

# HATIP

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## Nevirapine-based fixed-dose combination ARVs

By Julian Meldrum, with many thanks to advisory panel members including, in particular, Dr Vijay Anthony Prabhu (Chennai, India), Desmond Martin (President, Southern Africa HIV Clinicians Society) and Leon Regensberg (Aid for AIDS, South Africa).

This article refers to several presentations at the 2003 Conference on Retroviruses and Opportunistic Infections, held in Boston, USA - for which webcast details are given at the end.

Fixed-dose combination antiretrovirals (FDC ARVs) are products which combine two or more active drugs in one tablet or capsule. In many countries, they now offer the cheapest available route to a complete and effective ARV regimen. There are many potential advantages of using FDCs. The most obvious are the simplification of what is supplied to and taken by individual patients and reduced potential for inappropriate sharing of drugs.

In a managed healthcare system where costs are shared, as is planned in Thailand, these drugs can free up resources to provide more expensive second- and third-line treatment options to those who need them, which is a universal benefit. Standardisation of first-line regimens carries further potential benefits, including the development of simple education packages for healthcare workers and community members and possible economies of scale in laboratory monitoring tests.

Limitations at present include the lack of paediatric equivalents, inadequate provision for lead-in dosing (discussed in detail below) and a number of other shortcomings concerning availability, packaging and provision for reporting adverse events.

This may be the right way to go, for large-scale treatment programmes, but there is still a distance to be travelled before the products are fully suited to that purpose.

### Abbreviations used in this article

3TC = lamivudine

ARV = antiretroviral drug

AZT = zidovudine

d4T = stavudine

NNRTI = non-nucleoside reverse transcriptase inhibitor (e.g. NVP)

NRTI = nucleoside analogue reverse transcriptase inhibitor (e.g.

AZT)

NVP = nevirapine

### Fixed-dose products now available

AZT 300mg + 3TC 150mg + NVP 200mg

DUOVIR-N (Cipla Ltd)

ZIDOVEX-L-N (Imunus Aurobindo)

For lead-in dosing (or if NVP must be stopped)

### AZT 300mg + 3TC 150mg

- use separate drugs, or:

COMBIVIR (GlaxoSmithKline)

DUOVIR (Cipla Ltd)

VIROCOMB (Ranbaxy Laboratories Ltd)

ZIDOLAM (Genix Pharma/Hetero)

d4T 30mg + 3TC 150mg + NVP 200mg

GPO-VIR S 30 (Thai Government Pharmaceutical Organization)

STAVEX-30 LN (Imunus Aurobindo)

TRIOMUNE-30 (Cipla Ltd)

VIROLANS [capsules, d4T 30mg version] (Ranbaxy Laboratories Ltd)

For lead-in dosing (or if NVP must be stopped):

### d4T 30mg + 3TC 150mg

- use separate drugs, or:

LAMISTAR 30 (Genix Pharma/Hetero)

LAMIVIR-S-30 (Cipla Ltd)

VIROLIS [capsules, d4T 30mg version] (Ranbaxy Laboratories Ltd)

d4T 40mg + 3TC 150mg + NVP 200mg

GPO-VIR S 40 (Thai Government Pharmaceutical Organization)

TRIOMUNE-40 (Cipla Ltd)

VIROLANS [capsules, d4T 40mg version] (Ranbaxy Laboratories Ltd)

For lead-in dosing (or if NVP must be stopped):

### d4T 40mg + 3TC 150mg

- use separate drugs, or:

LAMISTAR 40 (Genix Pharma/Hetero)

LAMIVIR-S-40 (Cipla Ltd)

VIROLIS [capsule, d4T 40mg version] (Ranbaxy Laboratories Ltd)

### Links to company websites

[Cipla Ltd](#)

[GlaxoSmithKline](#)

[Hetero/Genix Pharma](#)

[Imunus Aurobindo](#)

[Ranbaxy](#)

### Quality issues and availability

WHO's Essential Drugs and Medicines team has established a project to document the procedures and certification of generic facilities used to produce medicines for HIV and AIDS treatment, which are not registered with the US Food and Drug Administration (FDA) or European drug regulatory agencies recognised by the European Medicines Evaluation Agency (EMA).

The Global Fund to fight AIDS, TB and Malaria has signalled that they will rely on this WHO list as a basis for approving the purchase of generic ARVs and other medicines, so the inclusion of products and of their makers on the list may have an increasing influence on their availability.

The Indian companies Cipla and Ranbaxy already have ARVs on the list; Hetero and Aurobindo products are being assessed. However, most of the products named are not listed by WHO. Ranbaxy's AZT/3TC is the one exception.

The Thai Government Pharmaceutical Organisation makes drugs primarily for domestic use, with a high level of attention to quality control. It is supplying them in limited quantities to Cambodia, Sri Lanka and Laos, and has recently agreed to supply them to Indonesia. It is also supporting a number of African countries in establishing local manufacturing.

Argentina, Brazil, China, Mexico and Vietnam are producing generic antiretrovirals, but with the exception of some AZT/3TC, these do not seem to include fixed dose combination products of the kind discussed here.

WHO Essential Drugs and Medicines - prequalification programme - more information is available through [this link](#)

## Affordability

Whatever the drug combination used, its success for an individual patient will depend on the ability of that person to take it consistently as prescribed.

Where patients are paying for their own treatment as in Kampala, inability to maintain those payments has emerged as the main reason for breaks in treatment, as reported in Boston by Byahihi-Tusiime. While the treatments discussed here are priced as low as US \$35 a month, they are still a long way from being affordable by most people with HIV.

In Uganda, Molly Tumusiime reports there have been times when people went short of food to pay for ARVs, or missed out on ARVs to pay for monitoring tests.

This is a powerful case for subsidising treatment to make it genuinely affordable, as has been done in Senegal's pioneering treatment access programme (described in Boston by Dr Salif Sow) - and as is planned in Thailand.

Failing that, the strategy reported by YRG-CARE of careful and thorough discussion with patients of their financial circumstances before starting on treatment may be helpful to some. However, this is a difficult role for hard-pressed clinical staff to assume. There has to be a limit to the clinic's responsibility, to ensure that the patient understands what treatment they need and how much it costs, and is able to access any support or discounts that may be available to them. Beyond that, it must be a decision for the patient themselves and their family.

PRABHU: ARV therapy has come a long way in India. The financial burden has steadily decreased and remains at around Indian Rs 1500/- (per month) for fixed dose combination triple ARV therapy. The pricing of these potent drugs has received widespread publicity. Generic pharma companies proclaimed their social consciousness and responsibility by introducing these fixed dose ARV drugs at lower prices. But in spite of intense pressure from different groups - patient positive networks, activists and others, these companies have not reduced prices any further, for a variety of reasons. The government does not help matters and continues to impose a sales tax on these drugs.

Most of our patients pay for their own treatment, unless they belong to a special group, of women and children, some of whom have access to "big NGOs", who finance their ARV regimens and provide them free of cost. But it is not without a price to pay. The women and children who are looked after by these NGOs have to stay in residential care homes where overcrowding and TB outbreaks are common. If they leave the homes then they are told that their treatment would be stopped. So while they are provided with food and shelter and ARV drugs, their freedom to move and do as they please is taken away. If they could only afford ARV drugs, they would be truly independent and free!

When patients are paying for their own treatment, I would agree with the Boston report from Kampala, that the main reason for breaks in treatment is the inability to maintain payments for ARV drugs even at low prices. AIDS and poverty go together. There is definitely a need for subsidising treatment to make it genuinely affordable. We try to give concessions to our patients by offering them drugs at distributor rates, but it is only a small fraction of what should be done.

Financial counselling is an academic idea, not transferable into a busy clinic setting. Patients when they visit a doctor want and demand treatment for their clinical condition and alleviation of their suffering. Asking a poor patient about his financial status and

employment rubs salt into his already open wounds, inflicting emotional trauma on a bleeding heart. Certain patients would turn around and say it is none of our business, and it really isn't. "Just treat me as I am, Doctor!"

NOTE: 1500 Indian rupees a month = US \$415 a year. Indian Gross National Income was US \$460 per person in 2001 (World Bank).

## Availability

PRABHU: ARV fixed dose drug combinations are available in major metropolitan cities and towns in India. Since only a handful of pharma shops dispense these ARV drugs, it is sometimes difficult to find out where they are or who dispenses these drugs. Patients in the rural areas have to travel long distances to the neighbouring big towns or cities, spending huge amounts of money, just to gain access to their drugs. Often the pharma shops run out of stocks especially at the end of the month or stock only certain brands and not others, not offering the entire range to the patients.

REGENSBERG: The generic fixed-dose combinations are not yet registered by the Medicines Control Council in South Africa, so we have had limited experience in using them on our programme. We have had some experience with using Triomune in Swaziland. The main problem was dealing with the induction period [discussed below]. The product appeared to be well tolerated, and although we have not yet analysed the data, anecdotally it seemed to be effective, possibly because of better compliance.

MARTIN: In South Africa the only fixed-dose combination registered and licensed for use at the present time is Combivir. Other fixed-dose combinations come from countries outside our borders and are supplied by pharmaceutical distributors who have accessed the drugs from generic manufacturers, particularly in India. My comments relate to my limited experience with these drugs and from discussions with colleagues. To a number of patients they are an attractive option because of price. However, continuity of supply has been problematic resulting in patients stopping therapies and unable to continue with higher priced drugs available in our local market. (Molly Tumusiime reports that the problem of irregular supply has been experienced in Uganda too.)

## Dosing schedules

All of the medicines listed above are taken as one tablet, twice daily (12 hour intervals), with or without food.

The only choices that should need to be made are whether to start with AZT or d4T, and if it is d4T then to choose a dosage (40mg or 30mg) on the basis of body weight (greater or less than 60kg).

Unfortunately, it is not quite that simple in practice.

## Lead-in dosing: starter packs needed

When nevirapine (NVP) is first started, it should be administered at half dose for the first 14 days, i.e. 200mg once a day instead of twice daily. However, the other drugs in the combination should be administered at full strength.

It is clear this often doesn't happen as it should. As described by Dr Martin, below, some patients are still starting on full-dose NVP, risking avoidable NVP reactions.

Others have been started on one triple combination tablet a day, so the nucleoside analogues are under-dosed, risking selection for drug-resistant HIV. Hosseinipour reported in Boston that this was done in Malawi, when Triomune first became available in Lilongwe

and Blantyre. Studies are now under way to find out whether this led to any avoidable drug-resistance.

Other patients are prescribed separate drugs for the initial period of treatment. However, as Dr Prabhu explains, there can be serious problems with this, because the quantities in which the drugs are sold are not matched to how they are meant to be taken.

There is an obvious solution to all of these problems: combining two different fixed dose combinations (with and without NVP) in a blister pack, marketed as a "starter pack".

Symbols on a 7-day, 14-dose blister pack could make it clear which tablet/capsule is the morning dose and which is the evening dose. This should be reinforced by clear written instructions in local languages.

7-day packs would also reinforce the point that the drugs must be taken daily (including at weekends) and make them convenient to carry.

If patients have to pay for them, they should cost exactly the same as the triple combination drugs, so there is no incentive to continue with the starter doses for longer than two weeks.

The companies will doubtless complain that they need regulators' approval for any variations in drug packaging, which costs them money and takes time. However, the public health need for this development is obvious and any company that undertook it should benefit from having its products recommended as first choice for patients starting on ARV treatment for the first time.

MARTIN: It is our experience (in southern Africa) that with Triomune patients begin on the higher dose from Day 1. It appears that dose escalation is just too much bother for the physicians to explain and the cost of buying the separate drugs is not something they feel able to inflict on their patients.

PRABHU: The lead in or build up dosing schedule of NVP in combination with d4T/3TC or AZT/3TC is confusing for some patients. NVP is available separately in a container of 60 tablets, which with the lead in dosage schedule leads to a wastage of about 15 tablets in the initial pill box. Patients do not seem to understand this and continue to consume NVP alone even when the LAMIVIR S 30 mg pill box [which also contains 60 tablets] is empty at the end of the month. They feel they must finish both boxes before starting on the next and end up taking NVP alone [which carries a high risk of selecting NVP-resistant HIV], even after any amount of explanation! The patients end up paying hard-earned money for NVP which they cannot and should not use.

### Other packaging issues

PRABHU: Certain patients who live far away [from where treatments are available] access their drugs through mail or courier. But on arrival at their home, the tablets are in powder form! These tablets are not packed for long journeys. Pill box covers are very loose and fall off at the earliest opportunity, making it very difficult to identify the drugs the patients are on, especially since doctors who prescribe these drugs do so in secret with no written prescriptions in the patients hands and no means of identification on the tablets themselves. Certain companies package their ARV drugs with a red AIDS logo boldly embossed on the packaging material, which patients find difficult to use, especially when they are travelling in public.

### Supporting adherence

No matter how simple the treatment, it is still vital to spend time making sure that the patient understands how the treatment works.

MARTIN: It has been my experience that provided adequate counselling is given prior to the commencement of ARVs, adherence to the regimens is remarkably good. This is often in the face of difficult work circumstances related to shift-work but the patients have been very innovative in developing strategies to remember their drugs. Clearly simplified dosage forms are preferable (twice-daily). Our experience has shown that the use of "the buddy system" has been the most effective. I think that in our populations where HIV is a rampant epidemic the patients who are able to access antiretrovirals do so with a commitment that will lead to impressive compliance. Peer counselors who themselves have had a turn around in their disease can be very helpful.

### Managing nevirapine skin rash

The main risk associated with NVP, especially in the early stages of treatment, is a skin rash which, in its most severe form (Stevens-Johnson syndrome) can be life threatening. Liver toxicity is also of concern and requires prompt action if detected.

If a rash develops, patients need to be advised to return to the clinic to evaluate it.

If the rash is mild, then it may be best to try and treat through, so long as patients understand the need to return if the rash gets any worse. Treatment with corticosteroids does not help (in fact it may make it worse).

If a rash is severe, or getting worse, then NVP must be stopped. Ideally, the nucleoside analogues should be continued for another week to try and prevent the emergence of virus with resistance mutations to NVP - so the possibility of using efavirenz (which is vulnerable to the same mutations) is kept open for the future.

Liver toxicity is a serious risk with NVP and monitoring for this is a key responsibility for prescribers.

Additional information on NVP and other ARV side effects is available on [aidsmap](#) (see links at the end of this article).

PRABHU: NVP skin rash is common, usually mild to moderate. Especially when it affects women and girls, much desperation sets in. The patients may already be suffering from HIV related pruritic papular dermatitis from which they are seeking relief. Usually with the advent of ARV drugs, their rashes come under control, which can be a good indicator of the success of treatment. But if such a patient develops a NVP associated skin rash, it becomes exceedingly difficult to distinguish failure of therapy from adverse drug reaction. Serial CD4 counts and HIV RNA viral loads are a luxury few patients can afford. Liver Function Tests might shed light on the subject by showing elevation of transaminases. Finally it boils down to a clinical decision taken on the table, to stop NVP or persist with it and manage the skin rash symptomatically. If the general condition of the patient continues to deteriorate, then it is obvious that ARV drugs are not working and NVP must be stopped and alternatives chosen. A risk versus benefit analysis, and knowledge of any prior ARV use, should guide the decision making process.

MARTIN: Information regarding toxicities involving the liver, skin rashes or Stevens-Johnson Syndrome are lacking: while patients are warned, there is no proper system for reporting adverse events for these unlicensed products. Because these patients have limited financial means laboratory monitoring (liver enzymes) is not carried out in the vast majority of cases.

### Are there downsides to simplified treatment?

The idea that HIV treatment can be reduced to one tablet, twice daily, is powerfully attractive to physicians as well as their patients. One risk is that "familiarity breeds contempt".

PRABHU: Generic pharma companies are as keen as any other to motivate and induce doctors to prescribe their drugs. "Prescriptions doctor for our product", "cheap and best", "reminders" are some of their slogans we hear day in and out. With all this pressure from pharma companies, and from patients who are desperate, it is very easy and simple to prescribe, but it needs more than strong will power, at times, to take a balanced decision not to prescribe.

I am no longer surprised to come across prescriptions for these drugs for a short duration of time, sometimes as short as a week's duration, as though we are treating a common cold! Sadly the concept that where HIV is concerned therapy is lifelong is missing amongst a vast majority of general practitioners [in India]. So if one combination does not work, then just change to the other - very simple - with the result that we are soon back to where we started.

MARTIN: A source of concern is that the widespread and often sub-optimal use of regimens containing nevirapine will lead to resistance to the nevirapine component and compromise mother-to-child nevirapine-based transmission interruption programmes.

### How effective are these combinations?

The major reason why NNRTIs such as nevirapine are preferred to protease

inhibitors for first line treatment, is that they are more easily tolerated (despite carrying risks, of which patients and providers must be aware). Superior virologic performance has also been reported, almost certainly because these combinations are less dependent than the protease inhibitors indinavir and nelfinavir, in particular, on taking treatment correctly in relation to meals.

One limitation is that NNRTIs are not effective against HIV-2 or HIV-1 group O viruses, so if these are present a protease-inhibitor based combination is likely to be needed.

A randomised trial which compared NVP, efavirenz, and a combination of the two drugs (the 2NN study, funded by nevirapine's maker, Boehringer Ingelheim), was reported at the Boston Retrovirus Conference (see links to news stories at the end of this article). It found that NVP and efavirenz gave comparable results in terms of viral suppression. However, there were two deaths (from liver failure) among people treated with nevirapine, which reinforces the need for care in its use.

Following a series of trials which have shown efavirenz to be comparable or superior to protease inhibitors, these reports are important for providers to have confidence that the fixed-dose combinations now on offer can be as effective as more costly treatment options. There is also some data on the equivalence of various NVP formulations, including generic ones. So far, this is reassuring.

### Stavudine (d4t) Vs Zidovudine (azt)

There is a groundswell of medical opinion, in countries where people with HIV usually start medical treatment at CD4 counts above 200, against using d4T as a first-line therapy. The prevalence of neuropathy and a (still-controversial) association between d4T and loss of fat (especially on the face) have relegated the drug to second choice for many. There is clearly a strong case not to prescribe higher doses of d4T than are needed. If a patient weighs less than 60 kg, the 30mg dose of d4T should be prescribed.

In settings where anaemia is widespread (and closely correlates with mortality risk) and patients usually begin treatment at very low CD4 counts, the actual risks are different and it may not be unreasonable for doctors to prefer d4T as their first-line treatment.

The reason why more combinations have been launched based on d4T rather than AZT, is that the higher potency of d4T, by weight, makes it cheaper (per dose) than AZT. At a retail level, this translates to a difference of around US \$5 per month (US \$35 vs US \$40) which clearly makes treatment more sustainable where patients pay for it.

Lipoatrophy has been seen in Thailand and India, and must be presumed to affect Asian populations as it does Caucasians/Europeans. There is some evidence from both longitudinal and cross-sectional studies that lipoatrophy is more frequent among Caucasians than among people of African descent. So the extent to which it will occur among African populations is still unclear. But for those who suffer from it, the implications will be much the same everywhere.

PRABHU: AZT is used by a large number of practitioners, though patient tolerance of AZT is low. Complaints of myalgias, headache are common, but what is worrying is development of severe anaemia, for which blood transfusions are used enthusiastically with all the attendant risks. Management of ARV drug toxicity is difficult.

When HIV is already far advanced and when clinical anaemia is obvious, then d4T is the preferred drug. Peripheral neuropathy is painful and slow to respond. Cessation of d4T is sometimes the option chosen, but because of other limited options, dose reduction is attempted to see if it responds.

The development of disfiguring fat atrophy is sometimes noticed by the patients, but generally attributed to the progression of HIV. Remarks that their friends or colleagues find them run down are common, since it is most visible in the face. Patients are worried that in spite of therapy they are losing fat, which for them connotes that they are losing weight and so deteriorating. Counselling and reassurance are at present all that we can offer our patients for this disfiguring problem.

MARTIN: Scant attention is paid [in Southern Africa] to differing dosage forms for Triomune so that a number of patients are overdosed with the 40mg d4T dosage form and the risk of drug-induced neuropathy is increased. d4T-containing fixed-dose regimens in the presence of treatment for tuberculosis will lead to increased occurrence of neuropathy.

### Alternatives to these fixed-dose combinations

While one pill or capsule, twice a day, may be the simplest treatment regimen available, others do come very close to it.

Triple nucleoside therapy - using a fixed dose combination of abacavir, AZT and 3TC (marketed as Trizivir by GlaxoSmithKline) is one option that has been explored in clinical trials. Unfortunately, there is now some evidence that this is inferior to AZT/3TC/efavirenz in the level and durability of viral suppression (see news report, listed at the end of this article).

Even at the concessionary price of US \$135 per month, Trizivir is not widely affordable (although a generic version, which may be cheaper, is promised by the Indian company Ranbaxy). In addition, there are serious concerns about hypersensitivity reactions to abacavir, affecting up to 5% of patients (although its association with a genetic predisposition, based on HLA types, may mean that some populations are relatively safe from it). Unfortunately, these reactions are hard to distinguish from common fevers and flu-like illness and may be life-threatening if unrecognised and/or treatment is continued or re-started. Trizivir may therefore need to be reserved for second- or third-line treatment, combined with one or more other drugs. The serious risk of deaths if reactions are not

identified argues against its widespread use by non-specialist physicians.

A dual nucleoside in combination with the once-daily non-nucleoside reverse transcriptase inhibitor efavirenz (available in some countries in generic versions, or at a discount or through donation schemes from the brand-name manufacturers) is almost as simple to take as the nevirapine fixed-dose combinations. Efavirenz may be safer than nevirapine but carries its own risks. Many patients experience disturbing psychological effects, especially in the first few weeks. There is evidence from animal studies that efavirenz may cause birth defects if mothers are treated with it, which is a concern for women who may wish to have children.

A number of drugs now being developed for once-daily use may yet emerge as serious alternatives to nevirapine. In particular, the US company Gilead's nucleotide analogue tenofovir may be better than abacavir in combinations with two nucleoside analogues. Gilead has committed itself to selling tenofovir at no profit in less wealthy markets, but the price may still be higher than for most of the other drugs discussed here ( US \$40/month as a single drug). The safety of tenofovir in pregnancy and for young children has not been established. Gilead is planning to introduce a fixed combination of tenofovir with FTC (emtricitabine, a more potent variant of 3TC).

Protease inhibitors all suffer from complex manufacturing processes and high dosage requirements which make them relatively costly. In most cases, dietary restrictions make them relatively difficult to take. It is therefore likely that they will continue to be reserved mainly for use where other drugs cannot be tolerated or do not work.

PRABHU: Introduction of triple nucleoside therapy is recent and experience with the combination drug limited. It may be useful in HIV patients co-infected with TB, when the interactions [of rifampicin] with NNRTI's are avoided. Its expense makes it unattractive as an initial ARV package for naive patients who are symptomatic, for whom a cheaper and more potent NRTI/NNRTI fixed dose combination pill may be more appropriate. Resistance to three NRTIs may be difficult to manage and the salvage regimen to be implemented may be even more expensive.

MARTIN: Trizivir is not yet available in South Africa however one would anticipate problems related to use of this drug. While its use in the presence of tuberculosis treatment is an attractive option its efficacy remains questionable. In our settings, where tuberculosis is the commonest opportunistic pathogen, there is an associated high viral load and the use of this particular combination will remain problematical.

A lot of patients who are accessing cheap drugs do not have ready access to healthcare facilities and one is concerned that abacavir hypersensitivity will go unreported with potentially fatal consequences.

REGENSBERG: I agree with your concerns and those of Dr Martin regarding abacavir. We believe it has a role, preferably in first line therapy, if the viral load is <100,000 and the patient is being treated for tuberculosis or if there is NNRTI intolerance. The branded drug is unfortunately still very expensive, however, so it is frequently unaffordable.

## Paediatric dosing

Best practice in paediatric treatment relies on liquid suspensions, of which a limited range are available, often only in branded versions, at very high prices.

For example, in Uganda, no generic suspensions are available, observes Dr Henry Barigye. A generic tablet of 3TC 150mg costs 270 shillings but 30mls (150mg) of the GlaxoSmithKline suspension costs 10,500 shillings, which is 40 times as much. For combined AZT 300mg/3TC 150mg, the costs are 655 shillings and 18,612 shillings - more than 28 times as much.

Even in India, there is no suspension available for d4T. Yet many babies and young children are anaemic and have problems tolerating AZT.

Professor Norman Nyazema, a pharmacologist who has served as a senior technical advisor to the Medicines Control Agency of Zimbabwe, insists there can be no short cuts. Splitting tablets is unacceptable as a basis for licensing a drug for use in paediatric treatment, and if doctors use a drug beyond its license, the manufacturer cannot be held liable for the consequences. Companies that claim they are meeting public health needs by providing low-cost generic formulations must be pressed to provide a full range, including suspensions for paediatric use.

There is no immediate answer to this dilemma. Liquid formulations suitable for children are clearly needed. Equally, many doctors will continue to split tablets to provide treatment for patients who will otherwise go untreated. What follows is not an endorsement of this practice, but reflects advice received on how to minimise its dangers.

When tablets are split, it is not possible to ensure the two halves are exactly equal in size. On the other hand, this may even itself out over time, especially if the two halves are given as successive doses to the same patient. If a drug is manufactured to international standards (Good Manufacturing Practices - GMP) then the distribution of the drug within tablets should be as even as its distribution between tablets. Whether a tablet is scored or not makes no difference.

The bigger problem is, that half doses (or quarters) may not be the right dose for a particular patient. The correct dosage varies in different ways for different drugs, which makes the splitting of FDCs even more of a problem. Splitting of Triomune (a triple combination) is even less advisable, because it appears to be made by sticking two tablets together.

The correct dosage of d4T and 3TC varies according to the weight of a child.

The formula for d4T = 2mg/kg/day, up to 30kg, split into two equal doses, and then 30mg twice daily for body weight between 30kg and 60kg. Thus, half the 30mg dose, twice daily, might be correct for a child weighing 15kg; and half the 40mg dose, twice daily, might be correct for a child of 20kg.

The formula for 3TC = 8mg/kg/day. Half of the 150mg dose, twice daily, would be correct for a person weighing approximately 20kg. A slight overdose of 3TC is likely to cause fewer problems than an overdose of d4T, but is still not advisable.

The dosage of AZT and nevirapine is varied according to the surface area of the child, which is best calculated using a nomogram based on the child's height and weight. This works by drawing a straight line between the height (on one scale) and the weight (on another scale); this crosses a third scale at a point which gives the surface area in square metres.

An example of such a chart is available online [here](#) (countries may have different national reference standards, which should be used for this purpose).

For AZT the daily dose is 360mg/square metre/day (divided into two doses).

For NVP the daily dose is 300-400mg/square metre/day (divided into two doses). The same procedure for lead-in dosing (described earlier in this article) applies to children as well as to adults.

PRABHU: The lack of choice in paediatric formulations is particularly worrying, since with the increasing number of MTCT interventions that are taking place, more paediatric AIDS cases are being diagnosed. Only AZT, 3TC and NVP suspensions are available. Anaemia which is so common in children makes it difficult at times to persist with AZT. d4T is chosen, but with lack of availability of paediatric formulations, adult tablets are split to provide for paediatric doses. This is not good practice, but in the absence of alternatives, we are left with no choice!

### Further information on aidsmap

[3TC - overview \(lamivudine\)](#)

[Abacavir - overview](#)

[azt - overview\(zidovudine\)](#)

[d4t - overview \(stavudine\)](#)

[Efavirenz - overview](#)

#### RELEVANT NEWS STORIES

[Major PI-sparing study closes Trizivir arm due to inferiority to efavirenz arms](#)

[2NN study shows nevirapine equal to efavirenz, but has better lipid profile](#)

[Tenofovir approved for first-line therapy in European Union](#)

### Boston presentations

The most relevant presentations at the Conference on Retroviruses and Opportunistic Infections held this February in Boston are all included in one webcast, of a Thursday afternoon session. In particular, Mina Hosseinipour on Malawian experience with Triomune, N Kumarasamy from YRG-CARE in India, and L Emberti Gialloretti, reporting on the use of ARVs in Matola, Mozambique. Paul Farmer, from Harvard University, reporting on experience in Haiti, and J Byahihi-Tusiime from Makerere University reporting on the affordability of treatment as a barrier to ARV adherence in Kampala, Uganda, also made relevant comments.

To view these webcasts, you need to have RealPlayer software installed on the computer - which is available as a free download but is quite a large program. The webcasts can be viewed [here](#)

Whatever computer you are using, it is best to choose the "Play Audio Only" version - you will still see the slides presented.

## about HATIP

A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

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

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