Introduction
Since the advent of triple therapy in 1996 [1**], there has been concern that antiretroviral therapy (ART) should be made available in resource-limited settings. However, when triple therapy was first marketed in Europe and the United States, the cost was prohibitive, averaging around US$20 000 per patient per year. Small-scale pilot treatment programmes began in 1998 in Uganda and Côte d’Ivoire via a United Nations Joint Programme on HIV/AIDS (UNAIDS)-brokered preferential pricing scheme [1**], but it was only in September 2000, when Indian generics manufacturer Cipla announced that they could produce triple therapy for a dollar a day, that treating AIDS in resource-limited settings became possible to contemplate on a large scale [2].

With the possibility of widespread treatment came concern that unregulated use of antiretroviral drugs in sub-Saharan Africa would lead to drug resistance. In order to avoid such ‘antiretroviral anarchy’ [3], the WHO published guidelines recommending a limited number of antiretrovirals for use in first-line therapy. The first guidelines, published in 2002, were the result of a consultation involving over 120 scientists in more than 50 countries [4] and included 12 antiretrovirals for first and second-line treatment [5]. At the same time, WHO’s essential drugs list was updated to include 10 antiretrovirals that were previously excluded because of their high cost [6].

This simplified, standardized approach was critical to the rapid scaling-up of treatment that has averted substantial AIDS-related mortality in the last 8 years [7**]. An estimated four million people are currently receiving ART, and almost all are using drug regimens that are consistent with WHO guidelines [8]. However, as treatment cohorts mature, long-term toxicity and resistance issues are becoming apparent. Increasing numbers of patients are switching to second line, and in some of the older treatment cohorts, the need for third line is becoming more pressing [9]. Such concerns have led to calls from some practitioners for a wider formulary [10]. With over 25 antiretroviral drugs approved [11] and another 14 in development [12], it is worth reviewing...
the options for improving first-line therapy in resource-limited settings.

**Evolution of the WHO guidelines**

The first WHO guidelines, published in 2002, recommended a choice of five different first lines based on a backbone of zidovudine and lamivudine (3TC), along with either efavirenz (EFV), nevirapine, abacavir, nefelnavir or a boosted protease inhibitor (bPI). The 2003 update, issued at the same time as the WHO 3 by 5 Initiative to promote ART scale-up [1**], recommended four different first-lines based on 3TC combined with either zidovudine or stavudine and EFV or nevirapine. Protease inhibitors were moved to second line, mainly due to cost, higher pill burden, refrigeration requirements (no heat-stable version was available at that time) and drug interactions. The potential role of tenofovir (TDF) in first line was acknowledged in these early guidelines, but experience, availability and cost were cited as limiting factors [5]. TDF was finally recommended as a first-line option in 2006 [13*], together with zidovudine or stavudine or abacavir, combined with 3TC or emtricitabine (FTC) and EFV or nevirapine. TDF and zidovudine were considered to be the preferred nucleoside reverse transcriptase inhibitors (NRTIs). In these guidelines, protease inhibitors remain reserved as second-line therapies, as their use in an initial treatment regimen would essentially rule out second-line options in the setting of limited formularies.

These latest guidelines recommend that the choice of antiretroviral regimen should be based on a number of programme-level factors, including availability of fixed-dose combinations (FDCs), toxicity profile, laboratory monitoring requirements, potential for maintenance of future treatment options, promotion of adherence (e.g. once or twice-daily dosing), prevalent coexistent conditions [tuberculosis (TB) and hepatitis B], use in women of childbearing age or who are pregnant, availability from local and international manufacturers and cost. These considerations are critical and provide important guidance when considering options for improving first-line therapy with existing and emerging antiretrovirals. The next WHO guideline revision is planned for late 2009.

**Improving current treatment regimens**

The reasons for considering improving current treatment options are both to improve clinical outcomes for individual patients and support broader public health goals.

**Clinical considerations for improving first line**

The most common first-line regimen in resource-limited settings, stavudine, 3TC and nevirapine, is used by over 60% of developing countries [8]. The main reasons for the high uptake of this regimen include low cost (currently less than US$100 per person per year), availability as a FDC that promotes adherence [14] and simplifies drug supply chains and its safety for pregnant women. Given these advantages, is there any reason to consider changing first-line regimens in resource-limited settings?

The first concern is regimen durability. Adverse events are the most common cause of treatment cessation [15], but in resource-limited settings, the diagnosis of certain serious adverse events is frustrated by the lack of access to appropriate tools, and events such as lactic acidosis may be underreported due to the difficulty of making an accurate diagnosis.

The safety profile of a drug is conditioned by the availability of alternatives. Stavudine provides an example of how such risk–benefit calculations can change over time. The US Food and Drugs Administration (FDA) approval for stavudine (d4T) was granted in 1994. Stavudine has a high affinity for mitochondrial DNA leading to mitochondrial impairment, and this situation leads to a wide range of adverse event such as sensitive neuropathy, lipoatrophy or life-threatening lactic acidosis. Stavudine toxicity in developing countries is of similar or greater extent to that observed in white populations of wealthy countries, with over one-third (34%) of patients reported to present with lipodystrophy in Rwanda [16] and almost half (46%) in western India [17]. In South Africa, the main causes of stavudine cessation are peripheral, sensory neuropathy, lactic acidosis and lipodystrophy. Although well tolerated during the first 6 months of treatment, nearly one-third of patients were found to have discontinued stavudine in routine programme settings in South Africa due to toxicity within 3 years, a higher rate than the 8% discontinuation rates for zidovudine and nevirapine over the same period [18**]. The presence of adverse events – even those thought to be ‘cosmetic’ such as facial lipoatrophy – can lead to suboptimal adherence [19], which in turns leads to the development of resistance mutations, as the genetic barrier of nevirapine-containing regimens is low.

Because of these side effects, stavudine use began to decline in the west as early as 2000 [20], and today it accounts for less than 2% of all ART prescriptions in Switzerland [21] and The Netherlands [20]. In 2006, WHO revised its guidelines to recommend a move away from a stavudine-based regimen to TDF, abacavir or zidovudine [13*]. WHO also recommends that, where stavudine-based regimens are the only realistic option, a 30-mg twice-daily dose should be prescribed for all adults regardless of weight (instead of 40 mg in adults weighting more than 60 kg) in order to minimize the mitochondrial toxicity, although this is likely to delay rather than avert the problem given that the mitochondrial toxicity is
cumulative [21–23]. A switch after 6 months from stavudine to a zidovudine-containing regimen could be a way of avoiding stavudine-related long-term toxicity, but this strategy was found to result in a higher incidence of anaemia and complicate patient management [24].

More than 3 years after WHO issued these recommendations, only three African countries – Namibia [25], Lesotho [26] and Zambia [27] – have adopted TDF as a first-line regimen in national guidelines. The main issue is the higher cost of TDF compared with stavudine [28*], although the price is falling as more generic versions enter the international market [29].

**Broader benefits of an improved first line**

There is increasing evidence that ART programmes must move beyond the traditional approach of treating visibly sick patients and those with severe immunosuppression. A move towards treating people earlier, for longer, is dependent on the availability of a more durable, less toxic first line.

Starting ART before severe immune suppression reduces incidence of opportunistic infections, and this incidence reduction may be even greater in resource-limited settings. A study done in Côte d’Ivoire reported a frequency of severe morbidity in untreated individuals between 200 and 350 CD4 cells/μl that was substantially higher than a similar study done in the USA [30,31]. Significant gains in survival have also been reported from developing countries: a randomized trial from Haiti comparing treatment initiation between early (>350 cells/μl) and late (<200 cells/μl) CD4 cell counts was prematurely stopped in mid-2009 due to the overwhelming benefit of earlier initiation; there was a four-fold difference in mortality and a two-fold difference in incident TB between arms [32]. These data suggest a higher survival gain when compared with data recently published from western countries cohorts, showing that the risk of death was 69% higher in patients initiating treatment below 500 cells in the USA (although the latter data were derived from observational studies) [33**].

In considering earlier initiation, the balance of risks between developing an AIDS disease and the risk of developing a severe side effect depends on the drug formulary used. The first generation of regimens used in developed countries included high-dose ritonavir or other first-generation protease inhibitors combined with NRTIs with high mitochondrial toxicity, leading to short-term intolerance, high pill burden and long-term toxicities. This, together with a high level of resistance to both the protease inhibitors and associated NRTIs, resulted in an initial risk–benefit calculation that favoured deferred treatment [34]. The arrival of new regimens with better toxicity and durability profiles tipped the balance in favour of earlier initiation, and this has been supported by recent observational data [33**]. Initiating antiretrovirals at a higher CD4 cell count allows for easier HIV management, and this is reflected in the cost of care, with costs far higher for immunosuppressed patients compared with patients with a preserved immune function [35,36].

At the population level, the role of treatment as prevention is gaining attention. HIV viral load is the most important determinant of HIV transmission in heterosexual couples [37,38] and from mother to child [39]. As ART in the absence of resistance lowers viral load to undetectable levels in more than 80% of the cases, the potential for limiting HIV transmission is evident. Mathematical models show that expanding coverage of combination ART (cART) could have a major effect on the HIV epidemic by rapidly reducing transmission to nearly zero [40,41**]. The broader benefits of high ART coverage have also been highlighted in a reduction in incidence of other diseases: a study [42] from Uganda showed that malaria incidence fell by 75% over a 4-year period as highly active antiretroviral therapy (HAART) coverage increased, and a study [43] from South Africa found three-fold reduction in TB prevalence over a 3-year period among HIV-positive patients.

**Overview of alternative first-line options**

Both earlier and wider ART access have implications in terms of the choice of a first-line regimen, as any strategy aiming for a broader access to antiretrovirals has to include drugs with acceptable safety profiles and minimal management requirements (thermostability and low pill count). Safety in pregnant women is another key issue, given that the majority of people who are started on ART are women of childbearing age [44]. Treatment options have to be redefined including new parameters to allow wider access to better drugs earlier in the course of HIV disease. Given the range of drugs available today, nevirapine and stavudine-based regimens can no longer be considered the best choice. The side effect profile of stavudine does not support its long-term use, whereas nevirapine cannot be given in individuals with high CD4 cell count (defined as above 250 cells/μl for women and above 400 cells/μl for men) due to the risk of life-threatening hypersensitivity reactions. A number of alternatives can be considered. These are discussed below and summarized in Table 1.

**The case for protease inhibitors in first line**

Ritonavir bPI regimens are currently included in WHO guidelines for second-line regimens [after non-NRTI (NNRTI)-based regimen failure]. Atazanavir has recently been added in the Essential Medicines List (EML) (revised March 2009, www.who.int/EML), and a
heat-stable formulation is currently under review by the WHO prequalification programme. The feasibility of having a bPI-based regimen in first line was only recently made possible by the availability of heat-stable ritonavir (the ‘booster’) and the generic manufacture of both heat- stable lopinavir and atazanavir. Darunavir/ritonavir (darunavir/r), a newly marketed protease inhibitor, has also shown promising potency and safety data in treatment-experienced patients [45,46], and the noninferior efficacy and safety of a once-daily dose of darunavir/r compared with lopinavir/ritonavir (lopinavir/r) in clinical trials has led to a recommendation to include darunavir/r in the US Department of Health and Human Services (DHHS) guidelines as a first-line therapy [47,48]. Darunavir/r also holds promise as a monotherapy, with one trial [49] reporting noninferior week 48 efficacy of darunavir/r monotherapy vs. darunavir/r along with NRTIs in patients with previously suppressed viral load (a second, similar trial found similar results, although noninferiority could not be concluded from the data [50]).

A randomized trial comparing bPI regimens with NNRTI regimens found a slightly lower efficacy but fewer resistance mutations when bPI-based regimens were used in the first line [51]. Another trial is underway to compare three different strategies: two NNRTI-based regimens (with nevirapine and EFV), one bPI-based strategy (with atazanavir) and one triple-NRTI regimen [52]. Whether a change to a bPI-based first-line regimen is indicated is likely to depend on the balance between convenience (fixed drug combination, long-term side effects and affordability) and robustness (high genetic barrier to resistance) [53]: it has for example been argued that the robustness of a bPI regimen would be advantageous

<table>
<thead>
<tr>
<th>Drug or formulation technology</th>
<th>Class</th>
<th>Stage of development</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Single drugs</td>
<td></td>
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</tr>
<tr>
<td>Darunavir</td>
<td>Protease inhibitor</td>
<td>Licensed</td>
<td>More effective and durable than LPV/r</td>
<td>Needs boosting</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Integrase inhibitor</td>
<td>Licensed</td>
<td>Indicated for treatment-experienced, multiclass-resistant patients; good safety; preferential price</td>
<td>Not currently indicated for naive patients but licence pending; once-daily use in clinical trial</td>
</tr>
<tr>
<td>Etravirine</td>
<td>NNRTI</td>
<td>Licensed</td>
<td>Active against mutant NNRTI-resistant HIV strains; likely to be used only in experienced patients</td>
<td>Low genetic barrier to resistance</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>NNRTI</td>
<td>Phase III trials</td>
<td>Potent, low dose (25 mg) and can be used once daily; low cost</td>
<td>Safety in pregnancy is unclear; possible interaction with rifampicin</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>Integrase inhibitor</td>
<td>Phase II–III (with booster GS-9350)</td>
<td>Potential for being coformulated as once-daily FDC with TDF, FTC and GS-9350 (NCT00869557, clinicaltrials.gov, GILEAD Sciences, Inc.)</td>
<td>Needs boosting</td>
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<tr>
<td>Boosted drugs</td>
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<tr>
<td>Ritonavir heat stable</td>
<td>PI booster</td>
<td>PI booster</td>
<td>PI booster</td>
<td>The only booster commercially available with other PIs</td>
</tr>
<tr>
<td>GS-9350</td>
<td>CYP3A inhibitor</td>
<td>Phase II–III</td>
<td>Developed for combination with elvitegravir, and potentially elvitegravir, TDF and FTC</td>
<td></td>
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<tr>
<td>SPI-452</td>
<td>CYP3A inhibitor</td>
<td>Preclinical</td>
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<td>Combinations</td>
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<tr>
<td>1. Heat-stable boosted PI</td>
<td></td>
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<tr>
<td>Atazanavir/ritonavir</td>
<td>Boosted PI</td>
<td>Licensed</td>
<td>Once-daily FDC</td>
<td>Lipodystrophy</td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir</td>
<td>Boosted PI</td>
<td>Licensed</td>
<td>Alternative PI for naive or experienced patients; can be used once or twice daily</td>
<td>Lipodystrophy</td>
</tr>
<tr>
<td>Darunavir/ritonavir</td>
<td>Boosted PI</td>
<td>Licensed</td>
<td>Can be used once or twice daily</td>
<td>Lipodystrophy</td>
</tr>
<tr>
<td>2. FDCs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF, lamivudine and NVP</td>
<td>NRTI/NNRTI</td>
<td>Licensed</td>
<td>Available as coformulation</td>
<td>Coformulation only available from originator</td>
</tr>
<tr>
<td>TDF, lamivudine and efavirenz</td>
<td>NRTI/NNRTI</td>
<td>Licensed</td>
<td>Available as coformulation</td>
<td>Coformulation only available from originator</td>
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</tbody>
</table>

FDC, fixed-dose combination; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; TDF, tenofovir.
in resource-limited and unstable settings in which stock ruptures and population migration/displacement are risks to treatment interruption [54].

**One pill a day: tenofovir, lamivudine/emtricitabine and efavirenz**

The combination of TDF, 3TC/FTC and EFV, known in the USA, Australia and Europe as Atripla (GILEAD Sciences, Inc., Foster City, California, USA), is a single FDC that received FDA approval as the first marketed once-daily ART regimen in 2006. FDA granted a tentative approval for the first generic fixed-dose combination including these three compounds in mid-2009. This combination is considered by many as the gold standard of HIV therapy and is recommended in DHHS guidelines as the preferred NNRTI-based combination [55].

The potential for TDF as a once-daily regimen was noted in the first WHO guidelines in 2002, and TDF, 3TC/FTC and EFV have been recommended by WHO as a first-line regimen since 2006. However, the main limitation to its widespread use is its higher cost compared with current regimens. There are also safety concerns related to the use of the companion drugs, EFV and TDF, although these concerns are based on limited data.

EFV is currently not recommended for use in pregnancy, which is a major limitation for developing countries. However, most of the data leading to this recommendation were from animal studies and retrospective reports. The predictive value of animal studies for humans is questionable – teratogenicity in animals does not mean teratogenicity in humans – whereas biases inherent to retrospective human data prevent a reliable assessment of risk. Prospective data collected over almost 20 years from the Antiretroviral Pregnancy Registry (APR, http://www.apregistry.com/index.htm) have shown no increased risk of birth defects in women exposed to EFV in the first trimester of pregnancy (International Interim Report for 1 January 1989–31 January 2009). Among 477 live births with first-trimester exposure to EFV, 14 birth defects were been reported, among which only two were severe (one case of myelomeningocele and one case of anophthalmia, including severe oblique facial clefts and amniotic banding). Such adverse events are not in excess of normal risk. Despite these data, use of EFV in pregnancy remains a controversial area and is not currently recommended. This highlights the need for evidence-based recommendations for resource-limited settings, for which choices are limited and care is provided by lower cadres.

Concerns about TDF mainly relate to the risk of renal toxicity. Although elevated renal toxicity has been detected in some cohort studies [56,57], these data are not supported by more recent observational data from routine programmes. In a report from the TDF-expanded access programme (n = 10,343), incidence of severe renal adverse events was 0.5% [58]. A trial [development of antiretroviral therapy in Africa (DART)] in Zimbabwe and Uganda (n = 3,316) reporting a 5-year follow-up of creatinine and glomerular filtration rate (GFR) in patients receiving and not receiving TDF-based first line found that severe GFR was infrequent on all regimens, and chronic kidney disease was only slightly more common in the TDF arm [59]. In Zambia, where TDF is now a part of the first-line regimen, patients on TDF were less likely to experience a drug substitution compared with other first-line regimens. Finally, recent data from a prospective cohort in the USA found no evidence of renal toxicity at 2 years [60]. However, it should be noted that in all these studies, patients with preexisting renal insufficiency were excluded from receiving a TDF-containing regimen, which might lead to an underestimation of severe adverse events. Renal toxicity has been found to be greater when TDF is used with ritonavir PIs, cautioning against its use in such combinations.

Another concern with TDF use relates to the potential increased risk of bone disease. HIV-infected adults receiving ART have more osteopaenia than uninfected adults [61], and TDF has been associated with an increased risk of osteopenia compared with stavudine in randomized trials [62]. However, the fraction of risk attributable to cART regimen components, HIV infection and patient characteristics is still unclear [63], and no recommendations have yet been issued regarding bone mineral density screening for TDF use.

In summary, a regimen including 3TC or FTC, EFV and TDF is one of the best available first-line regimens in terms of ease of simplicity and safety. Further support for its use in first line is provided by the finding that the benefit of once-daily therapy in terms of adherence is more pronounced at treatment initiation [64].

**New drugs in the pipeline**

Is there a place for using some of the emerging new drugs early in the management of HIV? For this review, we consider two new drugs from the integrase inhibitor class (raltegravir and elvitegravir) and two next-generation NNRTIs (etravirine and rilpivirine).

**Raltegravir**

Raltegravir was the first ART integrase inhibitor to be approved for use in the treatment of HIV infection. In treatment-naïve-patients, therapeutic efficacy in combination with two NRTIs (TDF and 3TC or FTC) was noninferior to an EFV-containing regimen, with more rapid virological suppression [65]. Tolerability is good, with few adverse events reported in clinical trials [66].
First-line ART in resource-limited settings Ford and Calmy 43

including when compared with EFV [67*]. However, its genetic barrier to resistance is low, meaning that resistance mutations develop quicker after virological failure compared with bPIs [68]. This finding suggests that if raltegravir is to be used as a salvage regimen in resource-limited countries where genotyping is rarely available and NRTIs resistance mutations are likely to have accumulated over time, it should be coadministered with strong support of newer agents such as darunavir/r and etravirine. Raltegravir has potential as a first-line option as it could be provided once daily and has the advantage (unlike other drugs such as darunavir/r) of allowing the protease inhibitors to be reserved for second line. In addition, its better safety profile compared with EFV, including lack of perceived teratogenicity, offers new options, particularly for women of childbearing age [69]. Other unanswered questions include variability in interpatient and intrapatient drug plasma levels that may complicate once-daily dosing (currently raltegravir is only approved for twice-daily dosing, although current data suggest very little effect of inter and intrapatient drug levels on efficacy), long-term safety data on the development of side effects such as lipodystrophy and interaction with anti-TB drugs. The latter is a likely concern because raltegravir is metabolized by uridine diphosphosphate-glucuronosyltransferase (UGT)-mediated glucuronidation, which is induced by rifampicin. The inclusion of patients from resource-limited settings in clinical trials should be strongly encouraged to avoid delays between first commercialization in wealthy country and use in resource-limited settings, as has been the case with other drugs.

Elvitegravir
Elvitegravir is currently still in clinical development, and a comparative trial with raltegravir is underway [70]. Elvitegravir requires boosting, and a new molecule, GS-9350, is currently being assessed as a potential booster, potentially in a FDC with TDF and FTC. If successful, this would result in a once-daily integrase inhibitor-based regimen. The relatively new integrase inhibitors are a new class, and their long-term side effect profile is unknown and will require good pharmacovigilance.

Etravirine
Etravirine is currently being approved for the treatment of treatment-experienced patients (100 mg tablets twice daily). Recent studies have shown the potential for a once-daily dosing, which would open the way to a suitable treatment of treatment-naive patients [71]. However, the pill burden (four pills) and dosage (400 mg).

Rilpivirine
Rilpivirine is a once-daily drug that in clinical trials has shown comparable virological suppression and immune restoration in treatment-naive patients at 96 weeks compared with EFV with lower incidence of rash, central nervous system disorders and lipid abnormalities [72]. Unanswered questions include cardiac safety (QT prolongations pushed manufacturer to switch from 75 to 25 mg), safety in pregnancy and interactions with rifampicin (rilpivirine is a cytochrome CYP3A4 inducer) [73]. Nevertheless, there is potential for NRTI-sparing regimens using a bPI combined with rilpivirine as a once-daily FDC. Moreover, the cost of active ingredient is low, making rilpivirine-containing regimens of particular interest for resource-limited settings.

Finally, it is important to note that clinical trials are generally underpowered to detect adverse events and are often done on selected groups of patients. The relative safety profile of new drugs compared with established ones will only become clear by comparing data derived from observational reports from general populations over time.

Moving forward
The scaling up of ART in Africa was conditioned on a substantial drop in the price of the triple-therapy stavudine, 3TC and nevirapine, and this is still the most widespread combination in use today. The public health approach to ART is premised on affordability and simplicity. Both of these conditions are determined by the pharmaceutical market. Affordability depends largely on market competition and the possibility of generic production, whereas simplicity is mainly an issue of pill burden, which in turn depends on the willingness of manufacturers to produce FDCs of pills that may belong to multiple patent holders. Finally, the use of certain drugs and combinations has been delayed because the relevant research questions have not been asked.

Affordability
Generic competition continues to be the main driver of affordable pricing. In 2009, the price of EFV, lopinavir/ritonavir and TDF (single dose and FDC) dropped steeply as generic production increased (Fig. 1). However, many of these generics were developed prior to the full implementation of the World Trade Organization (WTO) agreements that globalized pharmaceutical patent protection. Since 2005, key generics manufacturing countries, such as India, are obliged to grant pharmaceutical product patents [74]. Raltegravir, elvitegravir, darunavir/r, etravirine and the once-daily combination of TDF, 3TC/FTC and EFV are all examples of patented drugs that are currently priced out of reach for developing countries. Although the WTO agreements contain safeguard, such as compulsory licensing, to allow countries to overcome patents whenever they are a barrier
to public health goals, the use of these safeguards continues to be the subject to political pressure, and as a result, few countries have taken full advantage [75*].

Nevertheless, there is some cause for optimism. Whereas previously, the developing world has had to wait many years for the price of newer medicines to fall to affordable levels, several of the newer drugs, including rilpivirine and raltegravir, have already been allocated a lower price for developing countries. Originator pharmaceutical companies have traditionally been reluctant to market their new medicines at prices that are affordable reasonable for the developing world or share their intellectual property rights with other manufacturers, but there are signs that this is changing. UNITAID (www.unitaid.eu), a financing mechanism to purchase medicines for the treatment of AIDS, TB and malaria, took the initiative towards setting up a voluntary patent pool to stimulate generic production and the development of FDCs including paediatric formulations [76]. This mechanism, through which patent holders share their intellectual property in return for royalties over the sales, has already met with support from some antiretroviral manufacturers (http://www.aidsportal.org/News_Details.aspx?ID=10862). Critically, in order to be able to produce affordable FDCs, all manufacturers must engage.

**Simplicity**

The need for drugs with minimal side effects and contraindications is all the more important, given that increasing numbers of people are accessing care at the primary care level in rural areas. The critical shortage of doctors in these areas has forced programmes to develop task-shifting models of care through which initiation and follow-up of ART is managed by a nurse or other nonphysician clinicians. Such task shifting is recommended by WHO [77] and has proven to be safe and effective in observational studies [78] and randomized trials [79]; its success partially depends on access to simple regimens with minimal laboratory requirements. Similarly, the lack of qualified pharmacists at peripheral level [80] means that drug supply management is often overseen by lower cadres, making the

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Figure 1 Price reductions for key antiretroviral drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Price (US$) per patient per year</th>
<th>Month/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) 3TC, lamivudine</td>
<td>500</td>
<td>Dec 2002 to June 2009</td>
</tr>
<tr>
<td>(b) EFV, efavirenz</td>
<td>462</td>
<td>Dec 2002 to June 2009</td>
</tr>
<tr>
<td>(c) FTC, emtricitabine</td>
<td>346</td>
<td>Dec 2002 to June 2009</td>
</tr>
<tr>
<td>(d) TDF, tenofovir</td>
<td>237</td>
<td>Dec 2002 to June 2009</td>
</tr>
</tbody>
</table>

Simplicity

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availability of FDCs all the more urgent. Such considerations make the once-daily combination of TDF, 3TC/FTC and EFV particularly desirable.

Relevant research
Another important consideration is to ensure that questions pertinent to the developing world are answered early in the drug development process. The interaction between antiretroviral and anti-TB drugs provides a striking example of the extent to which this can be neglected. In some parts of Africa, over three-quarters of people with TB are HIV positive, yet after almost a decade of scaling-up antiretroviral care in Africa, only one randomized trial has been completed to compare the efficacy of coadministering the most widely used antiretrovirals (nevirapine or EFV) together with the most widely used TB drug (rifampicin) [81], although others are underway [82]. Another example is given by the need for optimal dosing studies for stavudine: the WHO amendment recommending a lower dose (30 mg) was only issued in 2006 after stavudine use had already been abandoned in the west. Despite the growing number of people switching to second-line treatment, no studies have ever been done to assess interactions between protease inhibitors and rifampicin in HIV-positive patients [83]. Similarly, interactions between antiretroviral and antimalarial and antiparasitic drugs are poorly understood due to lack of data [84]. The reason for this neglect is mainly because these coinfections, while prevalent in developing countries, hardly exist in the developed world. As such data are not required for regulatory approval, they are not sought in clinical trials. The need to support developing countries to help them generate their own data to validate and modify guidelines for the use of cART has been evident from the outset [85], yet developing country concerns are rarely part of drug development plans [86]. This situation can create significant delays in the development of guideline recommendations. In the absence of improvements in pharmacovigilance in resource-limited settings, cohort reports from monitoring and evaluation programmes will be essential to assess the safety and the efficacy of large-scale antiretroviral roll out over time [87].

Conclusion
The provision of ART in resource-limited settings began with a forceful combination of political, activist and media pressure that led to a rapid reduction in the price of treatment [1**]. Over the years, this pressure has waned as attention moved to implementation and scale-up. However, AIDS is a chronic, lifelong disease. With a continued supply of effective medication, a person diagnosed with HIV in the developed world can expect to live an additional 30 years [89]. In order to maximize life expectancy for people with HIV/AIDS in developing countries, we need to move beyond providing old medications that have long been abandoned in the west. It would not be possible, nor is there any need, to provide the range of antiretrovirals available in the western settings: a standardized approach to care can achieve similar outcomes to the individualized approach [90]. The challenge ahead lies in making the standardized approach as effective as possible by providing durable, tolerable first lines and ensuring a range of alternatives in case of intolerance or resistance. Although there are signs of greater efforts by some companies to make newer medicines affordable for the developing world, renewed political and activist pressure will be needed to ensure that patent and price concerns do not determine guideline recommendations.

Acknowledgements
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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 105).

1 Schwartländer B, Grubb I, Perniërns J. The 10-year struggle to provide antiretroviral treatment to people with HIV in the developing world. Lancet 2006; 368:541–546.
This viewpoint provides an overview of political and financial efforts to improve access to ART in resource-limited settings.


These WHO guidelines include recommendations that resource-limited settings should move away from stavudine to TDF when possible and recommend the use of viral load.

This study estimates the price reduction required for the switch from stavudine to TDF in South Africa to be cost-neutral.


This trial assessed EFV vs. lopinavir–ritonavir along with two NRTIs for initial therapy for patients with HIV-1 infection.


65 Riddler SA, Haubrich DR, DiRienzo AG, et al. Switching from stable lopinavir/ ritonavir-based to ritelgravir-based combination ART resulted in a superior lipid profile at week 12 but did not demonstrate non-inferior virologic efficacy at week 24 [abstract #70aLB]. In: 16th Conference on Retroviruses and Opportunistic Infections, Montreal, Canada; 8–11 February 2009.


This study presents randomized trial data that confirm better safety and efficacy of raltegravir compared with EFV.

68 Eron J, Andrade J, Zajdenverg R, et al. Switching from stable lopinavir/ ritonavir-based to raltegravir-based combination ART resulted in a superior lipid profile at week 12 but did not demonstrate non-inferior virologic efficacy at week 24 [abstract #70aLB]. In: 16th Conference on Retroviruses and Opportunistic Infections, Montreal, Canada; 8–11 February 2009.


First-line ART in resource-limited settings Ford and Calmy


This study summarizes policy options for developing countries to access affordable medicines.

76 Political activism needed for patent pools for HIV drugs. Lancet 2009; 374:266.


This comparative cohort study shows comparable outcomes among patients in Switzerland and South Africa.