Dose Optimisation: A Strategy to Improve Tolerability and Lower Antiretroviral Drug Prices in Low and Middle Income Countries

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Abstract: Four million people have been initiated on antiretroviral treatment in low and middle income countries. However, an additional 5 million people eligible for treatment are not receiving it. Of the 27-29 million people infected with HIV but not currently receiving treatment, most will need to start antiretrovirals as their disease progresses. Funding for access programmes is restricted, partly because of the Global Financial Crisis. Antiretroviral treatment programmes have to lower overall costs, so that the maximum number of people with HIV can be treated for limited budgets. Antiretroviral treatment can account for the majority of the total cost of access programmes.

During the development of antiretrovirals, several doses are normally evaluated in Phase 2 dose-ranging trials. In the case of efavirenz, lopinavir/ritonavir and raltegravir, there was no difference in efficacy between doses evaluated at Phase 2, but the higher doses were then taken into Phase 3 registration trials, leading to regulatory approval.

Re-analysis of the dose-ranging trials of raltegravir showed equal efficacy for doses in the range of 100 to 600mg twice daily. The main Phase 2 trial of efavirenz, DMP-005, suggests that a 400mg once daily dose should show equal efficacy to the standard 600mg once daily dose. The dose-ranging trials of lopinavir/ritonavir showed the highest efficacy at the 200/100mg mg twice daily dose, compared with the standard 400/100 mg twice daily dose.

Re-optimisation of doses could dramatically lower costs of first and second-line treatment for low and middle income countries. For example, it may be possible to manufacture raltegravir 100 mg twice daily for US $75-100, allowing first-line use in low income countries. Costs of efavirenz could be lowered by 30%, and lopinavir/ritonavir by 35%, using re-optimised doses. There may also be safety benefits to these new doses.

Keywords: Nucleoside analogues, protease inhibitors, non nucleosides, health economics, developing countries, pharmacology, HIV RNA, HIV clinical trials.

INTRODUCTION

Of the 33 million people currently infected with HIV/AIDS, over 90% live in low income countries [1]. Although 4 million people have been started on antiretroviral treatment in these countries, an additional five million people in low and middle income countres are eligible for treatment but are not receiving it [1]. Most of the 29 million people infected with HIV, but currently untreated, will require antiretrovirals at some time in the future, if they are identified and tested. In addition, there are an estimated three million new HIV infections every year [1].

Given these combined pressures, there is still a dire need for further upscale in HIV treatment programmes. We should therefore be planning for large upscale in HIV treatment programmes, in order to treat between 10-15 million people with antiretrovirals in low or middle income countries within the next 5 years. However, there are concerns over whether funding for access programmes will be large enough to allow this number of patients to be treated [2-4].

Drug costs are already accounting for as much as 60% of antiretroviral treatment program costs in several countries, and any effort to decrease drug cost is likely to have a major benefit. API (active product ingredient) production costs are the biggest driver of antiretroviral drug prices among generic manufacturers [3]: a given percentage reduction in dosage will translate into a virtually equivalent percentage reduction in drug pricing. Clearly, when millions of patients are being treated, small reductions in the annual per-patient cost of treatment could lead to significant reductions in the global cost of HIV treatment [5].

In this review paper, we discuss the use of dose optimisation to lower antiretroviral drug costs and improve tolerability and convenience.

HIV DRUG COSTS IN LOW INCOME COUNTRIES

Table **1** shows the minimum cost of antiretrovirals in low income countries (based on prices from the Clinton Foundation for Least Developed Countries [5], from Thailand (representing a middle income country) and the

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USA as a reference developed country. The cost of antiretrovirals in low income countries is typically 90-99% lower than in North America. The cost of manufacture in low income countries is closely related to the cost of the Active Product Ingredient (API) – this is the actual antiretroviral substance. This is particularly true for generic drugs [6]. Economies of scale and improved manufacturing techniques have lowered the minimum costs of antiretrovirals over the past ten years, and annual costs of $80 per person-year of treatment are now possible for combinations such as d4T/3TC/NVP [2, 5]. However the cost of protease inhibitors or raltegravir is substantially higher (Table **1**).

Table 1. Annual Per-Patient Prices of Antiretrovirals by National Income: Low (Africa), Middle (Thailand) and High (USA)

Drug	Dose	Annual Price Per Patient (US $)		
		Africa	Thailand	USA
lamivudine (3TC)	300mg OD	34	177	3923
stavudine (d4T)	30mg BID	25	84	4447
zidovudine (ZDV)	300mg BID	96	345	4584
didanosine (ddI)	400mg OD	240	1305	3988
tenofovir (TDF)	300mg OD	99	470	6719
nevirapine (NVP)	200mg BID	40	251	4912
efavirenz (EFV)	600mg OD	105	282	5869
lopinavir/r (LPV/r)	400/100 mg BID	470	2004	8586
atazanavir/r (ATV/r)	300/100 mg OD	n/a	3383	10635
raltegravir (RAL)	400mg BID	1113	3480*	9855

Data Sources:
Low income countries – Clinton HIV/AIDS website summary 2009 [5].
Thailand (middle income country). The Thai Red Cross AIDS Research Center (Exchange rate used was 33.45 Baht/1USD).
USA (Wholesale Acquisition Costs) – MedSpan Price Check PC.
*Unofficial price. Medication is not yet available in Thailand.

OPTIMISATION OF DOSES FOR ANTIRETROVIRALS

Many clinicians think of drug dosing as fixed and unchanging, but the doses of three antiretrovirals have been lowered since they were first launched. The dose of zidovudine was reduced from 1800mg daily to 600mg daily, after dose-ranging trials showed equivalent efficacy but improved safety at the lower dose [7]. The dose of didanosine was also reduced, for similar reasons [8].

The dose of the nucleoside analogue stavudine was reduced from 40mg to 30mg twice daily after a meta-analysis of dose-ranging studies showed the same efficacy at the lower dose, but with an improved safety profile. Patients who took the 30mg twice daily dose of stavudine had a lower risk of peripheral neuropathy and were less likely to discontinue treatment [9]. The World Health Organisation now recommends the 30mg twice daily dose of stavudine for all patients [10].

During the dose-selection phase of HIV drug development, clinical trials of 30-100 patients per arm are used to evaluate the efficacy and safety of several doses. In some cases, there is a dose-limiting toxicity at a higher dose, or a lack of efficacy at a lower dose, which makes the dose selection straightforward. However in most cases, these trials can show similar levels of efficacy between a range of doses. In these situations, pharmaceutical companies tend to progress with higher doses, to maximise the potential for long-term efficacy and possibly to ensure efficacy even when drug interactions lower the concentration of the new antiretroviral. However, choosing higher doses can compromise patient safety, and the higher doses are more expensive to manufacture. For example, if stavudine had been approved at the 30mg twice daily dose, thousands of cases of severe peripheral neuropathy could have been avoided, but the efficacy of stavudine would not have been affected. The dose selection for the non-nucleoside rilpivirine is a good example of this process. In the TMC-278 C204 trial, doses of 25-150mg once daily showed similar efficacy as first-line treatment with two nucleoside analogues [11]. At first a 75 mg dose was chosen for phase II trials from the TMC278-C204 trial; concerns about safety led to a dose reduction of 25 mg for phase II trials, without apparent concerns about virological efficacy.

DOSE SELECTION FOR RALTEGRAVIR

The STARTMRK trial has established the efficacy of the 400mg twice daily dose versus efavirenz in treatment naïve patients [12], while the BENCHMRK trials have shown efficacy for raltegravir in treatment experienced patients [13]. These pivotal trials all used the 400mg twice daily dose, which has been approved by regulatory authorities in North America and Europe.

Currently, raltegravir is not available for use in low income countries – but the cost could be set as much as for $1113 per person-year for the 400mg twice daily dose [2], and this high price could severely limit use in Africa or Asia. The Clinton Foundation has estimated a future price of $300-600 per person-year for raltegravir at this dose, if production can be up-scaled [14].

Raltegravir has been evaluated in treatment naïve patients at doses ranging from 100mg to 600mg twice daily. The efficacy and safety of this integrase inhibitor was very similar across the range of doses evaluated (Table **2**). The efficacy of raltegravir was first evaluated in a 10 day monotherapy study, in 35 treatment naïve, HIV-infected individuals [15]. The doses evaluated were 100, 200, 400 and 600mg twice daily. After 10 days of dosing, the $\log_{10}$ reductions in HIV RNA and the percentage of patients with HIV RNA <400 were the same at the four doses evaluated (Table **2a**).

Subsequently, a 48 week trial in treatment naïve patients [16] showed no differences in efficacy between raltegravir doses of 100, 200, 400 and 600mg twice daily, given with tenofovir and lamivudine (Table **2b**). The rises in CD4 count were greatest for the 100mg twice daily dose (+221 cells/uL) and lowest for the 400mg twice daily dose (+144 cells/uL).

In addition, a 24 week trial was conducted in treatment experienced patients [17], evaluating raltegravir doses of 200, 400 and 600mg twice daily. This trial showed no difference in HIV RNA suppression rates between the doses (Table **2c**). In this trial, the rises in CD4 count were greater

at the 400mg twice daily dose (+113 cells/uL) relative to the 200mg twice daily dose (+63 cells/uL).

Table 2a. Merck Phase 1b Trial of Raltegravir (RAL) – 10 Days of Monotherapy [15]

RAL Dose (BID)	100mg	200mg	400mg	600mg
N	7	7	6	8
Baseline CD4	415	343	256	569
Baseline HIV RNA	4.65	4.53	4.58	4.97
Race (% Caucasian)	57%	57%	50%	100%
Gender (% male)	100%	86%	100%	100%
10 Day Efficacy Data				
Percent HIV RNA <400	57%	57%	50%	50%
Log reduction HIV RNA	-1.93	-1.98	-1.66	-2.16

Table 2b. Merck Phase 3 Trial of Raltegravir in Treatment Naïve Patients (48 Weeks) [16]

RAL Dose (BID)	100mg	200mg	400mg	600mg
N	39	40	41	40
Baseline CD4	314	296	338	271
Baseline HIV RNA	4.8	4.8	4.6	4.8
Race (% non-Caucasian)	82%	65%	66%	65%
Gender (% male)	85%	73%	90%	73%
48 Week Efficacy Data (ITT)				
Percent HIV RNA <400	97%	85%	98%	90%
Percent HIV RNA <50	85%	83%	88%	88%
48 week CD4 rise (mean)	+221	+146	+144	+187

Table 2c. Merck 005 Trial of Raltegravir (RAL) in Experienced Patients [17]

RAL Dose (BID)	200mg	400mg	600mg
N	43	40	41
Baseline CD4	245	221	220
Baseline HIV RNA	4.6	4.8	4.7
Race (% non-Caucasian)	84%	78%	71%
Gender (% male)	84%	89%	91%
24 Week Efficacy Data (ITT)			
Percent HIV RNA <400	70%	71%	71%
Percent HIV RNA <50	65%	56%	67%
48 week CD4 rise (mean)	+63	+113	+94

Across the three dose-ranging trials, there is no consistent trend for improved HIV RNA reductions or greater rises in CD4 counts with increasing doses of raltegravir. The combined sample size for these dose-ranging trials, 312 patients – provides evidence for this lack of correlation between raltegravir dosing and efficacy.

If Clinton Foundation's predictions of cost for upscaled production of raltegravir are correct, the implication is that a 100mg twice daily dose could then be made for between $75-150 per person-year, which is similar to the minimum price efavirenz or nevirapine (Table **1**). If efficacy could be proved for a 100mg twice daily dose of raltegravir versus efavirenz in a large non-inferiority trial, this could then potentially allow first-line use of raltegravir in low income countries at an affordable price. If only the current 400mg formulation of raltegravir can be used, pharmacokinetic data is already available for raltegravir at the 400mg once daily dose, in combination with atazanavir [18]. There are clinical trials underway evaluating the 800mg once daily dose, and the pharmacokinetics of raltegravir, with a long terminal elimination half-life, may support once daily dosing [19]. However the dose-ranging trials in this review only evaluated twice-daily dosing.

DOSE SELECTION FOR EFAVIRENZ

The standard dose of efavirenz is 600mg once daily (manufactured in tablet strengths of 200 and 600 mg, both FDA approved). First-line treatment with two nucleoside analogues plus efavirenz is a widely accepted standard of care for developed and developing countries, based on multiple clinical trials showing efficacy advantages over other combinations [20]. The main side-effects of efavirenz involve the central nervous system (CNS). Efavirenz is also a known teratogen and is contraindicated in first trimester pregnancy. Phase 2 data suggests that efavirenz doses of 200 to 400 mg once daily show similar antiviral efficacy to the approved dose of 600mg OD. There is the potential for lower doses to also improve the CNS adverse event profile.

The DMP-005 trial of efavirenz was conducted in 1996-1997, and was presented at the 5th CROI meeting in Chicago, February 1998 [21], but was never published. 137 naïve patients were randomized to 24 weeks of treatment with zidovudine plus lamivudine with efavirenz at doses of 200mg, 400mg or 600mg once daily, or matching placebo. Summary baseline and 16 week efficacy data is shown in Table **3**. There was no difference in HIV RNA suppression rates between the three doses of efavirenz. These efficacy results were sustained to week 24. There were no systematic differences in adverse event profiles by treatment group, although there was a higher incidence of dizziness at the highest efavirenz dose, and more rash at the lowest dose. However, six patients withdrew from the efavirenz 600mg once daily arm owing to adverse events, versus none from the efavirenz 200mg group.

Genetic analysis of patients receiving efavirenz showed that plasma drug levels could be up to three times higher for those with a certain CYP2B6 allelic variant, seen most often in Africans [23]. In a separate analysis of 255 Dutch patients, females and those with low body weight had significantly higher efavirenz drug levels, and there was also an association between Asian or African race and higher efavirenz levels [24]. In analysis of the Swiss HIV cohort, patients taking efavirenz with higher drug levels were found to have a higher risk of nervous system side effects [25]. It is possible that efavirenz dose reductions may lower the incidence of these side-effects.

Table 3. DMP-006 Trial of Efavirenz [21]

Efavirenz Dose (OD)	200mg	400mg	600mg	Placebo
N	36	34	34	33
Baseline CD4	329	359	388	395
Baseline HIV RNA	4.81	4.76	4.64	4.66
Baseline weight (kg)	75	73	78	77
Race (% Cauc/Afr)	53/36%	71/18%	68/21%	61/33%
Gender (% male)	97%	89%	85%	76%
16 Week Efficacy Data (ITT)				
Percent HIV RNA <400	86%	85%	79%	39%
Percent HIV RNA <50	83%	68%	67%	15%
Percent HIV RNA <1	50%	39%	59%	8%
16 week CD4 rise (mean)	+136	+106	+110	+96

The initial dose-selection of efavirenz seems to have been influenced by a calculation of Cmin/IC50 ratios, which suggested an advantage for the 600mg once daily dosage. However the clinical relevance of this *in vitro* prediction is unclear given the results seen in DMP-005. In addition, the mean body weight for patients in the DMP-005 trial was higher than would be expected for an Asian or African naïve patient population, where efavirenz drug levels are also expected to be higher.

The ENCORE 1 trial is comparing the efficacy and safety of first-line treatment with efavirenz at the standard 600mg once daily dose versus the 400mg once daily dose, in 600 patients, treated for 96 weeks [22]. If the 400mg dose of efavirenz proved to be effective in this trial, the cost of efavirenz could be lowered by $30 per person per year in low income countries. Given that several million people are likely to use efavirenz in the low income countries, this dose reduction could translate to a cost saving of up to $100-200 million over 5 years.

DOSE SELECTION FOR LOPINAVIR/RITONAVIR

The approved dose of lopinavir/ritonavir is 400/100mg twice daily. Originally, the two protease inhibitors were co-formulated in a soft gelatin capsule with 133mg of lopinavir and 33mg of ritonavir (three capsules twice daily). The new heat-stable formulation (200/50mg – two tablets twice daily) showed 18% higher plasma AUC lopinavir levels and 24% higher Cmax levels than the soft gelatin formulation [26], but also less variable plasma drug concentrations, no food dependence, and no need for refrigeration [26]. A similar study in treatment naïve people with HIV also showed higher lopinavir exposures for patients given the Meltrex formulation, compared to the soft-gel formulation [27]. Co-formulated lopinavir/ritonavir tablets have also been used with additional ritonavir capsules, to further increase lopinavir exposure [28].

The Abbott 720 trial [29] evaluated three doses of lopinavir/ritonavir in treatment naïve patients. In sequential randomizations, two groups of treatment-naïve patients were given 48 weeks treatment with either:

Group 1

D4T/3TC + LPV/r 200/100 mg twice daily

D4T/3TC + LPV/r 400/100 mg twice daily

Group 2

D4T/3TC + LPV/r 400/100 mg twice daily

D4T/3TC + LPV/r 400/200 mg twice daily

In Group 1, significantly more patients showed HIV RNA reductions below 50 copies in the 200/100 twice daily arm, compared to the 400/100 mg twice daily arm ($p<0.002$), however this was driven more by adverse events than antiviral efficacy. In group 2, there was no difference in efficacy between the 200/100, 400/100 and 400/200mg twice daily doses of lopinavir/ritonavir. Summary results are shown in Table **4**. There were no significant differences in CD4 rise between treatment groups. Plasma drug levels of lopinavir were higher for the 400/200 mg BID arm compared with the 400/100 mg twice daily arm, suggesting that the ritonavir dose affects lopinavir drug levels. In Group 2, there was a significantly higher incidence of gastrointestinal side effects for the 400/200 twice daily arm, compared with the 400/100 twice daily arm [29].

Table 4. Abbot 720 Trial of Lopinavir/Ritonavir [29]

LPV/r Dose (BID)	200/100mg	400/100mg	400/200
N	16	51	33
Baseline CD4	471	335	275
Baseline HIV RNA	4.9	4.9	5.0
Race (% Caucasian)	75%	73%	66%
Gender (% male)	85%	94%	64%
48 Week Efficacy Data (ITT)			
Percent HIV RNA <400	100%	88%	73%
Percent HIV RNA <50	100%	75%	73%
48 week CD4 rise (mean)	+210	+250	+200

Despite the strong efficacy of the 200/100 mg twice daily dose seen in PI naïve patients, the the 400/100 twice daily dose was chosen for Phase 3 development. The aim may have been to target both PI naïve and PI pre-treated patients with a single uniform dose. However this leaves the possibility of using a lower lopinavir/r dose for PI naïve patients (including those failing first-line NNRTI based HAART in developing countries). The study population in this Phase 2 trial had a high baseline body weight and was composed predominantly of male Caucasians. People in developing countries are more likely to have low body weight, so drug levels of lopinavir (and therefore antiretroviral efficacy) are likely to be higher for people taking lopinavir/r in developing countries. Given the correlation between lopinavir dose and GI toxicity in the Phase 2 trial, lower doses of lopinavir/r may also be better tolerated in people with lower body weight.

Later in development, a clinical trial compared a 400/100 mg twice daily versus 800/200 once daily doses of lopinavir/r in 190 treatment naïve patients [30]. The mean

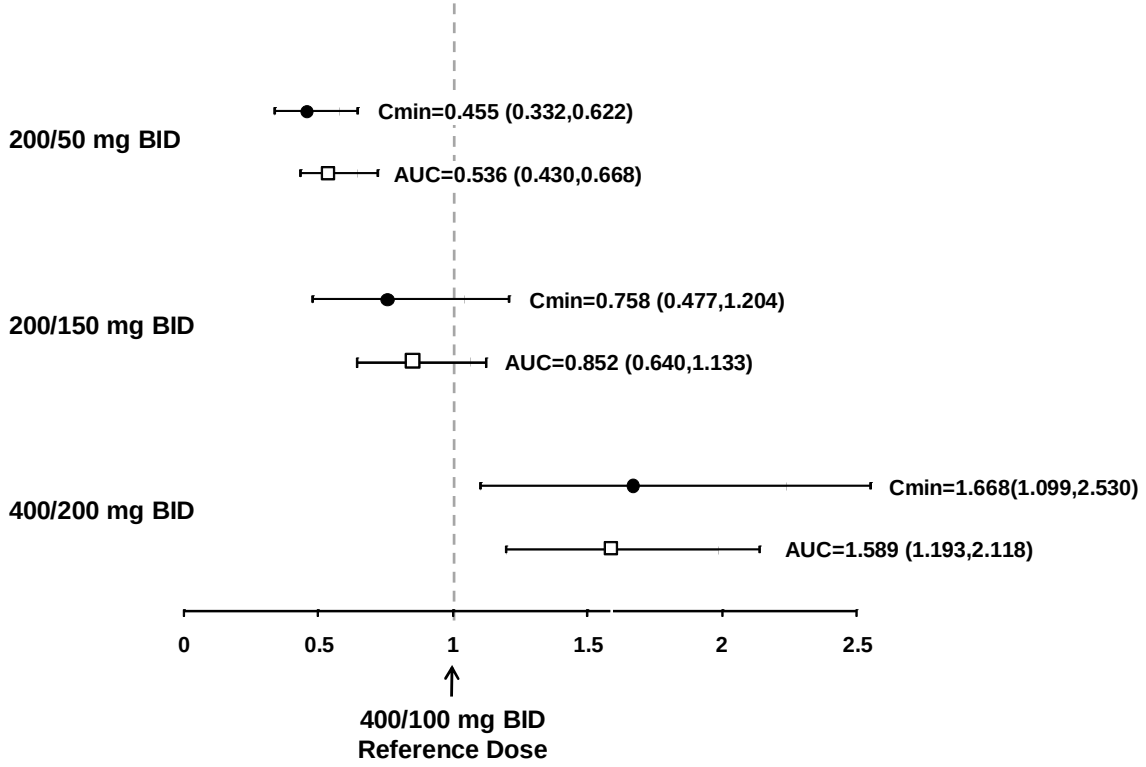
Cmin for the 800/200 once daily dose was 3.22 ug/L, which is similar to the Cmin for the 200/100 mg twice daily dose in the table above. The 800/200 mg once daily dose led to non-inferior efficacy compared to the 400/100 BID dose, and HIV RNA reductions were not correlated with lopinavir drug levels in this PI naïve population.

In a cohort study, 28 patients in France with HIV RNA levels below 50 copies/ml on lopinavir/r 400/100 mg twice daily had their dose reduced to 266/66 mg twice daily, using the old soft gelatin capsule formulation [31]. HIV RNA levels remained suppressed below 50 copies/ml for 48 weeks in 25 of the 28 patients, with two patients showing HIV RNA levels between 50-400 copies/ml and one true virological failure. Without a control group it is difficult to know the true efficacy of the lower dose, but these results do rule out a substantial loss of efficacy lopinavir/r dose reductions. In addition, the HIVNAT 019 trial evaluated two doses of lopinavir/ritonavir – 400/100 mg BID and 266/66 mg twice daily – in combination with saquinavir in 48 treatment naïve patients. This study also showed no differences in efficacy between the doses [32].

A meta-analysis of clinical pharmacology studies of lopinavir/ritonavir [33] suggests that the dose of 200/50 twice daily (one Meltrex tablet twice daily) would give lopinavir drug levels 50% lower than the standard dose. The pharmacokinetics of lopinavir are highly dependent on the dose of ritonavir used, and higher doses of ritonavir can compensate for lower doses of lopinavir. So an alternative is to use a 200/150 twice daily dose (one Meltrex tablet and one ritonavir tablet twice daily), which would then provide predicted lopinavir drug levels close to that of the approved dose. Summary results from the meta-analysis are shown in Fig. (**1**). A prospective clinical pharmacology trial is in progress, to validate the findings from the meta-analysis. If a 200/150mg twice daily dose of lopinavir/ritonavir could be established as efficacious, the cost of lopinavir/ritonavir could be lowered from $500 to $350 per person-year. The main efficacy trials of lopinavir/ritonavir were conducted using the soft-gelatin formulation, but the use of the new Meltrex formulation has led to lopinavir plasma AUC plasma levels 25-36% higher than the original soft-gel formulation in the Abbott 730 trial [27]. Use of the Meltrex formulation for the 200/150mg twice daily dose could raise the lopinavir drug levels, compensating for the slightly lower predicted levels at this dose. The higher dose of ritonavir in the 200/150 mg twice daily dosage of lopinavir/ritonavir might increase the risk of gastrointestinal side effects. However the increase in ritonavir is only 50mg twice daily compared to the currently approved dose of 400/100 mg BID; randomized trials are needed to show the clinical consequences of this change in dose. If the 200/50 mg twice daily dose could be established as efficacious, the cost of lopinavir/ritonavir could be lowered to $250 per person-year.

CONCLUSIONS AND IMPLICATIONS

1. The evidence from the dose-ranging trials of raltegravir, efavirenz and lopinavir/ritonavir suggest that there is the potential to re-define the doses of these three key antiretrovirals. Lower doses could improve the safety profiles of these drugs, lower costs and make co-formulations more feasible.



Each line shows the Geometric Mean Ratio and associated 95% confidence intervals for each new dose of lopinavir/ritonavir, relative to the standard dose of 400/100 mg BID.

Fig. (1). Predicted pharmacokinetics of lopinavir/ritonavir at alternative doses.

2. Large pivotal dose-ranging trials are needed to establish efficacy of lower doses of antiretrovirals [34]. The designs of these trials have been well defined and have been used to switch from twice daily to once daily dosing of lamivudine, abacavir and lopinavir/ritonavir [34]. Briefly, non-inferiority trial designs are used, with 600-700 patients randomised to receive either the new or the standard dose of the antiretroviral, combined with standard background antiretroviral treatment for the population being evaluated. A Data Safety Monitoring Board would then monitor ongoing results, and decide on the continuation of the trial at interim analyses.

3. There are potential risks as well as benefits from evaluating lower doses of antiretrovirals. There might be a higher risk of treatment emergent drug resistance, under-exposure leading to virological failure, or less ability to withstand drug-drug interactions which lower exposures. However these are theoretical concerns, which have not been bourne out of the dose-ranging programmes so far. Even so, large well-controlled trials are required to carefully evaluate new doses of antiretrovirals before they can be approved for widespread use.

4. If these new doses show equivalent efficacy to the standard doses in well-controlled non-inferiority trials, they should be adopted for use in developed as well as developing countries. There could be safety and economic benefits to any country switching to the re-optimised doses.

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