Optimising the manufacture, formulation, and dose of antiretroviral drugs for more cost-efficient delivery in resource-limited settings: a consensus statement

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It is expected that funding limitations for worldwide HIV treatment and prevention in resource-limited settings will continue, and, because the need for treatment scale-up is urgent, the emphasis on value for money has become an increasing priority. The Conference on Antiretroviral Drug Optimization—a collaborative project between the Clinton Health Access Initiative, the Johns Hopkins University School of Medicine, and the Bill & Melinda Gates Foundation—brought together process chemists, clinical pharmacologists, pharmaceutical scientists, physicians, pharmacists, and regulatory specialists to explore strategies for the reduction of antiretroviral drug costs. The antiretroviral drugs discussed were prioritised for consideration on the basis of their market impact, and the objectives of the conference were framed as discussion questions generated to guide scientific assessment of potential strategies. These strategies included modifications to the synthesis of the active pharmaceutical ingredient (API) and use of cheaper sources of raw materials in synthesis of these ingredients. Innovations in product formulation could improve bioavailability thus needing less API. For several antiretroviral drugs, studies show efficacy is maintained at doses below the approved dose (eg, efavirenz, lopinavir plus ritonavir, atazanavir, and darunavir). Optimising pharmacoenhancement and extending shelf life are additional strategies. The conference highlighted a range of interventions; optimum cost savings could be achieved through combining approaches.

Introduction

Substantial advances over the past decade have improved access to drugs for the treatment of HIV/AIDS in resource-limited countries, with the number of patients on treatment growing from less than 300 000 in 2002 to more than 6 million by the end of 2010.[1] As the number of patients in need of treatment continues to rise (14·2 million people still in need of treatment[1]), budgetary pressures demand a strong focus on maximising the value for money in treatment costs. Reducing the costs of antiretroviral drugs is essential to match the demand for treatment.

The Conference on Antiretroviral Drug Optimization was held on June 7–10, 2010, in Alexandria (VA, USA), to explore opportunities for reducing the costs of antiretroviral drugs in resource-limited countries. The conference was a collaborative project between the Clinton Health Access Initiative, the Johns Hopkins University School of Medicine (Division of Clinical Pharmacology), and the Bill & Melinda Gates Foundation. The participants were specialists in process chemistry and pharmaceutics, clinical pharmacologists, infectious diseases specialists, pharmacists, drug regulatory specialists, and medical ethicists. The objectives of the meeting were framed by a series of guiding questions with the potential to reveal viable strategies for expanding the numbers of individuals accessing antiretroviral drugs while containing costs (panel).

Present cost-saving strategies centre on the active pharmaceutical ingredient (API). The API makes up the largest portion of total product cost for generic drugs, so a reduction in this input would potentially have the greatest effect on decreasing the total cost of the product.[2] For a highly commoditised generic product, the finished product costs break down into three inputs: API (representing 65–75% of the total market price), formulation (10–20%), and packaging and profits (5–15%).[3]

Improved efficiencies of the API not only reduce costs, but also improve outcomes for patients,[4–6] and methods to improve these efficiencies can be defined by the cost of the API (ie, optimised material sourcing and manufacturing processes), the amount of API (ie, improved bioavailability of the API, which allows reduction of the approved dose),

***Panel:* Guiding questions used to frame the objectives of the meeting**

- Which antiretroviral drugs represent examples of reducing costs by use of alternative sources of raw material in the synthesis of active pharmaceutical ingredients (APIs)?
- Can synthetic pathways of any available drugs be streamlined into fewer steps, resulting in lower costs of synthesis of the API?
- Are there innovative techniques in drug formulation that yield enhanced bioavailability whereby lower doses of the drug produce similar plasma or tissue concentrations as the approved dose?
- Are there available drugs with evidence of uncompromised efficacy at doses lower than those approved by the US Food and Drug Administration?
- Can pharmacoenhancement of these drugs be exploited as a cost-saving strategy by allowing lower doses of the drugs to meet pharmacokinetic requirements for efficacy?
- Does the extension of the shelf life of the product offer opportunities for savings in product costs?

and alternative approaches (ie, pharmacoenhancement or extension of shelf life).

We explored these approaches through the key questions (panel), focusing on antiretroviral drugs for adults and adolescents (aged 15 years and older) since they comprised 79% (by volume) of the worldwide market for generic antiretroviral drugs in 2009 (unpublished).

There are important considerations for optimum regimen choices. Because the cost of second-line treatment in resource-limited countries is greater than the cost of first-line regimens and testing for resistance to antiretroviral drugs is not routinely available, it is important to maintain patients on first-line regimens for as long as possible.[7–9] Recent WHO HIV-treatment recommendations for adults and adolescents focus not only on costs, but also on factors that have been associated with greater durability of the regimen, such as pharmacokinetics, drug resistance profiles, dosing schedules, adherence, and tolerability. These factors are also associated with retaining the patient in care.[10–13]

As we mentioned, restricted access to virological monitoring[14,15] might result in more extensive resistance when failure is finally detected.[16] Consequently, delays in switching from failing first-line drugs to second-line regimens have been associated with shortened time to failure on second-line regimens and increased mortality.[17–19] The optimisation of manufacturing, formulation, and dosing will enable progress in expanding treatment coverage and also expand treatment options.

Approach of the conference

The conference was conceived to ensure that resources dedicated to the optimisation of antiretroviral drugs in the marketplace would be focused on the most clinically important drugs available and in development. The organisers generated the guiding questions (panel) after a systematic assessment of the crucial steps in the processes of chemical synthesis, formulation, pharmacology, and drug disposition. The answers to these questions would yield viable cost-reduction strategies that could be validated through research.

Content experts were identified on the basis of their involvement in relevant research, as defined by a review of published work and the uptake of this work. Most invitees were asked to present data that addressed the guiding questions, and to lead the discussions. Other participants, including those from government and regulatory agencies, were selected on the basis of their engagement in the key disciplines of interest or their ability to share a perspective affecting the optimisation of antiretroviral drugs (eg, legal and regulatory affairs, medical ethics). Specific drugs were prioritised for consideration on the basis of their effect on the market (table 1). Sources supplementing presented data and discussions are cited here and were identified with PubMed. Our search terms were "antiretrovirals", "pharmacokinetics", "dosing", "formulation", "manufacturing", "cost-effectiveness", and specific antiviral drug names; we limited our search to reports in English but did not limit our search by date.

WHO independently sponsored a follow-up conference to assess the best way to implement our recommendations—this conference, Short Term Priorities for Antiretroviral Drug Optimization, was held in London (UK) on April 18–19, 2011.[20] The process for this conference involved independent experts, most of whom were not participants at our conference, discussing ways to incorporate principles of treatment optimisation into guidelines for first-line and second-line regimens for populations of adult and paediatric patients. Additional discussion included the recommendation to coordinate the directives of our conference with WHO treatment guidelines as part of its Treatment 2.0 initiative.[21]

Outcomes

Optimising APIs can reduce generic drug costs substantially. The process for making APIs involves converting raw materials through a series of chemical reactions that define its manufacturing process.[2,22] The cost of the process depends on the raw material costs, the number and complexity of intermediate steps, and the efficiency with which the overall process converts those materials into the API. Any modifications to established protocols for the production of the finished product (ie, the tablet or capsule) are regulated and need the approval of a drug regulatory agency (eg, US Food and Drug Administration [FDA], European Medicines Agency [EMA]) or WHO prequalification programme.[23–25]

Expanding sources of raw materials

Finding less expensive suppliers of raw materials is one approach to reducing costs. The price of raw materials and the number of suppliers depends on the volume of raw materials needed to satisfy marketplace demand.[26] Demand is affected by marketplace volume, any special technologies needed to manufacture the product, and the various known uses for the raw material. An increase in demand can bring new suppliers to the market, creating competition that can lower costs.

Alternatively, improvements to the manufacturing process can potentially increase the efficiency with which raw materials are converted into the API. After the implementation of improved manufacturing processes, the cost of developing the API is reduced, either by allowing more to be made with the same material inputs, use of smaller quantities or less expensive reagents, or reducing manufacturing facility use. Process optimisation opportunities need to be carefully identified because they are opportunity specific.

Tenofovir exemplifies how successes in raw material sourcing and process optimisation led to lower costs, which fell by 57% from 2006 to 2010 (figure 1). The initial high price was driven by inefficiencies in the existing three-stage synthesis (specifically stages 2 and 3), resulting in low yields. Stage 3 was particularly

	Method	Project outcome	Present (expected) cost per patient per year*	3 year market impact (millions)†
Tenofovir	Process chemistry and dose reduction	API from $550 to $400; technology identified for dose reduction	$87 ($63)	$357‡
Zidovudine	Dose optimisation	Dose from 600 mg to 400 mg	$89 ($60)	$282–351
Stavudine	Dose optimisation and comparison with tenofovir	Compare 20 mg stavudine with tenofovir for efficacy and tolerability	$25 ($25)	NA§
Efavirenz	Reformulation and dose optimisation	Dose from 600 mg to 300 mg¶	$63 ($31)	$349–505
Lopinavir plus ritonavir	Dose adjustment	Dose from 800 mg to 665 mg for present formulation	$440 ($365)	$71
Atazanavir plus ritonavir	Process chemistry and reformulation	API from $1800 to $1000; dose to 200 mg plus 100 mg	$355 ($125)	$107–282
Darunavir plus ritonavir	Process chemistry, dose optimisation, and reformulation	API reduced from more than $2000 to $1000; dose optimised to 400 mg plus 50 mg; potential for reformulation assessed	$835 ($335)	NA‖
Rilpivirine	Depot injection product development	Monthly depot injection (less than $15)	·· ($15)	Would replace efavirenz ($30–45 per patient per year)
GSK-572	Product development support	Monthly depot injection (less than $25)	·· ($25)	Could replace efavirenz or tenofovir ($30–75 per patient per year)
CMX-157	Product development	One daily, weekly, or monthly dose (less than $20)	·· ($20)	Would replace tenofovir ($65–75 per patient per year)
Elvucitabine	Product development	Weekly or monthly dose (less than $15 per patient per year)	·· ($10)	Would replace lamivudine ($27 per patient per year)

API=active pharmaceutical ingredient. NA=not applicable. *Clinton Health Access Initiative 2010 ceiling price in US$ (unpublished). †Based on internal market forecasts for years 2012–14. ‡Benefit from process chemistry improvements only, potential 3-year benefit from reformulation additional $80 million to $300 million. §Benefit would be ability to shift to stavudine ($25 per patient per year) from tenofovir ($65–75 per patient per year). ¶Efavirenz dose optimisation is expected to support a dose reduction from 600 mg to 400 mg, efavirenz reformulation is also expected to support a dose reduction from 600 mg to 400 mg. The dose reductions would not be additive, and the combination would be about 300 mg per day. ‖Benefit would be ability to shift from lopinavir plus ritonavir to darunavir plus ritonavir in a cost-neutral manner.

Table 1: **Prioritised project portfolio by antiretroviral drug on the basis of potential economic effect**

challenging; manufacturers typically obtained less than 50% chemical yield, which nearly doubled the final drug price. By targeting the last two stages of synthesis, several improvements made to the reaction parameters substantially increased overall yields from 13% to 24% with the same raw material inputs and costs.[27–30]

Additional price reductions were achieved through bringing new supplies of the expensive tenofovir reagent, magnesium tert-butoxide, to the market as a result of increased demand; this reduced the cost of magnesium tert-butoxide (figure 1). These successes together resulted in a reduction from $207 per patient per year to $87 over the same period (figure 1; unpublished).

This example represents so-called low-hanging fruit. Tenofovir is a widely used drug, although in many countries its use is second line. Despite some toxic effects (eg, renal, bone), tenofovir might be more tolerable than alternatives such as zidovudine and stavudine, producing a more durable first-line regimen at a lower cost.

Manufacturing process development

In some cases, a reworking of the manufacturing process (ie, new process development) yields positive results. When fewer steps are needed to synthesise the product, the process becomes more efficient at converting raw materials into the API. This can reduce the amount of intermediate ingredients needed or allow less specialised, and therefore less expensive, equipment.

The manufacturing process for efavirenz can be streamlined by reducing the number of steps from four to two (figure 2).[31,32] Market adoption has been made possible by securing a local source for the key reagent and defining the appropriate level of catalytic technology needed for the process. As a result, the price of efavirenz fell by 75% from $240 per patient per year in 2006 to $60 in 2011 (unpublished).

Efavirenz is commonly used as a first-line drug and might produce higher rates of virological suppression with fewer toxic effects than nevirapine. Its major limitation is its contraindication in pregnancy and higher cost than nevirapine. Conference participants agreed that lower costs could expand its use, but companies must get approval to modify synthesis of an API. Other potential candidates for simplifying synthesis include the protease inhibitors atazanavir and darunavir, as well as some of the newer antiretroviral drugs in the development pipeline (eg, dolutegravir).

Reformulation

The form of the drug dispensed to the patient is composed of the active plus the inactive ingredients. For

most oral dosage forms, the product will have a calculated bioavailability, which is a measure of how efficiently the product is absorbed from the gastrointestinal tract into the bloodstream after ingestion. The fundamental physical properties of the active plus the inactive ingredients, along with the method used to constitute these ingredients into the delivered form, can affect the bioavailability of a product. Technologies and ingredients that maximise the product's bioavailability (ie, reformulation) can allow less API to achieve the desired drug concentration in patients' blood.[33]

Several formulation technologies have been developed and commercialised in the past few decades to address issues of poor solubility or absorption,[34] aimed at the optimisation of product bioavailability. Stabilisation technologies (eg, hot-melt extrusion, spray-drying techniques), in addition to solubilisers, increase the amount of drug dissolved and absorbed in the body. For example, hot-melt extrusion used to stabilise new heat-stable formulations of lopinavir plus ritonavir resulted in an 18% improvement in the product's bioavailability.[35,36] This process efficiency could offer opportunities to reduce the dose; however, this has not yet resulted in an approved product.

Conference participants concluded that optimising sustained release formulation technology could accomplish several important goals: allow the combination drugs with different dosing frequencies into fixed-dose combination (FDC) products, facilitate less frequent dosing, improve tolerability, diminish fluctuations in steady-state drug concentrations when a dose is missed, and allow for dose reductions. Furthermore, the smoothing of a drug's release profile could reduce side-effects that result from the high peak plasma drug concentrations often noted with rapidly absorbed standard formulations. Recent results of the VERxVE trial[37] showed that the once-daily extended-release formulation of 400 mg nevirapine was non-inferior to the twice-daily 200 mg pill; both groups were paired with a tenofovir plus emtricitabine FDC, showed similar safety outcomes, and will allow patients on nevirapine to take just one pill a day.

Formulation optimisation is straightforward and participants agreed that this approach should be pursued since the end result is an equivalent, less-expensive product. Precedent includes the increase in bioavailability of lopinavir plus ritonavir when formulated in a heat stable tablet and the dose reduction of fenofibrate after a reformulation to a product with higher bioavailability.

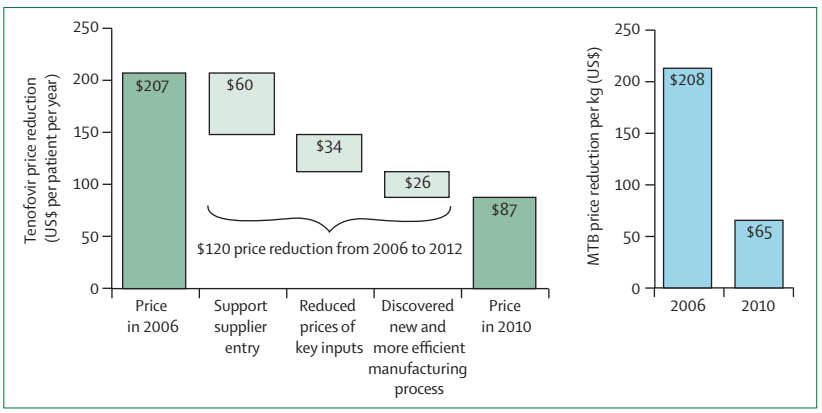

Figure 1: **New source for the raw material magnesium tert-butoxide reduces the cost of synthesis of tenofovir**
MTB=magnesium tert-butoxide.

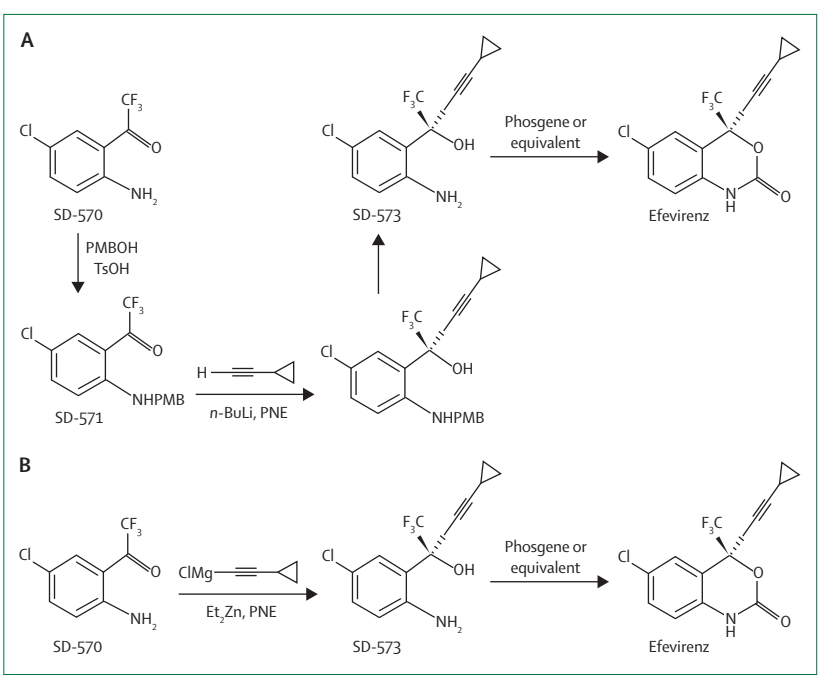

Figure 2: **Comparison of synthetic pathways for efavirenz**
The new streamlined pathway (B) generates the same product (efavirenz) in half the number of steps as the original route (A).

Dose optimisation

Since drug costs are a key determinant of numbers of patients on treatment in resource-limited countries, dose optimisation becomes an important strategy for expanding access to antiretroviral treatment. Selection of the drug dose for advanced development trials is frequently based on results from phase 2 studies and is often the dose with the highest probability of success in phase 3 efficacy studies. To maximise the probability of success, the highest tolerated dose is most often selected, even when phase 2 studies show lower doses with equivalent efficacy.[38] Higher doses have been associated with lower tolerability, resulting in a double disadvantage of higher costs and poor safety profiles. Notably, rilpivirine was approved at the lowest efficacious dose, although it has come into question if this was the optimum dose.[39–42] Several antiretroviral drugs have had post-approval dose reductions, including zidovudine, didanosine, and stavudine.[43–47] Next is a more detailed discussion on several drug dosage studies and their results (summarised in table 2).

Zidovudine was initially approved at a dose of 300 mg every 4 h, but the dose was later reduced to 250–300 mg twice daily. The initial 1800 mg total daily dose was selected on the basis of plasma pharmacokinetics rather than by monitoring the intracellular levels of active zidovudine triphosphates. The formation of zidovudine monophosphate increased with higher doses, yet there was little increase in intracellular triphosphate levels since the conversion to zidovudine diphosphate and triphosphate is a saturable process.[58] Researchers showed that increasing the extracellular concentration of zidovudine ten times, from 2 μM to 20 μM, only increased the concentrations of intracellular triphosphate from 8·4 μM to 11 μM. In this case, the pharmacology of drug activation supported the eventual optimisation of the dose, and concomitant reduction in toxic effects.[59] The approved dose was reduced to 600 mg daily after trials showing equivalent efficacy and improved safety, and studies suggested a much prolonged half-life of the intracellular triphosphate compared with the parent drug in plasma.[6,60,61]

As in the case of zidovudine, the triphosphate of lamivudine is the active moiety; the phosphorylation of lamivudine to the active metabolite is a saturable enzymatic process, and therefore, the concentration of triphosphate is not proportional to the concentration of lamivudine in the plasma at high concentrations.[62] A small randomised crossover study, ENCORE 2,[48] showed that intracellular concentrations of lamivudine triphosphate were significantly lower after giving a low dose (150 mg per day *vs* 300 mg), suggesting that the metabolic pathway for activating this drug had not been saturated. Therefore, lamivudine was not a candidate for dose reduction to 150 mg per day. This finding did not justify pursuit of a larger clinical trial.

In double-blind, placebo-controlled phase 2 clinical studies of efavirenz, there was no difference between the proportion of patients with HIV RNA levels of less 400 copies per mL at 24 weeks, whether they received a daily dose of 200 mg, 400 mg, or 600 mg of efavirenz combined with zidovudine and lamivudine.[49] The 200 mg dose had the highest proportion of participants with fewer than 400 copies per mL (not statistically significant), suggesting not only equal efficacy with the currently approved 600 mg dose, but perhaps better tolerability. The ongoing ENCORE 1 study,[63] which began in August, 2011, is at present comparing standard-dose efavirenz 600 mg once daily with a reduced dose of 400 mg once daily (both in combination with tenofovir and emtricitabine FDC) in treatment-naive patients followed up for 96 weeks.

The effectiveness of dose reductions in lopinavir plus ritonavir was assessed in a prospective, randomised, double-blind study comparing the approved dose of 400 mg lopinavir plus 100 mg ritonavir twice daily with a reduced dose of 200 mg plus 100 mg twice daily in a white population.[50] All patients receiving 200 mg plus 100 mg were suppressed to both fewer than 400 copies per mL and 50 copies per mL at 48 weeks, whereas 81% of patients receiving 400 mg plus 100 mg were suppressed to fewer

	Method	Doses studied	Outcome	Conclusion
Nucleoside/nucleotide reverse transcriptase inhibitors				
Zidovudine				
Volberding et al[6]	Randomised double-blind study	1500 mg per day *vs* 500 mg daily *vs* placebo	Incidence of AIDS was lower in the 500 mg and the 1500 mg group than the placebo	Lower dose showed equal efficacy and improved safety
Lamivudine				
ENCORE 2[48]	Randomised crossover study	300 mg daily vs 150 mg daily	Lower doses did not show adequate saturation	Not a candidate for 150 mg/day
Non-nucleoside reverse transcriptase inhibitors				
Efavirenz				
Hicks et al[49]	Double-blind, placebo-controlled phase 2 clinical trials	600 mg *vs* 400 mg *vs* 200 mg daily	No difference between the proportion of patients with HIV RNA <400 copies per mL at 24 weeks for all three doses	Lower doses of efavirenz might be equally efficacious
ENCORE 2	Double-blind, placebo-controlled phase 2 clinical trials	600 mg *vs* 400 mg daily	Ongoing 96 week study began in August, 2011	Not applicable
Rilpivirine				
Pozniak et al[39]	Randomised, active controlled, partly blinded phase 2	150 mg *vs* 75 mg *vs* 25 mg	All doses showed non-inferiority to efavirenz 600 mg	Lowest dose was approved
THRIVE[40]	Randomised double-blind, phase 3 study	25 mg *vs* efavirenz 600 mg	25 mg found non-inferior to efavirenz 600 mg	Separately each study showed non-inferiority, although pooled analyses showed increased failure rates for patients starting treatment with viral loads >100 000 copies per mL
ECHO[41]	Randomised double-blind, phase 3 study	25 mg *vs* efavirenz 600 mg	25 mg found non-inferior to efavirenz 600 mg	As for THRIVE

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	Method	Doses studied	Outcome	Conclusion
(Continued from previous page)				
Protease inhibitors				
Lopinavir plus ritonavir				
Murphy et al[50]	Prospective, randomised, double-blind trial	400 mg plus 100 mg *vs* 200 mg plus 100 mg	100% of lower dose had suppressed viral load to <50 copies per mL at 48 weeks; 81% of higher dose had viral load <400 copies per mL and 50% viral load <50 copies per mL	The improved virological outcomes with the lower dose might relate to greater tolerability than the approved dose
Jackson et al[51]	Pharmacokinetics study	400 mg plus 100 mg *vs* 200 mg plus 150 mg *vs* 200 mg plus 50 mg twice daily	100% patients on 400 mg plus 100 mg and 200 mg plus 150 mg doses twice daily achieved therapeutic plasma concentrations; 86% in 200 mg plus 50 mg group	Low concentrations of lopinavir after lower unit dosing could only be overcome through higher ritonavir dosing
Ritonavir				
van der Lugt et al[52]	Pharmacokinetic crossover study	Saquinavir plus ritonavir 1500 mg plus 50 mg (plus nucleoside reverse transcriptase inhibitor backbone) to saquinavir mg plus ritonavir 1500 mg plus 100 mg	100 mg daily to 50 mg daily with saquinavir produced similar saquinavir pharmacokinetics	Lower doses of ritonavir might be effective when coupled with saquinavir
Hill et al[53]	Meta-analysis of pharmacokinetic trials	100 mg *vs* 50 mg	Saquinavir, fosamprenavir, and darunavir could be boosted equally with a lower dose of ritonavir. Indinavir, tipranavir, and lopinavir were boosted more by higher ritonavir doses; atazanavir was inconclusive	Opportunity to use three protease inhibitors with lower dose of ritonavir
Estevez et al[54]	Crossover, single-blind, two period study	100 mg *vs* 50 mg with 300 mg of atazanavir	Atazanavir plus ritonavir has also shown equal boosting effects for ritonavir at 50 mg and 100 mg daily doses	Atazanavir could be paired with lower dose of ritonavir
Atazanavir				
Avihingsanon et al[55]	Pharmacokinetic analysis of Thai patients	300 mg plus 100 mg *vs* 200 mg plus 100 mg daily (with ritonavir)	Pharmacokinetic variables were lower in the lower dose group, viral load	200 mg plus 100 mg dosing might be sufficient in some populations of patients
Darunavir				
POWER 1[56]	Randomised, partly blinded, controlled phase 2 trial	800 mg plus 100 mg once daily *vs* 400 mg plus 100 mg once daily *vs* 600 mg plus 100 mg twice daily *vs* 400 mg plus 100 mg twice daily (with ritonavir)	Presence of baseline resistance, the proportion of participants with greater than one log decrease in the 600 mg plus 100 mg twice-daily arm was 100% for participants with just one protease inhibitor mutation and 76% for those with three. 600 mg plus 100 mg twice daily showed the highest virological and immunological responses	Darunavir use, even at reduced doses, produces responses in individuals with three primary protease inhibitor mutations, suggesting its potential for use as a third-line agent
Integrase inhibitors				
Raltegravir				
Markowitz et al[57]	Double-blind, randomised, controlled trial	600 mg *vs* 400 mg *vs* 200 mg *vs* 100 mg twice daily *vs* efavirenz 600 mg	By week 48, patients receiving raltegravir 100, 200, 400, or 600 mg twice daily suppressed HIV RNA to <50 copies per mL in 85%, 83%, 88%, and 88% of patients, respectively	Raltegravir might be efficacious at doses lower than the dose of 400 mg twice daily approved by the US Food and Drug Administration

Table 2: **Summary and findings of antiretroviral dose-reduction studies**

than 400 copies per mL and only 50% to fewer than 50 copies per mL. Furthermore, an increase in the lopinavir dose from 200 mg to 400 mg only produced a marginal increase in the trough lopinavir concentration, with both doses being well above the EC_{50} (effective concentration to inhibit viral replicaton by 50%) of lopinavir for wild-type HIV-1. These findings suggest that lopinavir trough plasma concentrations might plateau at a dose less than the approved coformulation. The improved virological outcomes with the lower dose might be related to greater tolerability than the approved dose.

Another study compared the pharmacokinetics of the standard dose of lopinavir plus ritonavir 400 mg plus 100 mg to 200 mg plus 150 mg and 200 mg plus 50 mg twice daily in 30 HIV-negative volunteers.[54] Results showed that all participants (100%) taking 400 mg plus 100 mg and 200 mg plus 150 mg doses twice daily achieved therapeutic plasma concentrations (compared with 86% of participants taking 200 mg plus 50 mg twice daily), suggesting low concentrations of lopinavir after lower unit dosing could be overcome through higher ritonavir dosing.

A pharmacokinetic analysis comparing the efficacy of reduced-dose ritonavir-boosted atazanavir in Thai patients showed that with 200 mg plus 100 mg daily versus the approved 300 mg plus 100 mg daily combination, atazanavir concentrations were significantly higher with the approved dose compared with the reduced dose.[55] However, the pharmacokinetic parameters in the reduced dose regimen for Thai participants were similar to those of the approved dose in white people based on historical data. Furthermore, the incidence of grades 3–4 hyperbilirubinaemia was reduced

from 36% in the standard dose group to 14% in the reduced dose group. Because of differences in pharmacogenetics and bodyweight, 200 mg plus 100 mg dosing might be sufficient in some patient populations and merits further research.

The POWER 1 trial[56] showed the efficacy of various doses of ritonavir-boosted darunavir, in treatment-experienced patients. By the end of 24 weeks, 67% of participants receiving 600 mg darunavir plus 100 mg ritonavir twice daily and 53% receiving 400 mg plus 100 mg daily had HIV RNA less than 400 and less than 50 copies per mL, compared with 63% and 43% of participants by intention-to-treat and time-to-loss-of-virological response analyses. In assessing responses on the basis of the presence of baseline resistance, the proportion of participants with greater than one log decrease in plasma viral load in the 600 mg plus 100 mg twice-daily arm was 100% for participants with just one protease inhibitor mutation and 76% for those with three or more. By contrast, for those participants who were randomly assigned to receive 400 mg plus 100 mg daily, the proportion with greater than one log decrease was 83% for those with one mutation and 62% for those with three.[56]

To improve clinical outcomes, the reduced dose regimen could be used in individuals who are naive to protease inhibitors and have no resistance mutations since the reduced dose will probably produce lower darunavir trough plasma concentrations than the approved dose.[64] These patients could employ darunavir as a second-line regimen, but regimens based on non-nucleoside reverse transcriptase inhibitors are still likely to be used first. Use of darunavir, even at reduced doses, produces virological responses in individuals with three primary protease inhibitor mutations, suggesting its potential for use as a third-line treatment.

A range of raltegravir doses (100, 200, 400, 600 mg twice daily) were assessed in a double-blind, randomised, controlled trial versus efavirenz (600 mg once daily), all in combination with tenofovir (300 mg once daily), and lamivudine (300 mg once daily).[57] The authors did not identify any significant differences in the short-term antiviral effects of any raltegravir doses. By week 48, raltegravir 100, 200, 400, or 600 mg twice daily suppressed HIV RNA to less than 50 copies per mL in 85%, 83%, 88%, and 88% of patients, respectively. Thus, raltegravir might be efficacious at doses lower than the 400 mg twice-daily dose approved by the FDA.

In a large trial of raltegravir,[65] which assessed a once-daily 800 mg dose versus the standard 400 mg twice-daily dose, antiretroviral efficacy was shown to be lower in patients on the once-daily dose. This finding suggests that once-daily dosing might not be possible with this drug.[65]

Key issues on the efficacy of dose-reduction strategies are whether reduced doses of the drug produce similar rates of viral suppression as approved doses; how reduced doses affect the viral dynamics of HIV replication in anatomical reservoirs (eg, CNS); whether reduced doses affect the rate of acquisition of drug resistance; how pharmacogenetics affect the efficacy when doses are reduced; whether reduced doses improve safety, tolerability, and adherence; and whether dose reduction alters the risk of drug–drug interactions.

We and others agree that dose reduction is one approach to reducing treatment costs, and has been shown to decrease toxic effects and improve tolerability, which might improve adherence.[5,11,66] One disadvantage of dose-reduction strategies is the weight of clinical evidence needed to change treatment recommendations. Although key clinical questions on the long-term efficacy of dose-reduction strategies remain, the potential benefits of dose optimisation should continue to be actively researched. Many antiretroviral drugs are well suited to dose optimisation, particularly since published data from short-term studies show equivalent efficacy of lower doses as the approved dose. The ENCORE studies will assess some of the most promising candidates. New and investigational drugs (eg, elvitegravir, dolutegravir) should also be considered for dose optimisation.

Alternative approaches

Pharmacoenhancement or pharmacological boosting refers to the use of an additional compound to improve the pharmacokinetic profile of a second targeted drug. This technique provides potential opportunities for dose optimisation and is already widely used with HIV protease inhibitors (eg, ritonavir combinations).[67] A non-randomised study of Thai patients infected with HIV showed that reducing the ritonavir dose from 100 mg daily to 50 mg daily with saquinavir produced similar saquinavir pharmacokinetics.[52] Furthermore, a review of 17 dose-ranging pharmacokinetic trials concluded that saquinavir, fosamprenavir, and darunavir could be boosted equally with a lower dose (50 mg *vs* 100 mg) of ritonavir.[53] A more recent pharmacokinetic study of atazanavir plus ritonavir has also shown equal boosting effects for ritonavir at 50 mg and 100 mg daily doses.[60] Besides ritonavir, other new boosting agents are in development—for example, cobicistat is under investigation as a booster for HIV protease inhibitors[68] and the integrase inhibitor elvitegravir.[69–71]

Studies were presented at the conference for some protease inhibitors, suggesting that 50 mg of ritonavir enhanced the pharmacokinetics of the target drug as well as 100 mg. Development of in-vitro models to detect the optimum ratio of drug plus pharmacoenhancer was mentioned as one approach to streamline clinical development.

The extension of a product's shelf life could result in drug cost savings and better availability for lower-volume products, such as paediatric formulations, by reducing the amount of product purchased per unit time. To extend shelf life beyond the typical 2 year limit, real-time stability testing is needed to show that the product remains stable and active throughout its marketed life;[72]

this means a 2–3 year lag time from testing to approval and commercialisation.

Shelf-life extension could particularly affect low-volume antiretroviral products because many expire before being sold. The supply chain requires that the product have 75% remaining shelf life at time of delivery, meaning at least 6 months to liquidate a product from the time of manufacture to the time of delivery. One consequence of this process is the need for more expensive modes of transport (air *vs* sea) to deliver the product. Additionally, the short turnaround time creates greater risk for small orders, resulting in higher prices and delay in accepting small orders until a sufficient demand for an entire manufacturing lot exists. To hedge against losses if the entire lot of product is not sold before it ages beyond the sellable point, suppliers need to either charge higher unit prices to make up this cost, or offer longer lead times until such point that additional orders can be secured.

Participants agreed that to have maximum effect, streamlined regulatory pathways for the approval of shelf-life extensions need to be developed and should be consistent across markets to mitigate inefficiencies in which manufacturers label the same product differently for different markets.

Shelf-life extension is one of the most feasible cost-saving measures because it involves no manipulation of the synthesis, formulation, or dosing of the product. Quality control measures could be instituted to validate that the product has sufficient activity at the time of sale.

Estimating economic impact

Even slight reductions in drug costs can substantially affect worldwide treatment savings related to antiretroviral drugs. Models built to predict the economic benefits of optimised regimens are a topic of great discussion and ongoing research. To answer optimisation questions, these models include parameters to capture the expected cost savings per unit of product, the expected volumes of product for future marketplace use, and the rates of market uptake. Estimating the effect of cost savings of different scenarios identifies priorities for maximum gains. Table 1 shows priority reformulation and dosage opportunities based on potential economic impact.

Interventions that reduce the cost of the API are the most straightforward to model, because the expected cost reduction for the new lower-priced product can be multiplied by the number of patients expected to take that drug per year; however, this method does not incorporate market shifts. In the tenofovir example from above, the net $120 savings per patient per year were a result of reducing the drug price. The worldwide market for generic tenofovir in resource-limited settings was estimated at more than 1 million patients in 2010, which accounts for $132 million in annual savings. Conversely, greater than 1·5 million more patient-years of treatment could be provided with the same annual budget. Since the number of patients on tenofovir increases over the next few years, greater savings will be realised through these price reductions.

Atazanavir offers an example where API cost reductions can result in large savings. In this case, optimisation of the API of atazanavir can reduce costs from about $1800/kg to as low as $1000/kg and an overall product reduction from $355 to $125 per patient per year; based on marketplace forecasts for 2013, this would generate an estimated $34 million in annual savings.

For interventions that reduce the amount of API, the rate at which a new product replaces the existing product in the marketplace should be considered for any reformulations that increase the product's bioavailability but do not affect its safety and efficacy profile. This rate will also depend on other factors (eg, incorporation of the new product into treatment guidelines, market uptake activities in individual countries, and market introduction of FDC products containing the new formulation relative to sales of the product as a single pill).

One concern raised by conference participants is whether the intervention changes the clinical profile of the product, which could be the case with sustained release formulations or dose optimisations. Any variation in the expected durability of the drug will modify the cost of the next-line regimen. In this context, the relative difference in timing for the average patient in transitioning to the new regimen and the long-term treatment costs need to be considered. For example, with a reduced-dose version of efavirenz (eg, 400 mg once daily), the present price of $63 per patient per year can be expected to drop to $47 per patient per year (assuming the API is 75% of total cost [$47·25] and other costs are $15·75, then reduce the API cost by two-thirds [400 mg over 600 mg] to $31·50; then add the $15·75 other costs) and is expected to reach $31 per patient per year with further reformulation options. This change has an expected 3 year market impact of at least $350 million.[3]

Follow-up recommendations

As a follow-up to our conference, the WHO London conference on Short-term Treatment Priorities identified a new co-formulated FDC of efavirenz 600 mg plus lamivudine 300 mg plus tenofovir 300 mg as a key target for first-line treatment for adults and adolescents in resource-limited settings over the next 3–5 years. Other outcomes of this conference included confirmation that efavirenz should generally be a superior choice to nevirapine in terms of efficacy and severity of toxic effects; that there should be reassessment of evidence supporting or refuting the teratogenicity of efavirenz; that the number of available formulations for use in neonatal and paediatric patients should be minimised or harmonised with adult formulations; and that there should be further clinical study of regimens containing reduced doses of high priority antiretroviral drugs, including efavirenz and certain ritonavir-enhanced protease inhibitor combinations.

Conclusions

To maintain success in HIV treatment scale-up without increases in funding, opportunities to decrease the cost of treatment must be explored. Our conference identified several strategies to reduce costs of antiretroviral drugs, especially the most widely used generic products.

Alternative sources of raw materials (eg, magnesium tert-butoxide in tenofovir synthesis), refining or streamlining the synthesis of APIs to fewer steps (eg, efavirenz) are examples for reducing costs of APIs of key antiretroviral drugs. Innovations in pharmaceutics can introduce new strategies of product formulation that improve bioavailability, thus needing less API to achieve target plasma drug concentrations. For some approved drugs there are existing data supporting efficacy at doses below the approved dose. Initiatives like ENCORE and others systematically assess the potential for lower doses of candidate drugs, which can lead to cost reductions. Ritonavir as a pharmacoenhancer might boost some drugs as effectively at 50 mg as when given at 100 mg, and should be considered in this category. Extending the shelf life of the drugs is a cost-saving strategy that could be employed by modifying existing procurement and regulatory procedures. The potential for synergy exists by combining these interventions, thus maximising cost savings and expanding the numbers of patients with HIV who are treated.

Contributors

CF and DHBR were co-chairs of the Conference on Antiretroviral Drug Optimization, participated in summarising the outputs of the conference and the writing of this report. KWC participated in the conference and led the writing and coordination of materials for this report. ADL co-wrote the initial draft and assisted with revisions. JRC assisted with editing revisions and economic impact analysis.

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Conflicts of interest

CF has received research funding from GlaxoSmithKline, has served as a consultant for Bristol-Myers Squibb, Boehringer-Ingelheim, GlaxoSmithKline, Merck, Roche, Schering-Plough, Tibotec, Vertex, and ViiV Healthcare; and has received honoraria from Abbott Laboratories. The other authors declare no conflicts of interest.

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