Are the best antiretrovirals being used in Africa?

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INTRODUCTION

Although the '3 by 5' initiative of the World Health Organisation (WHO) did not achieve its goal of getting three million HIV-infected patients from resource-limited regions (RLRs) onto highly active antiretroviral therapy (HAART) by the end of 2005, several hundred thousand Africans are estimated to be on treatment [1,2] and many more are likely to start treatment during 2006. The simple answer to the question 'Are the best antiretrovirals (ARTs) being used in Africa?' is 'no', but to answer this question constructively, we should suggest what would be the best ART for Africa. To do this, the issues of cost and funding for ART in Africa must be considered from the outset. The WHO, other international organisations and the drug industry have achieved remarkable reductions in the cost of ART since 2000 [3]. The generic combination of nevirapine (NVP), stavudine (d4T) and lamivudine (3TC) is now available at US$ 15 per month [3] and is therefore the most commonly prescribed ART in sub-Saharan Africa (SSA) (see Table 1) [4]. There are a number of reasons, however, why this regimen is not the 'best' for Africa; the momentum achieved since 2000 should therefore not be allowed to dissipate. The cost of other regimens must be urgently reduced so that an ART for Africa may be chosen not merely because it is the cheapest. Indeed, the cheapest ART regimens may not be the most cost-effective, particularly if they are less efficacious in the long term and will cause significant morbidity as a result of side effects.

In this paper, we discuss: the costs of various adult-dose ART regimens; evidence for the effectiveness of different regimens in and for Africa, with particular emphasis on first-line drugs; ART toxicity in Africans; the effect of single-dose nevirapine (SDN) and unstructured treatment interruptions on drug resistance; the issue of regimen sequencing in the context of late switching to second-line therapy, including the best second-line ART for Africa; and the importance of drug interactions. We conclude by suggesting what would be the best and most cost-effective ART for Africa in the medium and long term.

CURRENT DRUG COSTS

The ability of drug companies to produce antiretroviral drugs generically, particularly in India and Brazil, has been the single most important factor in reducing the cost of ART for RLRs [3]. The originator drug companies have responded by reducing their costs, but their products are still considerably more expensive than the generic equivalents. There is also no uniform approach to setting prices for developing countries. Each company determines its own criteria for which countries or institutions are eligible for discounted prices; in most cases, only those countries which come under the United Nations Conference on Trade and Development's (UNCTAD's) Least Developed Country category benefit from such discounts (first category prices). Prices quoted by manufacturers may not represent the actual prices because of mark ups such as cost of distribution and import taxes. Table 2 lists the current costs of the various ART regimens including originator and generic versions, if available [abacavir (ABC) has been left out of the first-line options as it is too expensive to be considered at this time]. At the time of writing, generic versions of efavirenz (EFV), didanosine (ddI), ABC and lopinavir/ritonavir (LPV/r) had not yet been approved by the WHO; a generic version of tenofovir has not yet been produced. It is important to note that some programmes such as the President's Emergency Plan for AIDS Relief (PEPFAR) only provide drugs that have been approved by the Food and Drug Administration (in addition to WHO approval), thus excluding almost all generically produced ARTs at this time [5].

EFFECTIVENESS OF ART IN AFRICA

Only two clinical trials have compared the relative effectiveness of ART regimens in Africa. The 2NN study [6] involved 430 patients from South Africa, and concluded that nevirapine was as effective as EFV when given with the same nucleoside analogue backbone as d4T and 3TC. For all

Table 1: Estimated number of patients on ART in African countries where the generic combination nevirapine/stavudine/lamivudine (NVP/d4T/3TC) is the most commonly prescribed ART regimen

Country	Number on ART (latest available estimates) [4]
Uganda	64000
Tanzania	8000
Rwanda	10000
Democratic Republic of Congo	5000
Malawi	19000
Burkina Faso	4000
Kenya	38000

ART, antiretrovirals.

study participants (including patients who were not from South Africa), 70% had undetectable viral loads (<50 HIV-1 RNA copies/ml at 48 weeks). The Developing ART for Africa (DART) study, which has enrolled 3300 patients in Uganda and Zimbabwe, recently published data on 300 patients taking the combination of zidovudine (ZDV), lamivudine and tenofovir [7]. At 48 weeks, 55% of patients had undetectable viral loads (<50 copies/ml). Elsewhere, there have been a number of cohort studies based in Africa describing the outcomes of patients taking non-nucleoside (NVP or EFV), thymidine analogue (d4T or ZDV) and 3TC-based regimens [8–11]. A recent meta-analysis of ten such studies showed that, overall, 57% of patients had undetectable viral loads at 48 weeks (<400 copies/ml). It is important to note that patients who received free ART were 31% more likely to be undetectable at 48 weeks than those patients who paid for their drugs [12].

Extrapolating data from studies performed in Europe and North America is not ideal but still provides useful guidance regarding the relative effectiveness of various regimens for Africa. Most 'western' guidelines suggest a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first line with a boosted protease inhibitor (PI)-based second line for a combination of reasons, particularly adherence and tolerability [13,14]. Boosted PI-based regimens should also be reserved for second-line ART in Africa for the reasons above but also because of their increased cost, storage requirements, interactions with rifampicin and issues of ART sequencing (discussed below). The best choice of nucleoside backbone is not clear-cut either, although the GS934 study suggests that TDF/FTC may be better than ZDV/3TC [15]. A number of studies have shown that triple nucleotide regimens are less durable than NNRTI- or PI-based ART [17,18]. The combination of ZDV/3TC/TVF has not been extensively studied but some recent data do suggest (as does the DART study) that this triple NRTI combination may be more durable than its predecessors [18,19].

Kaletra (LPV/RTV) is now the most commonly prescribed boosted PI in SSA [20]. Evidence suggesting that it may give durable suppression, even as monotherapy [21], makes it an attractive choice for second-line ART when the other components of the regimens may be compromised. Data from our clinic in Uganda support its role as an effective second-line drug despite concerns regarding storage of its currently available formulation in hot climates [22].

Drug toxicity of ART in Africans

If there is little evidence of a difference between the effectiveness of the various regimens, what about their tolerability? Again, there is a shortage of clinical data from SSA. There is, however, some evidence that Africans will not be spared the extensive side effects of d4T. Although the incidence of severe peripheral neuropathy was low in the 2NN [6] and Cameroon [9] studies, data from Uganda, Malawi and Botswana show that peripheral neuropathy is becoming increasingly prevalent in d4T-treated patients, with symptomatic disease occurring in up to 56% of patients [10,23,24]. The frequent co-administration of isoniazid for tuberculosis (TB) will only add to this problem [25]. Pancreatitis [23] and lactic acidosis [26] can also occur, although facilities for diagnosing these conditions are often unavailable. Lipoatrophy is also becoming increasingly common [24].

ZDV-related side effects appear to be less common but significant anaemia does occur and can be fatal when it is severe and blood transfusion is not available. In Botswana, 39% of patients starting ZDV and 3TC had to change treatment because of anaemia [23]. In the DART trial, 6% of patients suffered a grade 4 episode of anaemia (<6.5g/dl).

Table 2: Current drug regimen cost (per month) from originator and generic manufacturers*

Regimen	Originator (1st category price) US $	Generic (WHO approved) US $	Generic (All) US $
NVP/3TC/d4T	47	15	13
NVP + 3TC/ZDV	56	21	21
EFV + 3TC/ZDV	49	44	44
EFV + FTC/TDF	55	n/a	55*
EFV + 3TC + TDF	52	52*	50*
ZDV/3TC +TDF	37	32*	32*
EFV + 3TC + ddI	58	n/a	45
NVP + 3TC + ddI	65	n/a	22
NVP + 3TC + TDF	59	29*	27*
RTV/LPV + ddI + ZDV	83	n/a	64†
RTV/LPV + ddI + ABC	139	n/a	102‡
RTV/LPV + TDF + ABC	132	n/a	107†,‡

NVP, nevirapine; 3TC, lamivudine; d4T, stavudine; ZDV, zidovudine; EFV, efavirenz; FTC, emtricitabine; TDF, enofovir; ddI, didanosine; RTV, ritonavir; LPV, lopinavir; ABC, abacavir.

* Information from references 3 and 28. /, fixed combinations; n/a, not available.

† The price of TDF with or without FTC included in this combination is the 1st category price; there is no generic version of TDF with or without FTC.

‡ The price of LPV/RTV included in this combination is the 1st category price because the generic drug is more expensive.

Of these patients, 6% died, although only one death was thought to be directly attributable to anaemia [27]. The greatest risk of ZDV-associated anaemia is within the first 3 months of starting ART.

There are no published data on the safety of TDF in Africa; the DART trial has, however, used tenofovir to treat nearly 2500 patients since the start of the study in 2001. As yet there have been no data published by this group regarding TDF-related toxicity [29].

The gene associated with ABC hypersensitivity has been shown to be less prevalent in African racial groups [30]. Once more, data from SSA is lacking; DART has used ABC on 300 patients and has yet to publish data on toxicity.

Both NVP and EFV can cause cutaneous hypersensitivity reactions and hepatotoxicity. Data from South Africa clearly show that NVP should be avoided in those with high CD4 counts (i.e. women with CD4 counts above 250 cells/μl) [31]. This is not usually an issue in SSA, where the majority of patients are started on ART with CD4 counts below 200 cells/μl [9] and data from the other African cohort studies suggest the incidence of NVP reactions is not as high in these patients [10,23,31]. Dose escalation reduces NVP toxicity but is often difficult due to the lack of availability of the individual 'lead-in' drugs [33]. Concern over the teratogenic effects of EFV precludes the use of this drug in pregnant women and those likely to conceive while on ART [34]. There are little data on the toxicity of Kaletra in Africa but from our experience this drug is well tolerated [22].

Single-dose NVP and unstructured treatment interruptions

It is now clear that SDN has caused NNRTI resistance in a large proportion of women and will continue to do so [35]. Whether or not this will translate into reduced potency and/or durability of NNRTI-based ART when taken subsequently by these women is unclear [36], but a study from Thailand showed that there is indeed a reduction in the proportion of patients who are undetectable at 6 months [37]. Should first-line ART in African women who have received SDN (and their sexual partners) be PI-based? Certainly, all possible efforts should be made to improve what is clearly a dangerous intervention in the medium and long term, for example by combining SDN with 1 week of ZDV/3TC [38] or just giving SDN to the infant [39].

A related and very important issue is that of unstructured treatment interruptions. The vast majority of African patients, who pay for their own medications, have had to stop their drugs abruptly because they have run out of funds. Even those who receive free ART may run out of drugs if they are unable to attend a refill appointment because they cannot afford transport to the clinic [40]. Because of the long half-life of the NNRTI drugs it is likely that these interruptions will have the same resistance consequences as SDN in pregnancy [41]. Enhancement of free ART programmes and longer prescriptions may help to reduce these problems but is NNRTI-based ART really advisable in such circumstances?

Choice of first-line ART and regimen sequencing

In Africa, there is a considerable lag between the roll-out of ART and the provision of laboratory capacity to monitor this treatment. Viral load monitoring is unavailable and/or unaffordable to the vast majority of patients. Patients are therefore switched to second-line ART late, according to immunological and/or clinical criteria [20]. This means that patients are being allowed to fail virologically for a long period of time [42], which encourages the accumulation of resistance mutations [43]. First-line ART for Africa should therefore be a regimen which results in as little impact as possible on the second-line regimen. For example, an NNRTI plus TDF (or ddI) plus FTC (or 3TC)-based regimen would preserve ZDV for use with Kaletra, in a potent and hopefully durable second-line regimen. In contrast, the most commonly prescribed current regimen of an NNRTI plus thymidine analogue and 3TC may result in numerous thymidine-associated mutations which may render ineffective all possible partner drugs to a Kaletra-based second-line (e.g. TDF, ddI and ABC) [44,45]. It may, therefore, be more cost-effective to invest in a more strategic first-line regimen to preserve an effective second-line regimen and reduce the need for expensive viral-load testing at the same time.

Drug interactions

TB is the most common AIDS-defining illness in Africa [46]. It may present before ART is started and could delay the start of this treatment. TB can also occur after the initiation of ART, which might result in treatment needing to be stopped. The best ART for Africa should not interact with rifampicin; rifabutin is not available as it is too expensive and rifampicin-sparing anti-TB regimens such as those used in Uganda have been shown to result in a higher TB relapse rate and may encourage the spread of multidrug-resistant TB [47]. A number of studies suggest that it would be unwise to use NVP with rifampicin [48] and RTV-boosted saquinavir is no longer recommended [49]. The remaining options are EFV or triple-nucleoside-based regimens for first-line ART [13].

Other factors

Excellent adherence to ART is essential to the prevention of treatment failure and drug resistance [41]. Combination or fixed-dose formulations of drugs may improve adherence [50]. A limitation of the currently available/affordable formulation of ddI is that it needs to be taken on an empty stomach, which may also affect adherence [51].

Conclusions

There are a number of reasons why the combination of NVP, 3TC and d4T is not the best ART regimen for Africa. The best regimen for Africa must be tolerable for the majority, durable and, if possible, forgiving of treatment interruptions. ART regimens should be chosen with optimal sequencing in mind given the likelihood that patients will be

Table 3: Choice of first-line ART regimen for Africa*

Regimen	Cost	Effectiveness	Tolerability	Pill burden and adherence	Rifampcin interaction	Treatment interruptions	Sequencing
NVP/3TC/d4T	5	4	1	5	1	1	1
NVP + 3TC/ ZDV	4	4	3	3	1	1	1
EFV + 3TC/ ZDV	2	4	4*	3	5	1	1
EFV + FTC/TDF	1	5	4*	5	5	1	4
ZDV / 3TC + TDF	3	3	4	3	5	4	4
EFV + ddI + 3TC	2	4	2†	2	5	1	4
NVP + ddI + 3TC	4	4	2	2	1	1	4
NVP + TDF + 3TC	3	5‡	4	3	1	1	4

NVP, nevirapine; 3TC, lamivudine; d4T, stavudine; ZDV, zidovudine; EFV, efavirenz; FTC, emtricitabine; TDF, tenofovir; ddI, didanosine.
*Choice of first-line ART regimen for Africa according to current cost, likely effectiveness, tolerability, Rifampicin interaction, treatment interruption safety and sequencing potential (scored 1–5; 1, worst; 5, best).
†Would have to be avoided in women pregnant or likely to become pregnant
‡Extrapolating from 2NN study which shows nevirapine equivalent to Efavirenz [7]

switched after prolonged periods of virological failure. There must be alternative regimens for those who are unable to take first choice regimens but any ART formulary should be simple and sustainable. Finally, any ART for Africa must be affordable - if it is not today, we must campaign for it to be affordable tomorrow.

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