Evolution of adult antiretroviral therapy for programmatic delivery in Africa and the potential role for new therapeutic approaches

Graham S Cooke[1,2]
[1]*Africa Centre for Health and Population Studies, PO Box 198, Somkhele, Mtubatuba 3935, KZN, South Africa*
Tel.: + 27 355 507 566
Fax: + 27 355 507 565
E-mail: gcooke@africacentre.ac.za
[2]*Imperial College, London, UK*

Access to antiretroviral therapy (ART) is steadily improving across sub-Saharan Africa. This review discusses the possible evolution of programmatic combination drug therapy and the potential relevance of therapeutic developments, including new classes of antiretrovirals. There are still relatively few published data from resource-poor settings to inform antiretroviral policy, highlighting the need for further research within populations that have the greatest need for treatment.

This review will focus on antiretroviral therapy (ART) currently used as part of roll-out in sub-Saharan Africa (SSA), how ART policies might evolve and where therapeutic advances might be relevant. From the outset, it is important to note that the majority of patients who need treatment in Africa still do not have access to any care [1,2] and the choice of particular drugs is perhaps not the greatest short-term public-health concern. However, patient concerns about drug toxicity and tolerability are likely barriers to access in themselves, and as expanding access to programs acts as a driver to increasing costs, issues around drug treatment are again likely to come to the fore. With a constantly evolving scientific and economic environment, it is likely that recommendations for treatment will also evolve rapidly. Although the WHO has taken a commendable lead on producing guidelines (**Box 1**) [3] and many countries reflect this in their preferred starting regimens [4], it is also likely that more heterogeneity will develop between countries. Factors, including cost, efficacy, adherence, interactions and sequencing, that influence the choice of programmatic antiretrovirals have been well discussed elsewhere [5], as has pediatric treatment [6]; this discussion concerns possible changes in adult ART programs now that they have been established and how new classes of medication might play a role in addressing the limitations of current treatments.

Limitations to current first-line therapies

Side effects due to non-nucleoside reverse transcriptase inhibitors (NNRTIs) are significant but uncommon [7], and nucleoside reverse transcriptase inhibitor (NRTI) toxicity, particularly due to stavudine (d4T), remains the greatest concern, included as it is in many (but not all) first-line regimens across Africa. To initiate d4T as part of highly active antiretroviral therapy (HAART) for a naive patient in a developed country would be highly unusual, and without good justification it would probably be negligent given the level of toxicity and availability of other agents. As ART roll-out expands, first-hand African experience of the toxicity experienced in early cohorts is growing substantially (particularly with high levels of neuropathy), and is being reported more commonly. Early estimates are that between 15 and 24% of patients are changing first-line regimen [7,8,101–103] in the early phases of treatment, largely owing to adverse events attributed to d4T.

Given the rapid and recent roll-out of ART across Africa, there is relatively little peer reviewed evidence, and there remain few prospective data on the incidence and severity of toxicity. In a cohort from the Western Cape from South Africa, 21% of patients had substituted d4T after 3 years of treatment [7]. Published evidence suggests that lactic acidosis, one of the more severe side effects [9], occurs at a rate of between 16 and 19 cases per 1000-patient years [10,11], and there appears to be a significant increase in risk in women and in those with increasing weight [12].

In response to the need for the collection of high-quality, standardized data, the WHO has recently proposed establishing a pharmacovigilance program. However, whatever the true rates and nature of d4T toxicity are, it seems likely that with falling drug prices, programs will increasingly look to find alternative options for first-line drug choices. Strategies currently proposed to alleviate the suffering from d4T aim to either reduce dosing or substitute it within first-line treatment options.

Reducing d4T dosing

A recently published meta-analysis of d4T efficacy [13] that looked at both published [14,15] and

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future medicine part of fsg

Box 1. Antiretroviral combinations recommended for programmatic delivery.

First-line treatment options

- Standard strategy
  - ABC + 3TC + NVP/EFV
  - TDF + 3TC + NVP/EFV
  - AZT/d4T + 3TC + NVP/EFV
- Alternative strategy
  - AZT or d4T + 3TC + TDF or ABC

Second-line treatment options

- Nucleoside reverse transcriptase inhibitors
  - ddI + ABC or TDF + ABC or TDF + 3TC (+/-AZT)
  - ddI + ABC or ddI + 3TC (+/-AZT)
  - ddI + 3TC (+/-AZT) or TDF + 3TC(+/-AZT)
  - EFV/NVP +/-ddI
- Protease inhibitors
  - Lopinavir/ritonavir or atazanvir/ritonavir

3TC: Lamivudine; ABC: Abacavir; AZT: Zidovudine; d4T: Stavudine; ddI: Didanosine; EFV: Efavirenz; NVP: Net present value; TDF: Tenofovir.
Adapted from WHO guidelines [52].

unpublished studies found evidence suggesting equal efficacy of 20–30 mg twice-daily d4T dosing compared with 40 mg dosing, but that the higher dose was associated with more toxicity. This has led to a WHO recommendation that 30 mg d4T should be the standard dose for adults, regardless of weight. This relatively simple issue of d4T dosing is a good example of the difficulties of even small changes to well-established guidelines. For example, whereas in Malawi a rapid switch was made, in South Africa, 40-mg d4T tablets had been stockpiled to secure drug supply, and thus at the time of writing, many prescribers in the state program are obliged to keep with the higher dosing for individuals over 60 kg.

Given the price differential for first-line drugs, using lower doses of d4T could prolong the usefulness of d4T, and there have been calls for studies of head-to-head first-line treatment with lower-dose d4T and against other agents (e.g., tenofovir) in African populations [13]. However, as costs of alternative first-line agents continue to fall, enthusiasm for such studies could be short-lived.

Substitution of d4T

A changing view on the dosing of d4T might not be able to stop the gathering momentum to substitute the drug in first-line regimens where affordable. In South Africa, for example, the issue has been taken up by the high-profile Treatment Action Campaign. All potential replacements have drawbacks, usually related to a combination of cost and toxicity. The best candidate for replacement is probably tenofovir, although abacavir is also an option recommended by the most recent WHO guidelines. Tenofovir has the advantage of a better toxicity profile (at least when compared with 40 mg twice-daily d4T [16]), activity against hepatitis B, which is prevalent across Africa [17], and once-daily dosing, which should help with adherence. To aid adherence further, tenofovir is now available as part of a generic version of the Atripla™ tablet (tenofovir/emtracitibine and efavirenz). The greatest concern with tenofovir remains its renal toxicity. Although data from its manufacturers, Gilead Sciences (CA, USA), report a low rate of renal impairment (2.2%) following expanded access to the drug [18], it is associated with an increased risk of renal failure and renal tubular diseases [19], particularly in those with impaired renal function. There are some data suggesting the prevalence of renal impairment in African populations might be high [20], and even if the risks of renal impairment can be cut by screening patients, the increased cost of monitoring has to be weighed against the costs of lactate measurement for patients on d4T or hemoglobin monitoring for patients on zidovudine (AZT) when planning programmatic combinations.

One African country, Zambia, has already chosen to include tenofovir in first-line treatment regimens [104], having calculated that the additional drug costs will be off-set by a reduced burden of toxicity. However, for many others the costs involved remain a substantial obstacle. These costs are coming down with increasing competition between manufacturers, increased demand for product and concerted efforts on price negotiation. However, conservative estimates suggest that to switch from a fixed-dose combination of d4T/lamivudine (3TC)/nevirapine to tenofovir/3TC/efavirenz would still typically increase costs from US$99 per patients/year to US$426 per patients/year [21]. With Aspen pharmaceuticals in South Africa recently announcing it was to produce generic tenofovir and Clinton Foundation negotiations with generic producers in India, it has to be hoped that prices will fall further.

Whether abacavir would be a better substitute for d4T in Africa remains to be seen. Head-to-head studies of Kivexa® (abacavir/lamivudine) and Truvada® (tenofovir/emtracitibine) are

ongoing outside Africa. One early result from the Bicombo study suggests that amongst virally suppressed patients on HAART, those randomized to switch to an abacavir-containing combination were more likely to discontinue therapy [22]. However, abacavir is gaining favor in many countries where genetic testing for the *HLA-B*5701* allele is able to screen out many at high risk of hypersensitivity reaction, the most dangerous side effect of abacavir [23]. Genetic screening for African populations is not inconceivable in well-funded programs where a single one-off cost can be balanced against the need for continual monitoring. This could be particularly relevant in areas where skilled healthcare workers are in short supply and the cost of a one-off test that can be easily interpreted can be balanced against the need for skilled clinical workers to monitor treatment. However, it is implausible to imagine the widespread uptake of genetic testing in the near future and its utility might differ between African populations [24]. Nonetheless, hypersensitivity reaction appears less common in populations of African descent compared with Caucasian populations [25], and this supports early data from a substudy of the Development of Antiretrovrial Therapy in Africa (DART) trial in Uganda, where investigators found a lower rate of adverse events in the arm randomized to active abacavir than to nevirapine (2 vs 4%) [26]. However, regardless of the rates of toxicity, a major obstacle to the widespread introduction of abacavir remains cost (currently upwards of US$429/patient/year [21]) despite there currently being four WHO prequalified generic manufacturers.

With the recognition that d4T is causing great toxicity and that the most acceptable substitutes are still not yet affordable for many programs, substitution with AZT in first-line regimens is likely to be appealing to programs where it is not in the first-line combination already. Also a thymidine analogue, it means that the sequencing of second-line treatment is unaffected and for programs with AZT as part of second-line treatment, it can be replaced with one of the more expensive agents in the hope that prices will fall further with time. In populations presenting late with a high prevalence of anemia, AZT will not be without its challenges too [27], with one study finding a higher proportion of patients substituting for AZT than d4T [28].

Second-line medication & its problems

Reports to date suggest low rates of virological failure with first-line combinations in resource-poor settings [29,30]. Even if failure rates are low, the numbers of patients now established on treatment will mean ever more patients switching to second-line treatments, and it is unlikely to be long before the issue of second-line treatment pushes to the fore. Whereas first-line treatment might now cost under US$100/patient/year, second-line treatment remains upwards of US$600 year [21]. This will have major financial implications and organizations such as Medecins Sans Frontieres have warned of a new impending crisis over drug costs.

Problems with protease inhibitors

At present, a large part of the costs discussed above is driven by protease inhibitors (PIs). All current second-line treatment options include a PI, and in most countries these are manufactured under patent by the original intellectual property owners. Thus, without competition, costs remain high. One hope for the 2006 revision of WHO guidelines on second-line treatment was that they would have a significant effect on prices, allowing manufacturers to focus on producing high-volume drugs at lower prices. However, the original draft had a footnote suggesting a broad choice of potential PIs [3], and updated recommendations seem likely to focus on lopinavir/ritonavir and atazanavir/ritonavir in the expectation that this will drive greater price competition.

With Roche's recall of nelfinavir, all available PIs also require ritonavir as a boosting agent. Ritonavir requires refrigeration, an obvious challenge in conditions where power is, at best, interrupted frequently, and more often simply not available. Now, a newer heat-stable formulation of lopinavir/ritonavir (Kaletra®) tablets has been developed to replace the current capsules, and its manufacturers (Abbott, IL, USA) plan to make it available at the same cost as current supplies to qualifying countries (notwithstanding the recent spat between Abbott and the Thai government). The tablet preparation has other advantages for resource-poor areas with a lower pill burden and lack of food restrictions. However, at this time there is not a generic, heat-stable, ritonavir preparation. Such products are in development and, once available, should offer more feasible options for second-line treatment.

An alternative option that is being given some consideration is the possibility of reducing the dose of PIs (discussed in [31]), which has the potential to reduce costs and toxicity without a decline in efficacy. It has to be hoped that falling

prices will make PI-based combinations more widely available. If not, is there scope for a PI-free second-line combination? It is rather far-fetched, but the new categories of drug, including not only integrase inhibitors, but also CCR5 antagonists, make this a theoretical possibility. Whether CCR5 blockers could be a treatment option in populations presenting with late disease remains to be seen.

Removing, replacing or reducing NRTIs in second-line treatment?

Assuming a PI remains the cornerstone of second-line treatment and that doses cannot be reduced significantly, might it be possible to reduce the number or dose of NRTIs without compromizing efficacy? One approach that could have relevance for Africa and other resource-poor settings is treatment intensification/simplification. Intensification/simplification approaches are similar to treatment strategies employed in TB or tumor chemotherapy and either use an increased (intensified) regimen for a limited period before reducing to standard maintenance treatment (e.g., the Forte study [32]), or after a fixed period reduce from standard treatment to a more limited drug combination (e.g., the Trilege study [33]).

The history of intensification/simplification has been disappointing in HIV treatment [34–40], with simplified regimens usually performing significantly less well. However, with the emergence of more potent regimens, there has been encouraging work with strategies simplifying to PI monotherapy, particularly lopinavir/ritonavir [37,38], but also with data related to atazanavir [39] and indinavir [40]. If drug costs come down further and PIs make up a smaller proportion of second-line drug costs, an approach with PI monotherapy might look economically more appealing.

A more straightforward approach, that of initiation with PI monotherapy, has been tried in the monotherapy antiretroviral Kaletra (MONARK) study. The finding that patients receiving monotherapy had more episodes of viremia when compared with PI-containing HAART [41], and the work with simplification to atazanavir [42], have led some to conclude that simplification is an inferior approach with the implication that it should be discarded [31]. This might be true, but there are important points to consider before the strategy is abandoned altogether, particularly for second-line treatment. Real-life conditions might serve to reduce the benefit of the NRTI backbone. It is likely that for many patients in public-sector programmes in Africa, they will remain on failing regimens for longer than if they were in well-resourced programmes. It is likely then that they will accumulate more NRTI resistance mutations that would reduce the marginal benefits of combination therapy, but evidence does not yet exist to support this. Secondly, analogous to d4T, some degree of inferiority might be acceptable if the economic savings generated allow more people access to second-line care (although as the case of d4T shows, this is a difficult argument to sustain long-term). Thirdly, initiation of monotherapy should not be confused with an intensification/simplification approach that has shown evidence of success previously [32]. Such a strategy could even benefit from the newer PI such as darunavir or tipranavir [43,44] or the possibility of increasing PI doses to improve virological suppression [45]. To add further complexity, intensification/simplification in second-line treatment does not have to result in PI monotherapy. An alternative approach might be to reduce patients to a single NRTI and protease inhibitor that would also allow significant cost reductions.

A second NRTI-reducing strategy is to use PIs with something other than NRTIs. If there is no cross-class resistance between NRTIs and newer drugs, this would immediately avoid the problem of drug sequencing and accumulating drug resistance. Until recently, such possibilities were limited, but the arrival of the new class of integrase inhibitors offers such an opportunity. The product closest to licensing is Merck's raltegravir, which has shown good potency and low toxicity in early studies, but does have a low barrier to genetic resistance [46]. Whilst it is likely to remain expensive for the foreseeable future, the ever-changing shape of the global antiviral market does not necessarily mean this will remain so for long. Such new classes of drugs have the potential to eventually bring greater flexibility to programs in developing countries.

Other important therapeutic areas in sub-Saharan Africa

There are other issues affecting SSA that could, more speculatively, benefit from emerging drugs, including Preventing Mother-To-Child-Transmission and HIV/TB treatment. Countries differ in the threshold at which individuals, pregnant or otherwise, can initiate treatment.

With some programs looking to raise the starting threshold of ART to all with CD4 counts under 350, another issue becomes a greater concern – what should public-health programs recommend to pregnant mothers who need to start ART? With CD4 counts under 200, the risks of nevirapine toxicity are low, but with earlier initiation, the risks increase [47]. The only other NNRTI available is the potentially teratogenic efavirenz, which should be avoided, at least in the first trimester, and for women who might become pregnant again. In developed countries with more treatment options, a PI might be used [48], but with limited access to other drugs, this might not be in the patient's best interests, nor is it easy to administer in a program with scarce human resources. A new agent for first-line therapy that had a good safety profile in pregnant women would be a helpful addition.

Co-administration of TB treatment and antiretrovirals is extremely common in SSA [49,50]. NNRTIs and ritonavir-boosted PIs all have pharmacokinetic interactions with rifampicin [51], the cornerstone of TB treatment. Most recommendations for the treatment of newly diagnosed TB/HIV coinfection recommend a delay in starting ART of up to 8 weeks [52], in part because of concerns about drug toxicity and interactions. As an alternative to standard antiretroviral regimens, some have proposed triple nucleotide combinations, but such combinations are generally less potent virologically and have a greater risk of developing resistance [53–55]. Evidence is accumulating that in the field, these interactions with NNRTIs might not be as clinically important as first thought [54,56], although increasingly patients already on second-line treatment will be in need of treatment for TB. New agents which lack interactions but also have durable potency would increase treatment options.

Conclusion & future perspective

It should be seen as a mark of success that there is a discussion at all concerning improvements to the antiretrovirals used in public-health programs. However, with accumulating evidence of the limitations of current regimens and a dynamic global drug market bringing down prices, there are reasons to be hopeful that better-quality treatment regimens will become more widely available.

For those fortunate to have access, the new array of emerging antiretrovirals could lead to the most substantial changes in prescribing practice since the arrival of PIs. Whilst price of any new drugs is likely to be prohibitive in the short term, new classes of drugs could improve the ease with which programmatic treatments can be constructed in developing countries. As these new drugs begin to be studied, their potential applications in resource-poor regions should be borne in mind and, given the paucity of data from clinical trials in the developing world, the recent call for a greater proportion of HIV programme resources to be spent on research should be welcomed [57].

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Executive summary

- With the steady progress in antiretroviral roll-out, evidence is beginning to emerge of the limitations of stavudine-containing regimens.
- Strategies to reduce toxicity include dose reduction and changes to first-line Nucleoside reverse transcriptase inhibitors.
- A dynamic global drug market is reducing prices to the point that it could be cost effective to change first-line treatment options.
- Second-line treatment costs are still high and there are a number of therapeutic approaches to try to tackle this, including removing, replacing or reducing Nucleoside reverse transcriptase inhibitors in second-line treatment.
- New drug classes, whilst expensive in the short term, could have a role to play in resource-poor countries and might have a role in special patient groups, including pregnant women and patients receiving TB treatment.

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