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Second-line therapy

Key points

- **The need for second-line therapy is still low but this may change over the next few years.**
- **Lack of viral load testing means that many people who are failing treatment go undetected for long periods; this results in high levels of drug resistance, especially to the nucleoside analogue (NRTI) class.**
- **High-level NRTI resistance could make it difficult to assemble a second-line drug combination.**
- **A WHO expert consultation recommended two NRTI backbones for use in second-line treatment: tenofovir plus 3TC or FTC, or abacavir/ddl.**
- **The consultation recommended a boosted protease inhibitor should be used in second-line treatment, either lopinavir/ritonavir or atazanavir/ritonavir.**
- **If boosted protease inhibitors are used, it is important to ensure that they are products that have received tentative approval by the US FDA for PEPFAR use, or WHO prequalification. There are quality concerns about some versions of lopinavir/ritonavir not approved by these agencies.**
- **Responses to second-line regimens have been good in the small cohorts of patients reported so far, but there is very little information about the effects of the regimens recommended by the WHO expert meeting. Several large trials are planned in sub-Saharan Africa to test their effectiveness.**
- **Studies are also looking at several other approaches to second-line treatment. These include giving a boosted protease inhibitor as the only treatment (monotherapy) or using two drugs from new classes (a protease inhibitor and an integrase inhibitor)**
- **All second-line drugs remain significantly more costly than first-line drugs, so preventing failure of first-line treatment is critical.**

The need for second-line treatment

It's widely accepted that second-line treatment is the next challenge facing countries currently scaling up antiretroviral therapy.

But what are the practical implications of beginning to provide second-line treatment? How likely is it to work for the patients who have already experienced the failure of their first ART combination?

A 2007 survey by the WHO AIDS Medicines & Diagnostics Service showed that the market for second-line ARV treatment is still small, and is not growing as rapidly as expected. The survey was unable to determine whether the reason for lack of growth in the numbers on second-line was the cost of second-line treatment, or a lack of access to tests that would spot immunological or virological failure on treatment, or the possibility that people are doing better than anticipated on first-line treatment and don't need to switch. (We

covered the subject of how to spot treatment failure in HATIP in [September 2007](#)).

And in the field, second-line therapy isn't such a burning issue at present.

"The major issue in southern African countries, rather than second line, is getting people onto first line therapy. In reality, second-line therapy is still a small problem," Dr Catherine Orrell of the University of Cape Town told HATIP.

But studies in the developing world show wide variations in first-line failure rates, and accumulating evidence suggests that when it is eventually initiated, second-line treatment is likely to prove challenging.

Studies of drug resistance in people failing first-line treatment in developing countries are beginning to show a consistent and worrying trend – between a third and one-half of all patients failing the standard first-line regimens have high-level cross-resistance to nucleoside analogues – particularly AZT, abacavir and ddl, all of which are recommended for use as second-line nucleoside analogues by various national guidelines.

They also have a resistance profile that may result in a reduced response to tenofovir, the only other reverse transcriptase inhibitor recommended for second-line treatment by the World Health Organization.

The reason for this worrying state of affairs is not poor-quality drugs, as some ill-informed news reports have alleged, but the absence of viral load testing that can detect viral rebound early (we covered this issue in [HATIP #80 in January 2007](#)). The higher viral load rises, and the longer a patient is left on a failing nucleoside analogue-based drug combination, the more likely they are to accumulate resistance mutations that will compromise the effectiveness of second-line treatment.

Nucleoside analogue resistance: an introduction

In a person who is not taking treatment, the population of viruses will tend to be those most 'fit' to reproduce. Resistant viruses will occur at random, and form only a tiny part of this population.

While taking anti-HIV drugs, drug-sensitive HIV will be suppressed, that is, prevented from reproducing. If few or no drug-resistant viruses are present, and drug levels stay high enough, HIV should remain suppressed. However, any drug-resistant viruses will still be able to reproduce. Over time, this "selective pressure" can shift the pool of HIV in the body to include fewer drug sensitive viruses and more resistant strains.

Drug-resistant virus may be present from the time of infection (see [Transmission of drug-resistant HIV](#)), may develop before treatment begins, or may develop after starting treatment, particularly if drug levels are not constantly kept high enough to suppress the virus from replicating.

The most likely reason for low drug levels is non-adherence – whether due to interruption of drug supplies or because the patient does not take the drugs every day. Once viral load begins to creep above the limits of detection (50 copies/ml), numerous studies have shown that the risk of developing drug resistance increases.

Most resistance is caused by changes in the genetic material of HIV. Just as the human body is based on the genetic code in its DNA, HIV carries its own code in the RNA that makes up its genetic material, or genes. Random changes (mutations) in these genes cause changes in the resultant virus, some of which lead to drug resistance.

HIV (like all living organisms) uses complex proteins, called enzymes, as a "toolkit" with which to operate. A viral gene is actually

a set of instructions for building a particular enzyme. Each enzyme (for example, reverse transcriptase) is a specific sequence of building blocks called amino acids, which form a long tangled chain. There are twenty different amino acids, each referred to by a single-letter code.

The gene that corresponds to each enzyme is a long molecular "blueprint" for that enzyme. The gene is a long chain of RNA laid out like a string of beads, in which each "bead" (actually called a codon) describes which amino acid comes next in the enzyme-building sequence. Changing just one amino acid can alter the resulting shape of the completed enzyme. This changes its physical and chemical properties and can possibly lead to the development of drug resistance.

Resistance mutations are referred to by a number which identifies the codon (the position along the gene where the mutation has taken place). The number often has letters before and/or after it; e.g., M184V. The first letter refers to the amino acid found in non-mutated or 'wild type' HIV. The second letter refers to the new amino acid that is inserted by the mutant HIV. The first letter is sometimes omitted (e.g. 41L).

For example: M184V is a mutation in the reverse transcriptase gene that causes resistance to 3TC (lamivudine). It is caused by a mutation at codon number 184 in the reverse transcriptase gene. This mutation means that an amino acid called methionine (M) is replaced by valine (V) in the reverse transcriptase enzyme. Virus with the M184V mutation is able to replicate in the presence of 3TC.

Resistance to the nucleoside analogue class of drugs arises in a number of ways.

Resistance to lamivudine (3TC) or emtricitabine (a chemically similar drug, also known as FTC) arises as the result of one change in the reverse transcriptase gene (the M184V mutation). It can arise quickly after viral load rebounds above the limit of detection, and is the most common form of drug resistance in people failing first-line treatment.

However 3TC resistance has some long-term benefit, because it reduces viral fitness, thus limiting viral rebound. So, maintaining 3TC resistance where complete viral suppression is impossible has been proposed as one strategy for limiting disease progression in treatment-experienced patients taking failing therapy. One study, which randomised people on failing treatment with 3TC resistance either to stop treatment completely or continue with 3TC alone, found a higher rate of immunological and clinical failure in the no-treatment group after 48 weeks (69% vs 41%).¹ However a larger study, in which people with HIV were randomised to continued 3TC or no 3TC in addition to a salvage regimen, was unable to detect any benefit of continued 3TC on the rate of viral suppression, and the study was not sufficiently powered to detect an immunological or clinical benefit.²

Resistance to AZT or d4T accumulates gradually as several different mutations emerge, one after the other. These drugs are known as thymidine analogues, and the mutations that give rise to resistance to AZT and d4T are called thymidine analogue mutations (TAMs). These mutations may accumulate in two different patterns that give differing levels of cross-resistance to other NRTIs, according to whether AZT or d4T is the drug used in first-line treatment (although see the note on the DART study below). If d4T is used first, the TAM-1 mutation pattern tends to emerge, leading to high-level AZT resistance and cross-resistance to other NRTIs (particularly ddI and tenofovir). If AZT is used first the TAM-2 mutation pattern tends to emerge, which leads to less NRTI cross-resistance.

Resistance to abacavir, ddI and tenofovir emerges through more complex `pathways` - several different combinations of mutations can give rise to resistance to each of these drugs.

- In the case of abacavir, resistance may arise as a result of high-level resistance to AZT or d4T and 3TC. When four or more TAMs are present, the virus begins to lose susceptibility to abacavir.
- ddI resistance occurs where the TAM-1 profile associated with d4T treatment is present; 3TC resistance does not seem to affect response to ddI.
- Tenofovir resistance emerges either where the K65R mutation is present, or where four or more TAMs have accumulated.^{3, 4} It is worth noting that if the K65R mutation emerges after first-line failure of tenofovir, HIV cannot develop high-level resistance to AZT as long as the K65R mutation is present in the dominant virus population.⁵

Snapshots of drug resistance from around the world

WHO recommends that every country should carry out drug resistance surveillance in cohorts of patients receiving first-line antiretroviral therapy at a range of sites reflecting the mix of clinic types providing HIV care. Genotyping should be carried out in all patients with detectable viral load after one year on treatment, and yearly thereafter for five years if resources permit.

In most countries national surveillance activities are just beginning, but a number of surveys carried out by independent groups and within a large clinical trial provide suggestive data.

China

The most comprehensive data come from China, where a national drug resistance survey was carried out in 2006/2007.⁶

The survey randomly sampled 10% of patients receiving first-line therapy through China's national ART programme, and carried out resistance testing in all patients with viral load over 1,000 copies/ml.

One-third of patients surveyed had a viral load above 1000 copies/ml, and 25% of all patients surveyed had some evidence of drug resistance (55% to NNRTIs, 36.8% to NRTIs and 1.7% to protease inhibitors).

Resistance patterns may have been influenced by the use of AZT/ddI and d4T/ddI as the nucleoside backbone during the earlier period of the ART programme - around 45% of patients took one of these backbones alongside nevirapine. The remainder received AZT/3TC or d4T/3TC with either nevirapine or efavirenz.

Malawi

[A prospective study of resistance](#) in 94 Malawians failing first-line treatment with d4T/3TC/nevirapine (failure defined as either the development of a new Stage 4 condition, or a decline in CD4 cell counts to 50% of the pre-treatment CD4 cell count baseline) found NNRTI resistance present in 93%, 3TC resistance in 84% and thymidine analogue mutations in 56%. Some degree of resistance to tenofovir was present in 23% of patients while 17% had nucleoside analogue mutations that confer resistance to the whole class of drugs.⁷

South Africa

[A study of resistance patterns](#) in 124 patients who experienced virologic failure of first-line ART found dual class resistance in 64% and at least three thymidine analogue mutations in 13%.

A recent opportunistic infection on treatment, or World Health Organization (WHO) stage 4 HIV disease prior to starting treatment, were the strongest predictors of the development of resistance.⁸

[Resistance data](#) from 110 patients who experienced failure of first-line therapy while receiving treatment in Gugulethu township found that the frequency of thymidine analogue mutations increased over time among patients failing therapy (the predominant regimen was d4T/3TC/efavirenz) and that unexpectedly, 10 of 110 had the K65R mutation associated with tenofovir resistance, despite no exposure to the drug. The findings confirm [a previous observation](#) that HIV-1 subtype C has a propensity to develop a K65R mutation after failure of a d4T-based regimen, unlike subtype B.⁹

Nigeria

In 79 evaluable samples from patients on ART (d4T/3TC/nevirapine or efavirenz) initially monitored for emergence of clinical symptoms or declines in CD4 cell count as potential indicators of treatment failure, 30% had four or more nucleoside analogue mutations (including 3TC) and 45% had at least two NNRTI mutations. [Fifty-three per cent of patients had no active NRTI left for use in second-line treatment.](#)¹⁰

Vietnam

A study of 248 patients on first-line therapy (d4T/3TC/nevirapine) with suspected treatment failure underwent viral load and resistance testing; genotypes were evaluable for 136 patients, of whom 89% had at least one resistance mutation. Nucleoside analogue resistance was found in 95% and NNRTI resistance in 88%. Forty-five per cent had at least three TAMs and 7.5% had the mutation Q151M, which confers resistance to the entire class of nucleoside analogues.¹¹

DART study (Uganda and Zimbabwe)

The virology sub-study of the DART trial reported on 24 and 48-week genotypic resistance patterns in 20 and 35 patients respectively.¹² Patients in this study were taking an initial regimen of AZT, 3TC and tenofovir. Since patients may have experienced viral rebound after week 24, and because baseline results were not available for all participants in the sub-study, this is not a strict longitudinal analysis (only 7 patients had sequences available for weeks 24 and 48). However, the proportion of patients with 4-6 TAMs grew from 4% to 39%, and all had the M184V lamivudine-associated mutation too.

The authors note that unlike patients in the other studies outlined here, the group of patients with 4-6 TAMs in the DART study still had two drug classes – boosted protease inhibitors and NNRTIs – to call on for second-line treatment (although 4% had baseline NNRTI resistance upon entry to the study).

The study also showed that contrary to previous expectation, thymidine analogue resistance did not always evolve along the pathway usually seen as a result of AZT treatment. At week 48, 57% had a mutation profile that showed a mixture of mutations from the TAM-1 and TAM-2 pathways.

Haiti

Analysis of viral suppression and drug resistance was reported from the GHESKIO cohort – patients receiving free antiretroviral treatment at a Port-au-Prince clinic. Of 79 evaluable patients, 51% had a viral load below 50 copies/ml, with >95% adherence highly predictive of viral suppression. A further 32 patients had viral load above 1000 copies/ml and could be evaluated for drug resistance.

Virus could be sequenced in 29 cases, of which 25 showed drug resistance mutations. One-quarter had two or more thymidine analogue mutations, and 72% had resistance to both 3TC and the NNRTI class.¹³

Consequences for second-line treatment

There is still little evidence about responses to second-line treatment in relation to resistance, to the viral load threshold used to determine switching or to the duration that elapses between virologic failure and a treatment switch.

Limited data to address these questions were presented at the Sixteenth Conference on Retroviruses and Opportunistic Infections in February 2009.

In particular, Mina Hosseinipour of the University of North Carolina presented treatment response data from 101 patients who met WHO clinical or immunological criteria for failure and switched to second-line treatment in Malawi. Resistance patterns in this cohort were described in the previous section.

Switchers initiated a regimen of AZT/3TC/tenofovir and lopinavir/ritonavir. Ten patients died during the 12-month follow-up period, 3 were lost to follow-up, and 85% of survivors had a viral load below 400 copies at 12 months. Twenty-five of the participants developed a new HIV-related infection in the first six months after switching.¹⁴

Although levels of NRTI resistance were high, Mina Hosseinipour said that resistance did not predict virologic response. But commenting on the presentation, Professor David Cooper of the University of New South Wales, Australia, said that “lopinavir/ritonavir is doing a lot of the work in these patients.” (The use of lopinavir/ritonavir monotherapy in second-line treatment is discussed later in this article.)

A large cohort from Johannesburg's Themba Lethu clinic also reported relatively good responses, with 89% of 382 patients still alive and in care a year after switching to second-line treatment with AZT/ddl/lopinavir/ritonavir. Seventy-eight per cent had an undetectable viral load.¹⁵ The mean time to switching was 200 days; “compared to most government hospitals this is fairly rapid switching,” said presenter Prudence Ive of the University of the Witwatersrand.¹⁶ No data on response according to resistance profile were available.

[Previously presented data](#), from MSF programmes and from Cambodia, also highlight the long delay between virologic failure and switching to second-line treatment. Nevertheless, 89% of 113 Cambodian patients who switched to second-line treatment consisting of lopinavir/ritonavir plus 3TC/ddl had undetectable viral load a median of 10 months later, and all were still alive.¹⁷

In a review of its programmes MSF found a switch rate of 4.8 per 1000 person years of treatment – lower than expected – with 86% of patients alive and in care 12 months later. Viral load data were not available, but good CD4 cell gains were reported (+135 cells at 12 months).¹⁸ Switching in response to a new AIDS-defining illness, or at a CD4 count below 50 cells/mm³, was associated with a higher risk of death.

Solutions for second-line treatment

In circumstances where somewhere between 10% and 55% of patients may have high-level nucleoside analogue resistance, what is the most appropriate second-line regimen?

If thymidine analogues were used in first-line therapy, [international experts have recommended](#) two nucleoside backbones – abacavir/ddl and tenofovir/3TC – should be prioritised

for development and purchase. One of these pairs should be used alongside a ritonavir-boosted protease inhibitor - either lopinavir/ritonavir (*Kaletra*) or atazanavir boosted by ritonavir. (Ritonavir, another HIV protease inhibitor, has a boosting effect on the levels of the other protease inhibitor, but no therapeutic effect in itself).

A boosted protease inhibitor is recommended because it is more potent and less prone to the development of resistance, even in patients with poor adherence. This is partly because high-level protease inhibitor resistance is slower to emerge than high-level resistance to other drug classes.

The recommendation came from a meeting convened by WHO in 2007 ([see meeting report](#)). The intention of the meeting was to consolidate country choices around a smaller number of drugs so that prices of the most desirable agents can be driven down by larger orders.

The WHO expert consultation made its recommendations on the basis of six considerations: efficacy, simplicity of dosing, toxicity, population coverage, potential for low cost, and compatibility with paediatric formulations to promote integrated care.

The experts judged that, weighing all the factors together tenofovir/3TC and abacavir/ddi were the most suitable backbones, and most likely to lend themselves to rapid development as co-formulations in fixed-dose combinations.

The decision to slim down the range of second-line drug choices follows requests for advice from national treatment programmes concerned about the potentially large number of drugs they might need to approve and include in their national formularies. Clearer guidance on which drugs are likely to prove most effective after the failure of standard first-line regimens was also required.

A smaller range of drugs may also help drug regulators to decide which generic and branded products to prioritise for registration around the world, and may encourage the growth of demand for the products, which should feed through into lower prices eventually.

But for the time being, the price of two drugs recommended for the second-line nucleoside backbone remains high.

Abacavir approved by the US FDA costs a maximum of \$300 a year for countries with purchasing agreements through the Clinton HIV/AIDS Initiative; WHO pre-qualified products for countries in sub-Saharan Africa outside this consortium cost between \$334 and \$437 a year. Countries in Asia and Latin America not able to purchase drugs through CHAI must negotiate prices individually.

Didanosine approved by the US FDA costs \$240 a year for a 400mg enteric-coated capsule version (\$150 a year for the 250mg capsule recommended for those weighing less than 60kg) for countries with purchasing agreements through the Clinton HIV/AIDS Initiative. For countries outside this consortium, Bristol Myers-Squibb offers the 400mg capsule at \$288 a year in sub-Saharan Africa and the low-income countries of Asia, and \$319 in southern Africa.

In comparison, a tenofovir/3TC tablet sourced through the Clinton HIV/AIDS Initiative purchasing consortium costs \$159 a year, although no product is yet pre-qualified by WHO.

It's a big price difference.

For many countries tenofovir will remain a second-line drug for the time being, due to its higher price (see [HATIP 111, June 2008](#), for further discussion of this issue). This means that tenofovir can be expected to exert a strong antiretroviral effect in second-line therapy. Even in patients who received tenofovir in first-line therapy in combination with FTC or 3TC, the drug can still be expected to be active in the majority of patients – although due to its limited use in settings where viral load monitoring is not routinely used, we don't

know what proportion of patients might develop resistance to tenofovir due to prolonged, failing treatment with the drug.

The two nucleoside backbones recommended by the expert consultation will be compared in a study being planned by the French Agence Nationale de Recherche sur la Sida (ANRS), which will randomise participants at a range of centres in Africa to one of the nucleoside backbones combined with lopinavir/ritonavir (*Aluvia*).

Experts consulted by WHO were less enthusiastic about tenofovir/ddi, a combination that might on the surface be expected to pack more of an antiviral punch in people with some nucleoside analogue resistance. The lack of enthusiasm was due to the combination's paradoxical effect on CD4 counts (they went down in over half of patients taking a full ddi dose, by around 150 cells in one year, [a Spanish study showed](#)¹⁹), together with an increased risk of toxicity when the two drugs are dosed together. A higher risk of virologic failure has also been seen when the two drugs are used in first-line treatment alongside efavirenz or nevirapine. European regulators were so unhappy about these risks that [they warned the two drugs should not be used together in 2005](#).

WHO-recommended second-line regimens

First-line NRTI choice	NRTI component in second-line	PI component
If AZT or d4T is used in first-line	Abacavir /ddi OR Tenofovir/3TC (FTC)	Lopinavir/ritonavir OR Atazanavir/ritonavir
If tenofovir is used in first-line	AZT/3TC	
If abacavir is used in first-line	AZT/3TC OR Tenofovir/3TC (FTC)	

Boosted protease inhibitors: lopinavir/ritonavir

Lopinavir was developed by Abbott as a protease inhibitor coformulated with low-dose ritonavir. *Kaletra*, or *Aluvia* in developing countries, is now available in a growing number of countries as a heat-stable tablet. Where *Aluvia* remains unregistered, the soft-gel form of *Kaletra* must be used.

Generic heat-stable versions of lopinavir/ritonavir are being developed by Indian companies and products manufactured by Matrix Laboratories and Aurobindo received FDA approval for PEPFAR use during early 2009. The Matrix product has already received WHO prequalification.

Aluvia is priced at \$500 a year in sub-Saharan Africa and lower income countries in Asia, and \$1000 a year in [lower middle-income countries](#). In December 2008 the Matrix product was available to countries in the CHAI purchasing consortium at \$550 a year. The Clinton HIV/AIDS Initiative believes that Indian manufacturers may be able to undercut Abbott's price by 30 – 40% within two years of receiving FDA tentative approval.

Lopinavir/ritonavir has been one of the most widely used protease inhibitors in Europe and North America. It has remained

popular because the drug has a high genetic barrier to resistance, and it is reasonably well tolerated.

Once-daily dosing of *Kaletra* is not recommended in treatment-experienced patients.

The chief side-effects of lopinavir/ritonavir are gastrointestinal and lipid-related.

In the major studies of *Kaletra*, moderate or severe diarrhoea affected 12 to 27% of participants. Two to 7% of patients interrupted therapy because of diarrhoea, but only 1% of all participants in these trials stopped *Kaletra* treatment. Diarrhoea and loose stools are most common during the first two months of treatment, but many people experience ongoing problems. Nausea related to lopinavir treatment is also a common reason for interrupting treatment, occurring in 2% to 12% of study participants.

The heat-stable lopinavir/ritonavir tablet appears better tolerated. Analysis of side-effects in 30 patients participating in a study of lopinavir/ritonavir monotherapy showed that after a switch to the heat-stable tablets, 46% of patients reported that the tolerability of their medication had improved, while the proportion who continued to experience diarrhoea declined from 33% to 3%.²⁰

Elevated lipids, including high triglycerides and cholesterol levels, occur amongst 10% - 25% of people on lopinavir/ritonavir, particularly among those who have high cholesterol or triglyceride levels before starting to take the drug. Raised levels of cholesterol may increase the long-term risk of heart disease, particularly if other risk factors such as smoking, older age and diabetes are also present.

Ritonavir reduces blood levels of methadone, which is used as a substitution therapy for opiate addiction in many parts of the world (although access is poor in the region where it is needed most: injecting drug users in Russia and many other countries in Eastern Europe and Central Asia are not provided with substitution therapy due to antiquated and unscientific attitudes towards its usage).

The only data available on this interaction suggest a 30-40% reduction in methadone exposure.²¹

Generic versions of lopinavir/ritonavir: need for caution

Other generic versions of lopinavir/ritonavir and ritonavir are available apart from the product already pre-qualified, but some of these products may be of poor quality, according to a study carried out by Abbott, the originator of lopinavir/ritonavir.

During its development of a ritonavir heat-stable tablet Abbott scientists used dogs to develop a validated surrogate for human pharmacokinetics as they tested a variety of formulations of the product. They subsequently used the dog model in order to compare the bioavailability of generic versions of lopinavir/ritonavir and of ritonavir with the branded versions, *Kaletra* and *Norvir*.

They found very poor bioavailability for versions of the two drugs produced by Emcure. The company's lopinavir/ritonavir combination product, *Emletra*, achieved a total plasma lopinavir exposure of just 4% of the levels achieved when the branded product was dosed. This was probably due in part to the fact that the boosting agent, ritonavir, reached only 1% of the exposure seen with the branded product.

Another product, *Ritocom*, manufactured by Hetero, achieved a total plasma exposure of 84% of that seen with the branded product, chiefly due to a lower peak level.

Cipla's *Lopimmune* performed just as well as the branded product.

Two of the three ritonavir products produced sub-optimal ritonavir levels. In the case of Hetero's product *Ritomune*, total plasma

exposure reached about one-third of the level seen with the branded product when ritonavir was dosed alone. However, a total ritonavir exposure of around 70% was observed when Hetero's co-formulated lopinavir/ritonavir capsule was dosed.²²

Boosted protease inhibitors: atazanavir/ritonavir

Atazanavir was developed by Bristol Myers Squibb. A generic version developed under voluntary license by the Indian company Emcure [was approved as bioequivalent by the US Food and Drug Administration for use by PEPFAR programmes in February 2008](#). Aspen Pharmacare in South Africa has also negotiated a voluntary license to produce the drug, for sale at a differential price in sub-Saharan Africa.

Although developed as a standalone product at a dose of 400mg once daily, the drug has been licensed for second-line treatment in Europe and the United States only when boosted with low-dose ritonavir. This is to ensure that drug levels remain well above the minimum level needed for viral suppression, an especially important consideration when there may be some degree of resistance to other drugs in the second-line combination.

Atazanavir is available in heat-stable tablet form, but must be boosted with low-dose ritonavir, which is still available only in soft-gel capsules. Although atazanavir is offered at \$353 a year for a 300mg daily dose, the cost of daily boosting with 100mg of branded ritonavir (*Norvir*) increases the cost by \$83, leaving little price difference compared to *Kaletra*.

However there may be scope for dose reduction in Asian populations. A pharmacokinetic study in 22 HIV-positive Thai patients already taking atazanavir showed that 200mg of atazanavir boosted with 100mg of ritonavir achieved similar blood levels to those seen in historical controls, with no cases of virologic rebound. Participants in the study also experienced a significant reduction in bilirubin (see below). Body weight was not associated with the trough level of atazanavir, leading the authors to suggest that Asians may clear the drug more slowly. A trial is clearly in order to determine whether a lower dose is appropriate.²³

Atazanavir has been well tolerated in clinical trials. In particular it caused diarrhoea and lipid elevations less frequently than the soft-gel formulation of *Kaletra*. For these reasons, and because of its once-daily dosing, atazanavir has become the most frequently prescribed protease inhibitor in the United States over the past few years.

However the drug has one side-effect that has caused complaint among patients, hyperbilirubinemia.

This side-effect is an elevation of bilirubin levels in the blood. Bilirubin is a waste product from the breakdown of red blood cells. Although it is not clinically harmful, elevated bilirubin levels can cause jaundice, a yellowing of the skin and the whites of the eyes.

Hyperbilirubinaemia tends to emerge within the first week of starting atazanavir treatment, but does not always cause jaundice. In one large study of patients starting HIV treatment for the first time, 33% of around 400 patients taking atazanavir developed severe hyperbilirubinaemia, but less than 1% discontinued treatment due to bilirubin elevations, and only 5% developed jaundice.²⁴ Another randomised study comparing boosted and unboosted atazanavir showed a significantly higher rate of grade 3 or 4 hyperbilirubinemia in those receiving boosted atazanavir (66% vs 24%) during 96 weeks of follow-up.²⁵

In Caucasians there is a genetic predictor for this side-effect, although the association proved less strong in a Thai study.²⁶ It is unclear whether the rates of hyperbilirubinemia observed in

international trials will remain consistent when atazanavir is used more widely in different populations.

Comparing lopinavir/ritonavir and atazanavir/ritonavir

Is one boosted protease inhibitor better than the other? Lopinavir and atazanavir have been compared in [only one head-to-head study in treatment-experienced patients](#). This study found that the two drugs had similar efficacy after 96 weeks of follow-up, but in some respects atazanavir was better tolerated. Twenty-five per cent of those who received *Kaletra* required anti-diarrhoea medication, compared with 6% of those who received atazanavir. Patients taking *Kaletra* were also significantly more likely to require lipid-lowering therapy than individuals taking atazanavir/ritonavir (20% vs 9%, $p < 0.05$). However, hyperbilirubinemia was much more frequent in the atazanavir group (53% vs 1%).²⁷

Abbott plans to recruit patients in developing countries to a large randomised trial that will compare the two drugs in people who have experienced the failure of a first-line regimen.

Protease inhibitors and lipodystrophy

Protease inhibitors have been blamed for lipodystrophy, particularly fat accumulation in the abdomen, but this may be unfair. [The results of the ACTG 5142 trial](#) in the United States showed that people who received lopinavir/ritonavir combined with two nucleoside analogues were significantly less likely to develop lipodystrophy than people who received efavirenz and two nucleoside analogues (17% of the lopinavir group vs 32% of the efavirenz group lost at least 20% of their limb fat during the 96-week study).²⁸

Participants received a range of nucleoside analogue backbones (d4T/3TC, AZT/3TC or tenofovir/3TC). Those who received d4T were most at risk of fat loss, and those who received tenofovir were least at risk. But even within the tenofovir-treated group, those who received efavirenz were twice as likely to lose fat as those who received *Kaletra*. The reason for these findings is still poorly understood, although evidence from a randomized comparison of atazanavir and atazanavir boosted by ritonavir, in which all participants received the drug d4T, found that those who received ritonavir had a significantly lower incidence of limb fat loss.²⁹

Another 96 week randomized study found that while boosted atazanavir had no effect on the risk of central fat accumulation, people randomized to switch from another boosted protease inhibitor to atazanavir/ritonavir were significantly less likely to lose limb fat. This difference was particularly evident among those receiving d4T or AZT.³⁰

It is well established that atazanavir does not cause lipid increases, and there is also limited evidence that it does not cause lipodystrophy, but a robust comparison with other protease inhibitors – or with efavirenz – is lacking.

What if the nucleosides are doing nothing?

The evidence of the studies cited earlier in this article suggests that for a substantial proportion of patients, nucleoside analogues in second-line treatment might be expected to have very little effect on HIV. In these circumstances patients may effectively be receiving monotherapy with a boosted protease inhibitor.

So why bother using them? The problem is that without resistance testing, it's impossible to tell whether they might be exerting an effect or not, and as discussed previously, 3TC may

exert an effect by maintaining a mutation that reduces viral fitness – if viral load remains detectable.

Another possibility, already being tested as a second-line randomisation within the DART study, is the use of *Kaletra* as monotherapy.

Kaletra has been tested as monotherapy in individuals who have sustained undetectable viral load for at least six months and who have no history of viral rebound during protease inhibitor treatment. Four randomised studies have shown no significant difference between lopinavir/ritonavir monotherapy and standard triple drug therapy in treatment-naïve patients or in those already taking *Kaletra* as part of their first antiretroviral regimen ([results of these studies are discussed in more detail at *aidsmap.com*](#))

However [the MONARK study](#), conducted in France, found a trend towards a poorer virological response to *Kaletra* monotherapy in participants who had non-B HIV sub-types.³¹ Another study, [conducted in Canada](#), found a higher frequency of low-level viremia (<400 copies/ml) in the monotherapy arm; these patients were all able to suppress viral load below 50 copies by resuming AZT/3TC alongside *Kaletra*.³²

The only data reported in treatment-experienced patients with virologic failure [come from London's Chelsea and Westminster Hospital](#), where 28 patients with experience of a median of five prior antiretroviral regimens and an average viral load of 55,000 copies/ml were switched to *Kaletra* monotherapy. Half achieved an undetectable viral load (below 50 copies/ml) after 12 months of monotherapy and 73% maintained a viral load at least 1 log below baseline after 12 months. The average CD4 cell increase was +115 cells/mm³ in those with undetectable viral load and +73 cells/mm³ in those with detectable viral load.³³

Atazanavir/ritonavir has also been tested as monotherapy, with positive results in two studies and a negative result in one.³⁴

Further data from two studies of PI monotherapy using darunavir/ritonavir are due to be presented at the International AIDS Society Conference in Cape Town in July. The UK Medical Research Council is also running a five-year study called PIVOT, comparing boosted PI monotherapy with a boosted PI plus two NRTIs to evaluate the long-term durability of the approach.

Sidestepping resistance with NRTI-sparing regimens

In a setting where sufficient drugs are available and affordable, a nucleoside-sparing regimen may be an attractive choice for second-line treatment. A combination of *Kaletra* and the new integrase inhibitor raltegravir could be expected to deliver a very high rate of viral suppression, for example. Others have shown interest in a regimen of atazanavir/ritonavir and raltegravir, due to the potential boosting effect of atazanavir on raltegravir.

Merck and Tibotec are sponsoring a study of darunavir/ritonavir and raltegravir as first-line therapy in the US.

But nucleoside-sparing second-lines are also being studied in resource-limited settings, and could eventually offer a better option than currently recommended second-line regimens if trials prove positive.

Dr Nick Paton of the UK Medical Research Council is planning a trial called EARNST (**E**astern and southern **A**frica **R**esearch **N**etwork for **E**valuation of **S**econd-line **T**herapy) that will randomise people in need of second-line therapy to receive either a boosted protease inhibitor and two NRTIs (as per current WHO guidelines), a boosted protease inhibitor with raltegravir, or a boosted protease

inhibitor with a 12-week induction dose of raltegravir, followed by boosted PI monotherapy.

The intention is to address the question of the best approach to second line treatment in a way that is most relevant to ART rollout programmes in Africa (and elsewhere). The trial will recruit 1200 patients (400 per arm) in South Africa, Uganda, Malawi and Zimbabwe and follow them for three years to look at clinical and immunological outcomes in addition to viral load.

"In addition to evaluating boosted protease inhibitor plus raltegravir, it also includes a third arm of PI monotherapy arm because standard of care with two compromised NRTIs plus a protease inhibitor probably amounts to this anyway, and it is important to know whether PI monotherapy is just as effective but with reduced toxicity and cost, and increased convenience," Dr Paton told HATIP.

"Raltegravir has a number of properties that make it attractive for rollout programmes. Although cost is prohibitive at present, that is likely to change rapidly and the Clinton Foundation are actively working on this.

"If EARNEST shows that second line boosted PI and raltegravir provides better clinical and immunological outcomes than standard of care, I think it is likely that this will become standard of care for second line therapy rather than being held back to third line. The non-overlapping resistance profile with first-line drugs would also make resistance testing redundant, which would also be attractive for a rollout setting."

Another study comparing a boosted protease inhibitor plus two NRTIs with a boosted protease inhibitor plus raltegravir is being planned by HIV-NAT, and will recruit participants in Thailand, Australia, South Africa, Latin America and Europe.

Second-line NNRTI use

There might be another option for second-line treatment: the new NNRTI etravirine (*Intelence*), manufactured by Tibotec. *Intelence* was approved for use in second-line treatment in combination with a boosted protease inhibitor in the European Union in 2008. The drug is active against virus resistant to the first-line NNRTIs nevirapine and efavirenz, although there is some evidence that it is less active against the Y181C mutation more commonly selected after nevirapine failure.³⁵

However the TMC125-C227 study, a phase II evaluation of the drug in treatment-experienced patients which recruited patients in South Africa, Thailand and Brazil [found that extensive resistance to elements of first-line therapy](#) seriously reduced the effectiveness of etravirine when it was used in second-line therapy in combination with two nucleoside analogues. Even in patients with just one NRTI mutation at baseline there was a trend towards a viral load rebound apparent by week 12.³⁶

Subsequently the drug has been developed for use alongside boosted protease inhibitors in second and third-line therapy. Etravirine is likely to remain quite an expensive drug to produce because the tablet must be film-coated, so the potential for low-cost production will hit a barrier below which the price cannot fall.

Conclusion

What's clear is that there is a lack of information on which to base recommendations, and further studies are clearly needed. These are now underway, but it may be some years before they yield enough data to make firm recommendations about the best regimen in second-line treatment.

Nevertheless, the wider registration of boosted protease inhibitors will be critical to improving access to second-line therapy, as will further reductions in price.

But the more pressing question is how to ensure prompt switching from a failing first-line regimen, given that all response data show the same trend: people who switch later tend to die.

While a [recent modeling exercise](#) suggests that there may be no long-term survival difference as a consequence of the monitoring strategies used to determine when to switch, there is growing pressure in the field to make viral load testing more easily accessible to assist in switching decisions, and so prevent late switches.

In addition, research from Rakai in Uganda [presented at CROI 2009](#) shows that the lack of viral load testing is having a perverse effect: almost as many people were being switched unnecessarily on the basis of CD4 count changes as were being missed due to lack of viral load testing.³⁷ The research group estimated that the 107 unnecessary switches would have cost an extra \$75,000 a year in second-line drugs.

But as we reported in HATIP #80 more than two years ago, the need for a point of care test that can answer the question 'is this patient failing treatment?' will only continue to grow.

In the interim there has been progress towards developing point of care tests, or tests that can be used more widely in the health system.

MSF is currently engaged in field-testing an assay in Kenya, while a number of studies have looked at dried blood spots as a collection medium for adult viral load testing and found them suitable for shipping samples to laboratories that can carry out viral load tests. Cavi's ExaVir assay is also becoming more widely available (see latter half of [this linked article](#) for further details).

The need for viral load testing requires bold action by UNITAID to make the appropriate tests available at affordable prices, so creating a market in which people who develop point of care tests will be rewarded for innovations.

But it also requires regular monitoring and follow-up of patients. As programmes attempt to maximise the impact of health care worker resources, they are seeing stable ART patients less and less frequently. If adherence remains good, that may not be a problem, but if adherence falters, delays of up to six months could have serious consequences.

Reviewers

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