NEW ANTIRETROVIRALS: WHAT'S IN IT FOR SOUTHERN AFRICA?

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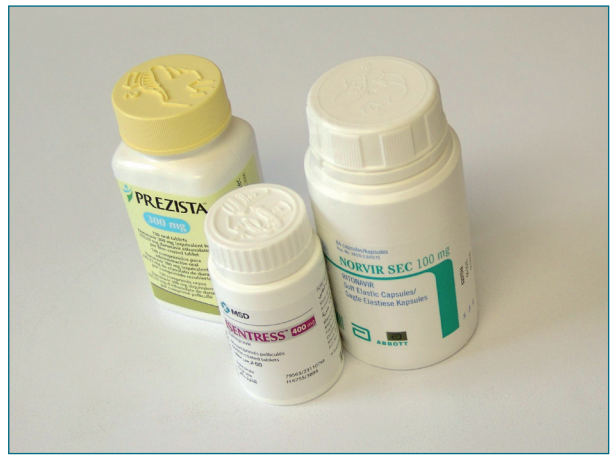
The rise of novel antiretrovirals (ARVs) has introduced a new evolutionary phase in HIV care. In developed countries, the 1980s and early 1990s were characterised by palliative care and opportunistic infection prophylaxis; the late 1990s by an attempt to use a limited and toxic antiretroviral arsenal effectively while cycling through high levels of resistance; and finally, the first half of this decade by working out the easiest-to-take regimens, using the steadily rising number of safer drugs. At present, there are 8 nucleoside analogues (NRTIs), 3 non-nucleoside analogues (NNRTIs), 10 protease inhibitors (PIs), and one each of the fusion, entry and integrase inhibitors to choose from, along with a new drug pipeline that targets both existing and new targets in the viral replicative cycle. The choice may seem quite vast, but the reality is that many of these drugs cannot be used simultaneously or in patients with extensive drug resistance. In addition, some drugs have unacceptable toxicities and are not favoured in current treatment regimens.

Previously, the only clinical consequence of HIV viral replication was thought to be a declining CD4 cell count, and development of resistance if on antiretroviral therapy (ART). Several recent studies have dramatically changed that understanding. Continuing viral replication seems to play a role in a bewildering array of illnesses not usually associated with HIV, including a diverse number of cancers, as well as chronic liver, kidney and cardiovascular disease.

Viraemia used to be regarded as a necessary evil. In the 1990s, an undetectable viral load was more the exception than the norm in developed countries, owing to drug toxicity and poor adherence. Increasing evidence that persistent viraemia is linked to the host of long-term consequences described above has changed the game. In 2009, a detectable viral load should probably be regarded as the notional equivalent of active cigarette smoking, and tackled with the same vigour.

Luckily, the pharmaceutical industry has rapidly brought several new and exciting but expensive ARV agents to the marketplace, providing new options for those with the money to pay for them.



The newcomers take on the establishment: will cost allow widespread use?

In developing countries, there are complex drug interactions between rifampicin and the azoles, which patients are often on at the time of ART. Side-effects to stavudine and nevirapine remain distressingly common. In addition, new insights on resistance, especially subtype C, which may compromise future options around tenofovir, have begun appearing. A recent developing world study demonstrating increased rates of NNRTI-based

regimen failure after single-dose nevirapine for prevention of mother-to-child transmission emphasised the clinical consequences of the low resistance threshold of these drugs. Drug resistance to any infectious disease in the presence of antimicrobial pressure is near inevitable, and needs to be factored into any treatment algorithm. In the case of HIV, the stakes are higher when cross-resistance is considered, as the treatment is lifelong, and treatment options in poorer areas are limited. Combinations of genotyping and phenotyping resistance testing remain prohibitively expensive for the developing world. Drugs that may overcome both primary and secondary resistance therefore become more important in both the developed and developing world scenario.

Essentially, Southern Africa needs safer, more effective and cheaper ART options.

Enter the classes of drugs with science-fiction names – the CCR-5 blockers, fusion inhibitors, integrase inhibitors, maturation inhibitors – as well as safer and more potent versions of existing classes, with chest-thumping names for trials, such as MOTIVATE, RESIST, TITAN and BENCHMRK. One ART advertisement even shows an HIV 'meteor' heading for a cellular planet, protected by a ring of the drug. Immediate results with these new therapeutics have left new-drug junkies open-mouthed, as patients with detectable viral loads for decades after being on every conceivable ART regimen are consigned to 'undetectable'.

INTEGRASE INHIBITORS

These drugs block integrase, which mediates the insertion of HIV DNA into the genome. The integration process is complex, and there is interest in directing new drugs at several steps in the integration process, which includes the assembly of a 'pre-integration complex', processing with subsequent strand transfer, and the final step of assembling a viable piece of double-stranded DNA.

The first drug to hit the market in this class is raltegravir (Isentress; Merck Sharp & Dohme (MSD)), which has generated the kind of excitement among treatment experts last seen with the onset of access to tenofovir or efavirenz. The drug is currently under consideration by the South African Medicines Control Council (MCC), and may be registered in the first half of 2009. Registered in late 2007 by the US Food and Drug Administration and the European Medicines Evaluation Agency on the back of trials showing high efficacy in patients with significant resistance from prior regimens, the drug has also been used successfully in drug-naïve patients, although it is not currently registered for this. Data from the BENCHMRK trial recently showed that raltegravir was comparable to efavirenz in treatment-naïve patients after 96 weeks of treatment, with the advantage of a more favorable side-effect profile. Whether the benefit is sufficient to trigger a change in first-line prescribing is controversial, and guidelines still overwhelmingly favour efavirenz in drug-naïve patients.

Raltegravir is dosed twice daily, has no food restrictions, and appears to have relatively limited impact on the different cytochrome systems. The drug interaction with rifampicin is under investigation, and caution will be required during co-administration in tuberculosis patients until more data are received. There is some excitement among basic scientists that raltegravir may decrease the size of the 'latent pool' of HIV-infected cells, although the clinical importance of this seems questionable.

However, the real excitement has been seen in those clinicians dealing with treatment-experienced patients, where the drug, when used with a new boosted PI, appears to control viraemia effectively and safely. Resistance assays are being developed, and early evidence suggests that there is cross-resistance with other agents in the integrase class.

The major questions that hang over the raltegravir head are side-effects and cost. As with all drugs, side-effects are still unclear, and the usual regulatory agency careful watching process is underway. It often takes several years for less common or long-term side-effects to become apparent – witness the highly publicised if controversial link between abacavir and myocardial infarction, only documented a decade after the drug became available. However, raltegravir has proved surprisingly popular, and a large number of patients have already been introduced to the drug in developed countries. Early safety data have been excellent, with no common serious side-effects. Initial therapy may be associated with mild gastrointestinal effects and dizziness, although the neuropsychiatric side-effects are significantly lower when compared with efavirenz in treatment-naïve patients. However, there have been several reports of increased muscle toxicity and caution should be exercised in patients at risk of myopathy or rhabdomyolysis. The effect on lipid levels is minimal. By the time we have broad access to (or need) this agent in southern Africa, we should have a good idea of what sort of safety concerns we need to be on the lookout for.

More immediately of concern is the cost. At the current $9 a day this is prohibitive, even for private care. Competitor products are in development, with a drug called elvitegravir (from Gilead, of tenofovir fame), dosed daily and also with similar good preliminary data, which looks likely to be registered in the next few years but is unlikely to cost much less.

NEW NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

Efavirenz and nevirapine are the 'non-nuke' backbone of almost all new initiations in the developed and developing world. NNRTIs are convenient, relatively non-toxic,

and highly effective. Concerns surrounding drug interactions, side-effects and efavirenz teratogencity are unlikely to displace them from their role in first-line therapy for at least the next few years. The genetic barrier of this first-generation NNRTI is low, with resistance occurring rapidly and completely after a single mutation. Most virological failure patients therefore experience the loss of this class with their very first failure. It is also of concern that transmitted NNRTI resistance is well described and a growing problem in developed world settings.

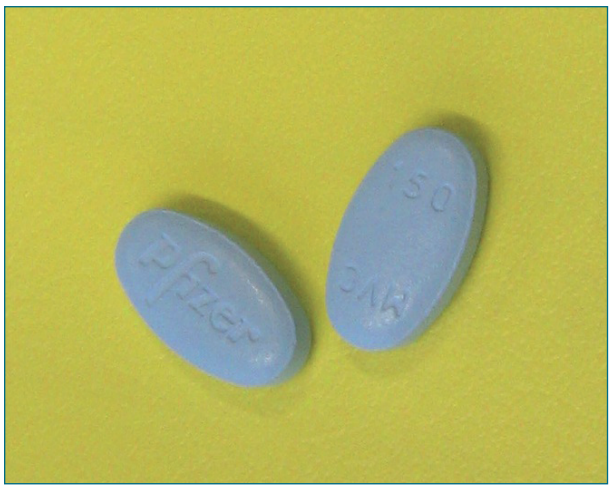
With a lot less fanfare than the other new drugs, the new-generation NNRTIs have entered the fray. Etravirine (Intelence; Tibotec), a second-generation NNRTI, requires multiple mutations, and is effective in treating most patients who have failed efavirenz or nevirapine. Etravirine is interesting, as it was initially tested in conjunction with another experimental PI, a high-risk strategy for the pharmaceutical company. Toxicity profiles appear negligible so far, with rash and nausea the commonest symptoms.

Etravirine seems to retain activity even in the presence of several mutations, behaving more like an NRTI than an NNRTI in this regard. However, specific etravirine-associated mutations seem to occur more frequently in patients who have non-clade B virus and have been exposed to first-generation NNRTIs. Drug interactions appear to be significant and etravirine should not be administered in conjunction with boosted tipranavir, fosamprenavir or atazanavir and definitely not with unboosted PIs, thereby limiting its use in salvage regimens. It is not recommended for use alone with NRTIs in patients who are PI-naïve and have previously failed an NNRTI, owing to sub-optimal results in this group.

Complex to make, etravirine is likely to remain prohibitively expensive for some time. The expense is compounded by the fact that resistance testing and interpretation is likely to be needed before using the drug, limiting its application in our setting. Interpretation of resistance is complex, with initial local data (personal communication, Professor Wendy Stevens, National Health Laboratory Services) suggesting that additional data will be needed before we can confidently predict responses in our region. Coupled with the fact that the southern African epidemic is predominantly clade C, and that first-generation NNRTIs are used extensively in first line with suboptimal virological monitoring, means that the jury will probably be out on this drug for some time.

CCR-5 INHIBITORS

The CCR-5 blockers (less commonly called chemokine antagonists) act on the major receptor that facilitates entry of HIV into the cell. Observations that mutations within the gene that codes for this receptor appear to profoundly modify the ability of the virus to enter, have led to the development of several therapeutic molecules,



Pfizer's other blue pill: maraviroc, the first CCR-5 blocker, requires a tropism test before it can be used.

altered chemokines and monoclonal antibodies. Development of these drugs was initially slowed after liver side-effects were observed, with one drug in the class, apliviroc (GSK), halted despite initial promising results.

Pfizer's maraviroc (the imaginatively named Selzentry in the USA; Celsentri elsewhere, licensed in 2007, and awaiting MCC registration in 2009) has been the first out of the starting blocks and has been approved in developed countries for treatment-experienced patients. Studies in these patients, done in record time to counter their competitors, have proven the drug performs well, and has a good short-term side-effect profile. The drug has been evaluated in head-to-head studies against efavirenz in naïve patients, but results have not been convincing, and it seems unlikely at present that the drug can compete with the non-nukes in first line as yet.

The major problem with maraviroc is the necessity for tropism testing. CCR-5 is not the only entry point for HIV, and the 'tropism' or predisposition determination for these alternative entry points requires an expensive and complex test, which is not foolproof. A patient with a CXCR4 tropism predisposition is much less likely to respond to the drug, so the test is essential. Resistance is usually characterised by a tropism switch to CXCR4, although this does not seem to have any direct immunological consequence. The drug also has a significant impact on the cytochrome systems, much like the PIs, with drug interactions with other ARVs and opportunistic infection medication, and requires dose modification in many common clinical circumstances.

An unexpected aside in one of the trials involving maraviroc may have special implications for our region. The MERIT study compared maraviroc with efavirenz in antiretroviral-naïve subjects. There was little difference in terms of antiviral activity, but those who were given maraviroc developed only one incident TB infection while those in the efavirenz group had six. Scientists are excited, and are exploring the biological plausibility of

this observation. Time will tell if this will strengthen the case for this drug, or possibly open up new TB prevention options.

Pricing of maraviroc is likely to be an issue, as with all these new drugs, and an access price locally has yet to be determined. Currently the drug is available under a section 21 MCC approval for just under $1 000 monthly, which is prohibitive. Already one developed country health care system (the Scottish National Health Service) has declined the use of these agents due to the cost.

The other potential CCR-5 blocker, vicriviroc, this time from Schering-Plough, has had a difficult time; an unexpected increase in malignancies, mainly lymphoma, was observed in one trial, and its predecessor, which is not structurally linked to vicriviroc, had unacceptable toxicity levels. This was counterintuitive, as patients with the previously described CCR-5 mutation are supposedly more protected against lymphoma (although the mutation seems to be implicated in progression of breast cancer), so this finding created consternation. There is some fear that this may be a class effect, but the strange correlation with cancer has not been seen with maraviroc. Subsequent statistical analysis suggested that the cancers were probably not linked. A theoretical link to West Nile virus suggested by another epidemiological study looking at CCR-5 mutations also stirred the pot, but no cases have yet been seen in treated patients. However, some clinicians are wary about this class of drug, which do not directly inhibit HIV replication, but rather play a more indirect effect on the immune system.

Entry inhibitors represent interesting candidates for pre-exposure prophylaxis from a biological plausibility standpoint (stopping the virus from penetrating at all, rather than arresting its development within the cell, as with current ART prophylaxis). If this concept turns out to be verified by trials, this use for this class of drug may turn out to be the most interesting yet.

PROTEASE INHIBITORS

For several years now, boosted PIs have formed the backbone of therapy after initial virological failure. Unpopular in first-line therapy because of their side-effect, metabolic and cost profiles, PIs have established themselves as robust and highly effective alternative agents, and are recommended in all second-line therapies in the developing world, with lopinavir/ritonavir (Kaletra) being the most popular. An alternative and competitively priced PI, atazanavir, is available and better tolerated, but requires co-administration with separate ritonavir, due to patents being held by different pharmaceutical companies. There is a more appealing option with the registration of Alluvia, Kaeltra's heat-stable formulation. With the rise of new agents, many of the older PIs, including nelfinavir, saquinavir and indinavir, have fallen steadily into disuse. Treatment expectations with the newer PIs are so high that international and local guidelines recommend a zero tolerance to detectable viral loads when these agents are used. Protease mutations appear more complex than most other ART mutations, with a wide array of primary, secondary and background polymorphisms, some of which confer high-level resistance to the agent, and others that may confer hyper-susceptibility. The newer agents both select for mutations which require weighting systems in order to assess the effect of the multiple mutations they select for, making interpretation complex and requiring experience. The realisation that not all resistance is equal, that boosted PI resistance may be more 'forgiving' of sub-optimal adherence, and that failure is rarely associated with significant PI mutations, has opened the way to effective third- and fourth-line regimens using these drugs, always in their boosted form.

New second-generation PIs darunavir (Prezista; Tibotec) and tipranavir (Aptivus; Boeringer-Ingelheim) both require boosting with ritonavir, but require a large number of mutations before they lose efficacy. The drugs carry the usual long list of drug interactions seen with PIs, making their administration complex.

Initial efficacy and toxicity data with boosted darunavir (approved by the FDA in 2006), when compared with Kaletra, are very encouraging, and Tibotec is positioning the drug as a serious competitor to lopinavir/ritonavir after demonstrating good results in heavily treated patients and in those with moderate resistance, as well as in PI-naïve patients. Darunavir remains active in patients who are heavily treatment-experienced with demonstrated resistance to all other PIs, including lopinavir/ritonavir. In the TMC115 studies, 60% of subjects who had decreased susceptibility to tipranavir showed a decrease of more than 1 log in viral load after 24 weeks of treatment with darunavir, with over a third achieving complete suppression. This was clinically highly significant in the era before the advent of integrase inhibitors. There is some element of cross-resistance between darunavir and tipranavir, although half of isolates with darunavir resistance still demonstrated some susceptibility to tipranavir. At this point, the actual sequencing of PIs – which should we use first so as to preserve the subsequent ones? – is a matter of much debate among clinicians.

Darunavir/ritonavir is dosed at 600/100 mg twice daily and must be taken with food. It is both a substrate and an inhibitor of CYP3A and therefore has similar drug interactions to lopinavir/ritonavir. Among the severe side-effects reported are skin rash (including Stevens-Johnson syndrome). Darunavir contains a sulfa-moiety and must be administered with caution in patients who are allergic to sulfa drugs.

Interesting studies using darunavir as monotherapy after an initial intensification phase are also underway, despite the disappointing results seen in the monotherapy studies with lopinavir/ritonavir. Other studies are looking at paediatric populations, and initial results have been very good in treatment-experienced children and adolescents.

Aspen, South Africa's generic giant, has agreed to distribute darunavir (Prezista) in sub-Saharan Africa at a price of $3 a day, which remains expensive for the state sector but makes it an enticing option for managed care organisations.

Tipranavir is slightly older, registered in 2005 by the FDA for resistant patients and with a paediatric formulation registered in 2008. It is dosed twice daily with food, and requires a relatively high dose of ritonavir (200 mg twice daily) for effective boosting. Tipranavir and darunavir appear equally virologically effective. Drug side-effects are similar to other PIs in nature, with a curious report linking to the drug to intracranial haemorrhage still under investigation. However, the drug has also performed very well in salvage regimens, firmly establishing itself as an option in treatment-experienced patients.

CONCLUSION

ART clinicians and their patients have an impressive new armamentarium looming. However, the cost and unknown toxicities of these drugs mean that the longer we can preserve the first-line therapies we have, the better. For the developing world most, if not all, of these agents are currently unaffordable in the public and even the private sector. Toxicity data are often delayed, and will be widely publicised if significant, so we can afford to be cautious. For the small number of experienced patients who require these drugs, mechanisms exist for them to be accessed through the application (section 21) process set out by the Medicines Control Council.

First-line therapy, comprising two NRTIs and an NNRTI, is unlikely to change in the immediate future. In second line, the choice of boosted PI seems fairly evenly matched, although preliminary data suggest that the well-established lopinavir/ritonavir has some less toxic competitors, mainly from new PIs but potentially even from the other newcomers. While raltegravir looks increasingly attractive as a second-line alternative to existing choices, as does etravirine, both remain unaffordable at this time. A very rapid change from first-line regimens that include first-generation NNRTIs appears to be the only way to preserve etravirine; close virological monitoring may be the answer to the relatively low genetic barrier of raltegravir. Use of the CCR-5 inhibitors is limited by their reliance on extremely expensive tropism assays and they will have little to no immediate place in the developing world unless both their pricing structure and their tropism assay reliance are resolved.

Debate rests as to how a third-line regimen should be structured, but it is likely to be expensive, if not particularly toxic, and will still require significant expertise on the part of clinicians. Optimal use of these agents would depend on expensive genotyping assays, beyond the reach of many public sector programmes in southern Africa.

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