widely available than reliable and reproducible chemistry in Africa.”

The balancing act between first-line and second-line therapy

Prof. Gilks summed up the dilemmas facing national treatment programmes as they strive to balance the cost of first-line therapy and the efficacy of second-line therapy.

“There is going to be a major trade-off between what programmes put into first-line therapy and second-line. We think first-line is our best shot for obtaining durable viral suppression.”

In other words, the first-line regimen should be as tolerable and potent as possible – even if it proves more expensive. But, the more that countries spend on first-line treatment, the less will be available to spend on second-line treatment.

“Between 500,000 and 800,000 people could need second-line treatment by 2010,” Prof. Gilks warned.

Conversely, using a cheaper first-line regimen which has a high failure rate and leaves patients with a high level of cross-resistance to nucleoside analogues may make second-line treatment more difficult.

“[We recognise that] current second-line regimen recommendations are not very practical and there is a lot of pressure on WHO to be

clearer about the NRTI backbone and the preferred protease inhibitor, partly in order to consolidate the market and drive down prices further," said Prof. Gilks.

He highlighted data from WHO showing the current utilisation pattern of second-line regimens in resource-limited settings (three-quarters of the 40,000 second-line patients are currently in Brazil).

Twenty-four per cent are taking AZT/ddl and lopinavir/ritonavir, 19% are taking ddl/3TC and lopinavir/ritonavir (despite no evidence that this is an effective second-line regimen, since first-line failures are highly likely to have resistance to 3TC already), and 6% are taking saquinavir plus lopinavir/ritonavir.

"It is very easy to construct a second-line regimen when someone has been on tenofovir, using AZT," said Dr Moses Kamya. "Perhaps the use of cheaper AZT second-line squares out [the higher cost of tenofovir] first-line."

However Anil Soni of the Clinton HIV/AIDs Initiative highlighted the biggest potential variable in the cost of second-line therapy: the willingness or otherwise of countries to consider atazanavir/ritonavir as the recommended second-line protease inhibitor.

"Lopinavir/ritonavir will never be as cheap as atazanavir/ritonavir – that will determine the cost of second-line therapy and few countries are considering that choice at the moment."

WHO is due to publish new, more definitive guidelines for second-line treatment soon, making clearer which ritonavir-boosted protease inhibitor is preferred, said Prof. Gilks.

The other variable affecting the long-term cost of second-line treatment will be the cost and availability of new drug classes in developing countries. Integrase inhibitors – which according to Anil Soni could be quite cheap to make – and chemokine antagonists may be available by the end of this year in the United States and Europe, but their accessibility in the nations most severely affected by HIV is still in doubt.

"I think we have to lobby very hard both the manufacturers and the implementers to start looking at these drugs in resource-limited settings," said Prof. Gilks. "They present a potentially exciting option where we could use two drug classes in first-line and two completely different classes in second-line."

WHO to monitor ARV side-effects worldwide

High levels of drug changes

The HIV Implementers' Meeting heard of high levels of drug changes in people taking first-line therapy, due to peripheral neuropathy caused by d4T.

In Uganda, Willy Were of CDC-Uganda reported that 10% of patients receiving treatment through a home-based care programme developed severe peripheral neuropathy, and this side-effect was vastly more frequent than any other severe side-effect. Seventeen per cent of patients switched from d4T during 18 months of follow-up, compared with 4% who switched from nevirapine due to adverse reactions (chiefly rash).

Participants in the study had a 73% probability of remaining on their original three drug, first-line regimen after 18 months, and a 16% probability of experiencing a severe adverse event by this point. Severe peripheral neuropathy was significantly more likely to occur in people aged 35 years and over (hazard ratio 2.88 (confidence

interval 1.22 – 2.71), and in those taking TB treatment at the same time as d4T.

A similar pattern was seen in Cote d'Ivoire, in a report from Dr Eugene Massou. He told the conference that among 2012 patients receiving one of three first-line regimens (d4t/3TC plus nevirapine (32%) or efavirenz (25%), or AZT/3TC/efavirenz (38%)), the incidence of peripheral neuropathy was also vastly greater than any other serious side effect.

17.9 cases per 100 patient years of d4T treatment were observed, compared with 3.9 cases of anaemia per 100 patient years of AZT treatment and 6.3 cases of rash per 100 patient years of nevirapine treatment. Median follow-up was 16.9 months.

Patients receiving d4T and nevirapine were more than three times more likely to modify their treatment than patients taking AZT/3TC/efavirenz (34 changes per 100 patient years compared to 10.5 changes per 100 patient years).

In Rwanda 83% of changes reported at two health facilities were from d4T, almost entirely due to peripheral neuropathy.

In Kenya however peripheral neuropathy was not reported as a major cause of treatment changes by Lillian Kocholla of Mbagathi Hospital in Nairobi. She reported on 486 changes made to first-line therapy among more than 2000 patients receiving antiretroviral therapy. Sixty-five per cent of changes were due to lipodystrophy and only 11% due to virologic failure of first-line treatment, with peripheral neuropathy leading to treatment changes in less than 5%.

Need for common definition of toxicities

The findings led some audience members to ask about the definition of peripheral neuropathy used for switching treatment in Kenya, and Dr Eric van Praag of Family Health International remarked that his field experience in Tanzania had shown that conduct of a neurological examination for peripheral neuropathy was a skill that tended to get forgotten very quickly by doctors after basic training.

Prof. Charles Gilks said that reaching common definitions of all the toxicities being seen by treatment programmes would be very important for pharmacovigilance programmes. "We need common definitions because because I'm not sure what Mbagathi hospital is describing is the same as what's coming out of Rwanda. I also think more training is needed so that health care workers know what to look for."

Without common definitions and diagnostic procedures it would be difficult to define the true incidence, he said. WHO will convene an expert consultation to reach agreement on definitions within the next few months, he went on.

Differences in the incidence of side effects may reflect real differences between populations rather than observation bias, however. Lactic acidosis, another life-threatening side-effect of d4T, has been observed at an unusually high frequency in women with higher body weight (> 75kg), possibly due to fat accumulation in the liver as a result of greater body weight. Much higher body weights have been seen in South Africa in women starting treatment.

Prof. Gilks told **aidsmap** that evidence and programme management were beginning to favour the use of AZT/3TC as the nucleoside analogue backbone in resource-limited settings not only for reasons of safety, but also because the use of this backbone would allow a smaller formulary to be maintained, thus avoiding stock-outs and simplifying procurement. He pointed out that AZT/3TC could also be used in prevention of mother to child transmission and in post-exposure prophylaxis for health care

workers and following sexual assault, both major problems that needed to be addressed within treatment programmes.

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about HATiP

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The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

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