

Review

A better state of ART improving antiretroviral regimens to increase global access to HIV treatment

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With 5.2 million people already receiving antiretroviral therapy (ART) in low and middle-income countries and 33.4 million people estimated to be living with HIV globally, there is an urgent need to develop better antiretroviral (ARV) regimens that are less costly and less complex to implement than the current standard of care. We think it is technically possible to develop such improved regimens soon, and discuss some illustrative examples of how new ARVs and treatment simplification approaches might simultaneously improve outcomes and dramatically reduce costs. Such regimens would: 1) include new ARVs that are more tolerable, durable, and inexpensive to manufacture; 2) contain a reduced number of ARVs; and/or 3) be amenable to directly observed dosing on a weekly or a monthly-basis. However, success will not only require technical solutions, but also good will and mechanisms to foster collaboration within the international community. Therefore, we also suggest a few priority actions that interested parties can take to help expedite the widespread availability of better ARV regimens.

Key words: HIV treatment, antiretroviral drugs, manufacturing costs, corporate social responsibility, incentives for research and development.

THE COMPELLING NEED FOR MORE AND BETTER ANTIRETROVIRAL THERAPY

Despite herculean success in providing antiretroviral therapy (ART) to 5.2 million people in low and middle-income countries (LMICs) of the 33.4 million people living with HIV globally, the looming need is staggering. (UNAIDS et al., 2009; WHO, 2010). Under new WHO guidance which recommends earlier initiation at a CD4 count of 350, 10 million people currently in need remain unreached. Countries are also moving toward better ART regimens that are less toxic but more expensive. Thus, a generic fixed-dose combination (FDC) of 3 ARVs called “triomune” (nevirapine, stavudine, lamivudine), was initially the most common regimen in LMICs because of its low annual cost of \$79 for the drugs alone, but is now being replaced due to toxicity (CHAI, 2010). In comparison, a once-daily generic regimen similar to

“tripla” (efavirenz, tenofovir disoproxil fumarate, emtricitabine), the most commonly used first-line regimen in affluent countries, costs \$200 per patient year. Unfortunately, both regimens have a relatively weak resistance barrier and therefore some patients will eventually need to switch to second-line regimens that include the much more expensive boosted protease inhibitors (bPIs). With the vast majority still on first-line, annual costs needed for ART in LMIC are already estimated by UNAIDS to be \$9 billion in 2010.

Furthermore, we appear to be moving toward provision of ART even earlier in infection, partly for primary prevention such as to prevent infection within discordant couples and mother-to-child transmission (PMTCT) (Thompson et al., 2010; Donnell et al., 2010; Shapiro et al., 2010). Meanwhile, new HIV infections continue to far outpace the number of people initiating treatment, and other vital health needs are legitimately demanding attention for limited resources threatened by the global

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economic downturn. With overstretched health systems already beginning to buckle under the weight of implementing ART, sustaining the current progress will be difficult, let alone going beyond to reach the tens of millions of people who will need treatment in the coming decades.

We think that an attainable “game-changer” is urgently needed – a better state of ART - improved ARV regimens that are less costly and less complex to implement (UNAIDS, 2010a). An ideal ART regimen would approach 100% efficacy and be simple to implement with low service delivery costs - currently the largest costs of providing ART. The regimen should also have minimal toxicity, no laboratory monitoring requirements, good heat stability, and a very high barrier to the development of resistance. ART services could then be increasingly implemented at the community-level, reducing the strain on the health system. Ideal regimens would also be appropriate for pregnant women, children, and patients with tuberculosis or hepatitis B.

Lastly, an ideal regimen must be very inexpensive to produce. At a hypothetical manufacturing cost of a regimen of ~\$30 per patient year, the costs of the production alone would be only about \$1 billion annually were all 33.4 million people currently living with HIV to receive it.

Is a much more ideal ART regimen possible soon? We believe so and describe three potentially complementary possibilities by which new ARV regimens might simultaneously improve outcomes and dramatically reduce costs. These involve using regimens which: 1) include new ARVs that have more ideal characteristics; 2) contain a reduced number of ARVs; and/or 3) are amenable to directly observed dosing on a weekly or even a monthly-basis, which might minimize resistance and the need for monitoring for treatment failure.

However, success will not only require technical solutions, but also good will and mechanisms to foster collaboration within the international community. Therefore, we conclude by suggesting priority actions to make better regimens widely available soon.

THREE APPROACHES TO IMPROVE OUTCOMES AND REDUCE COSTS

For reference, first-line regimens in LMICs typically consist of three components: 1) a non-nucleoside reverse transcriptase inhibitor (NNRTI), either nevirapine or efavirenz; 2) a cytidine analog, usually lamivudine; and 3) a second nucleoside or nucleotide (N(t)RTI), either stavudine, zidovudine, or increasingly TDF. Second-line regimens typically consist of a bPI with 2 other N(t)RTIs. Other classes of drugs include integrase inhibitors and receptor blockers, but these are currently not widely used in LMICs. Table 1 includes information about some important drawbacks of current ARVs and regimens.

Utilizing more tolerable, durable and inexpensive to manufacture ARVs

With regard to ARVs with more ideal characteristics, several new medicines that are either already approved or in clinical development may have utility for LMICs. We highlight 4 illustrative examples as follows. We chose these because they not only have promising clinical characteristics, but also would likely be inexpensive to manufacture based upon their low daily doses.

Rilpivirine (Tibotec/Johnson and Johnson): This is an NNRTI given at 25 mg daily recently reported to be non-inferior to efavirenz at 600 mg daily in a pooled analysis of two phase III trials of treatment-naïve patients (Cohen et al., 2010). Discontinuations due to adverse events and lab abnormalities were less frequent with rilpivirine than efavirenz, although virologic failure was more frequent. Rilpivirine also has *IN VITRO* activity against viruses that are resistant to efavirenz and nevirapine (Azijn et al., 2009). Unfortunately, it is not compatible with the commonly-used TB medicine rifampicin.

S/GSK1349572 (ViiV/Shinongi): This is an integrase inhibitor entering phase III trials which was highly effective and very well tolerated in treatment-naïve patients at doses of 10 to 50 mg daily (Arribas et al., 2010a). Its back-up compound, S/GSK1265744, was also extremely potent at 30 mg daily in phase IIa trials (Min et al., 2009). S/GSK1349572 appears superior to the already approved integrase inhibitor raltegravir, as well as the investigational integrase inhibitor elvitegravir currently in phase III trials, by having a much more robust *IN VITRO* barrier to resistance. Prolonged *IN VITRO* passage of wild-type virus in the presence of a S/GSK1349572 resulted in only a 4.1 fold changes in susceptibility, as opposed to >100 fold changes for both raltegravir and elvitegravir over the same period (Kobayashi et al., 2011). If this robust resistance profile is also observed in clinical studies, S/GSK1349572 might be a cost-effective alternative to bPIs for second-line treatment, which require combined daily dosages of 400 mg (atazanavir/ritonavir) to 1000 mg (lopinavir/ritonavir).

Elvucitabine (Achillion): This is a cytidine analog dosed at 10 mg daily that had similar safety and efficacy to lamivudine in phase II trials (De Jesus et al., 2010). Alternatively, emtricitabine, another cytidine analog, is already approved at 200 mg daily, has a similar potency at 25 mg daily to lamivudine at 150 mg twice-daily (Rousseau et al., 2003).

More potent tenofovir pro-drugs: HDP-tenofovir (Chimerix) and GS 7340 (Gilead): Hexadecyloxypropyl (HDP)-tenofovir is a tenofovir prodrug in phase I trials

Table 1. Illustrative possibilities for more ideal ARV regimens.

An Ideal ART regimen	Current ARVs and regimens	Possible improvements with new agents and approaches
High efficacy, approaching ~100%.	Highly effective in patients who are compliant. Compliance may decline over time and because of side effects.	Fewer discontinuations due to side effects with some new agents. Once-weekly or once-monthly dosing may improve compliance.
High tolerability, with minimal short and long-term toxicities.	Nevirapine causes hepatotoxicity and rash, and efavirenz CNS side effects. TDF causes renal and bone toxicity. Zidovudine causes hematologic and mitochondrial toxicity.	Rilpivirine and S/GSK1349572 have lower incidence of side effects than efavirenz. HDP-tenofovir and/or GS-7340 may have less renal and bone toxicity than TDF. Reducing the number of agents can reduce toxicity.
High durability, with a very low risk of resistance.	Widespread resistance can occur against several agents with NNRTI-based first-line regimens. bPI-based regimens for second-line have a more robust resistance barrier.	S/GSK1349572 has a high <i>IN VITRO</i> barrier. Once-weekly or once-monthly directly observed dosing may reduce resistance. Reducing the number of agents may also reduce multi-class resistance.
No lab monitoring required.	Lab monitoring for toxicity and virologic monitoring for treatment failure is recommended, though access often limited in reality.	Rilpivirine and S/GSK1349572 may not require labs for toxicity in low-resource settings. Weekly or monthly directly observed ART may minimize need for viral load and CD4.
Very low cost to manufacture.	Efavirenz/TDF/lamivudine once-daily costs ~\$200 ppy. bPI-based second line combinations are >\$400.	Regimens with new low cost to manufacture agents might cost less than \$50 per year and may be effective for first and second-line.
Fixed-dose combination; once daily or less dosing.	Efavirenz/TDF/lamivudine is a once-daily FDC. No once daily FDCs yet available in LMICs for other agents, including bPIs for second-line.	Once-weekly oral and once-monthly injectable regimens may be possible with new low-dose agents. S/GSK1349572 may be more amenable than bPIs to inclusion in FDCs for second-line.
Safe for use in pregnant and lactating women.	Nevirapine causes hepatotoxicity, especially at higher CD4. Efavirenz causes neural tube defects in non-human primates, but human data shows no increased risk to date.	Rilpivirine is not teratogenic in preclinical tests. S/GSK1349572 and other integrase inhibitors may have special utility for PMTCT due to more rapid viral load decline.
Compatible with TB meds.	Nevirapine and bPIs interact with rifampicin, but efavirenz is compatible.	Rilpivirine is not compatible with TB medicines. No data on S/GSK1349572-rifampicin interactions.
Hepatitis B compatibility.	Efavirenz/TDF/lamivudine treats Hepatitis B, minimizing concerns about lamivudine resistance.	Elvucitabine is active against hepatitis B. It is not known to what degree low dosages of HDP-tenofovir and/or GS 7340 have adequate activity against Hepatitis B.
Pediatric-friendly.	bPIs are required for infants exposed to nevirapine in PMTCT, but are not available in FDCs. Current regimens for children are twice-daily.	Lower-dose, once daily regimens in FDCs would be more ideal for patients and caregivers. S/GSK1349572 and rilpivirine may be amenable to such combinations.
No cold-chain requirement.	Liquid formulations of lopinavir/ritonavir needed for children require a cold chain. Tablet formulations now exist of ritonavir and lopinavir/ritonavir that do not, and these are becoming more widely available in LMIC.	Data is not yet publicly available on cold-chain requirements of S/GSK1349572, a possible low-cost alternative to bPIs for second-line.

that has a much longer *IN VIVO* half life as a pro-drug in preclinical studies than TDF and therefore may require a

substantially lower dose (Painter et al., 2007). It may also cause less toxicity due to less plasma exposure to

tenofovir. Similarly, GS 7340 is an alternative tenofovir prodrug that also produces much higher levels of intracellular tenofovir *IN VIVO* than TDF (Lee et al., 2005). Interestingly, Gilead halted the development of this drug in 2004, stating that it did not believe “that GS 7340 has a profile that differentiates it to an extent that supports its continued development” (Gilead, 2004). However, after a more than 6 year hiatus, Gilead recently presented data from a phase Ib trial implying the drug is once again in active development. Doses of 50 or 150 mg of GS 7340 were well tolerated and substantially more potent than 300 mg TDF following 14 days of monotherapy (Markowitz et al., 2011).

Clearly, the cost of drug production depends not only on the dose required, but on the manufacturing process. However, current prices of the 10 generic adult ARVs included on the Clinton Health Access Initiative 2010 price list vary by about 10-fold per mg, with nevirapine costing the least at 0.025 cents per mg per day and ritonavir the most at 0.25 cents per mg per day. One might thus roughly estimate that generic versions of most single low dose drugs given at 25 mg/day might be priced at scale from \$2 to \$23 per patient year¹, although such generalizations will not hold true for all drugs. For example, HDP-tenofovir and GS 7340 which have complicated prodrug motifs might be more expensive to manufacture than TDF per mg, which could limit any potential cost savings.

Reducing the number of ARVs in a regimen

This is a second approach that might decrease cost, toxicity, and also limit the degree of cross-resistance to several different types of antiretrovirals. Although no dual-therapy first-line regimens have yet been shown to be equivalent to NNRTI-based triple regimens (Riddler et al., 2008), a lopinavir/ritonavir+raltegravir regimen was recently reported to be non-inferior at 48 weeks to a triple regimen of lopinavir/ritonavir + 2 N(t)RTIs (Reynes et al., 2010). Better possibilities may exist with new lower-dose ARVs. For example, if drug-drug interactions prove acceptable, an oral combination of rilpivirine and S/GSK1349572 should be prioritized for development, as it might be very inexpensive to manufacture, require no laboratory monitoring, and be highly efficacious in both treatment-naïve and experienced patients. This could make it possible to switch most patients on first and second-line regimens to the same regimen, thereby simplifying supply chain, monitoring, and clinical care.

¹ Order of the costs of drugs per mg is as follows: nevirapine \$37/year, 400 mg/day, .025 cents/mg/day; lamivudine \$32 per year, 300 mg/day, .029 cents/mg/day, efavirenz, \$75/year, 600mg/day, .034 cents/mg/day; zidovudine \$93/year, 600mg/day, .042 cents/mg/day; tenofovir disoproxil fumarate \$87/year, 300mg/day, .079 cents/mg/day; abacavir \$222/year, 600mg/day, .10 cents/mg/day; lopinavir/ritonavir \$440/year, .13 cents/mg/day; stavudine \$24/year, 40mg/day, .16 cents/mg/day; atazanavir \$265/year, 300mg/day, .24 cents/mg/day; ritonavir \$87/year, 100mg/day, .25 cents/mg/day.

Further, even monotherapy may be effective under certain circumstances. bPIs function relatively well as maintenance monotherapy for patients who have achieved undetectable viral load on multi-drug regimens before simplification (Arribas et al., 2010b; Wilkin et al., 2009; Nunes et al., 2009). However, while no resistance to bPIs has developed in these studies, their high cost is problematic. S/GSK1349572 with its robust resistance *IN VITRO* profile might eventually offer a much lower-cost alternative for such an induction-maintenance approach. However, any such studies would need to be undertaken with caution only if and when more evidence becomes available regarding the *IN VIVO* safety, efficacy, and resistance profile of S/GSK1349572.

Once-monthly or once-weekly ART

A third possible approach to improve outcomes and reduce costs is directly-observed administration of once-weekly oral regimens, once-monthly injections, or a mix of the two. In some contexts, this might maximize compliance and thereby reduce resistance. A 5 days on, 2 days off intermittent treatment approach has been shown to be effective in selected patients who have already achieved undetectable viral load (Reynolds et al., 2010; Cohen et al., 2008). Thus, it might be possible to simplify to once-weekly dosing, if at least two out of three drugs in a regimen maintain therapeutic levels for a week. Elvucitabine and HDP-tenofovir have potential for once-weekly dosing given the very long half-lives of their relevant metabolites (Colucci et al., 2009; Hawkins et al., 2005). Additionally, Tibotec is developing an injectable formulation of rilpivirine to be given once-monthly. Intramuscular injection were well-tolerated in humans in phase I trials up to a dose of 600 mg, with models predicting that a once-monthly injection of 600 mg would produce similar troughs as a daily dose of 25 mg (van t' Klooster et al., 2008; Verloes et al., 2008). Tibotec is looking for other low-dose agents for a combination long-acting injection. Interestingly, ViiV also recently initiated phase 1 clinical trials of a long-acting injection of its investigational integrase inhibitor S/GSK1265744 at injection doses of 100 to 800 mg (Glaxo Smith Kline 2010).

However once-monthly or once-weekly regimens have potential downsides. For example, in patients who are lost to follow-up (LTFU), these regimens might lead to a prolonged exposure of virus to sub-therapeutic concentrations of ARVs, thereby possibly increasing the risk of the development of resistance, particularly if agents were used that have a weak barrier to resistance. Moreover, once-monthly injections would have some alternative program requirements and might be less acceptable for some clients. While these are important considerations, we think that long-acting ART strategies, particularly once-monthly (or even less frequent) ART injections that could be given via a directly administered

approach, merit further development as these could optimize adherence in patients who are retained in care. This might minimize the need for laboratory testing, including viral load monitoring, resistance testing, and also perhaps CD4 counts, particularly for clinically well patients starting treatment at a higher CD4.

Prioritizing better regimens for pediatric HIV and PMTCT

Importantly, as new ARV regimens and treatment modalities are tested, the special needs of children and women should be prioritized rather than falling to the “bottom of the barrel” as in the past. WHO now recommends a bPI for HIV-infected infants who are exposed to nevirapine in PMTCT. However, current liquid bPI formulations for young children require a cold chain, have poor palatability, and are not available in FDCs with other ARVs that are easily dividable and dispersible in breastmilk or water.

Lower-dose, once-daily FDCs with robust resistance barriers would be better for children and caregivers. Cheaper, simpler regimens would also be useful for PMTCT, as option B of the new guidelines already recommends ART for all pregnant and lactating HIV+ women.

CATALYZING COLLABORATION TOWARD AN ATTAINABLE “GAME-CHANGER”

Short, medium, and long-term research priorities for better HIV treatment

In considering future research priorities, it is important to continue to pursue approaches to reduce the costs of combinations of already approved antiretroviral drugs through dose-optimization strategies (Hill et al., 2010), developing formulations with better bioavailability, improving manufacturing process, and negotiating lower prices for active pharmaceutical ingredients and drugs. However, the non-drug costs of providing ART are currently about double that of the ARVs themselves (UNAIDS, 2010b). Therefore, reducing the costs of ARVs alone will not result in a dramatic reduction of the total costs of providing ART, at least in the next several years when the vast majority of patients will still be receiving first-line regimens.

In the longer-term, it may eventually be possible to develop an effective cure for HIV, perhaps through improved drug therapies that eliminate the latent reservoir of HIV and/or therapeutic vaccination approaches which effectively limit viral replication. Such approaches are certainly worthy of continued research and the prospects for these have been reviewed extensively elsewhere (Lewin et al., 2011; Bowman et al., 2009). Currently, without yet even proof-of-concept in

human trials (with the exception of one patient who received a genetically modified bone marrow transplant (Hutter et al., 2009)), we anticipate that it would be a decade or more before such approaches could be shown to be effective and widely scaled up.

In contrast, we think that excellent prospects exist in the nearer term to make substantial improvements on an already proven concept - ART. Improved ART regimens which are more amenable to administration at the community level and obviate laboratory monitoring for toxicity and resistance may make it feasible to dramatically reduce service-delivery costs. The development of a low cost ARV regimen with a robust barrier to resistance is therefore a high priority for future research to simplify treatment and also to reduce future costs of second-line treatment for patients already on ART.

Approaches to increase investment into better ARV regimens for LMIC

To realistically bring a product, especially a combination product, through development requires cooperation of a range of stakeholders, especially pharmaceutical companies. ViiV, a GSK and Pfizer partnership, recently took an important initial step in committing to offer voluntary licenses for all of its current and future HIV drugs for generic manufacturing to supply least developed countries. Other large pharmaceutical companies with promising new HIV drugs, such as Gilead and Tibotec/Johnson and Johnson, should follow suit. However, the most immediate bottleneck on the critical pathway to making better regimens available is conducting clinical trials of combinations that have more ideal characteristics for LMICs, including being very inexpensive to produce. This will require companies to proactively partner with one another. Interested parties should review what combinations would theoretically hold most promise for LMICs, publish a comprehensive analysis, and regularly disseminate a report delineating progress. Shareholders and clients should then hold corporations accountable to demonstrate they are prioritizing the testing of these combinations. While the demonstration of social responsibility on an unprecedented global scale alone should be a powerful motivator, other “carrots” to incentivize corporations should also be considered. Some possible approaches are outlined in Table 2.

We think that offering a generous tax credit for R&D of ARV combinations that are expected to be more ideal for low resource settings may be a particularly feasible and potent action that could be implemented quickly. To sufficiently motivate corporations the credit should be above and beyond any already existing general R&D tax credits. Such credits could also be applied to subsequent steps in the critical pathway that have proven to be

Table 2. Approaches to incentivize corporations to develop more ideal combinations for low-income countries.

Approach	How it could work	Existing examples
Patent pools agreeing	Patent holders license out their intellectual property (IP) to the pool. Others then license the IP directly from the pool, to the already-negotiated terms, including any royalties. This may reduce transaction costs and barriers to creating FDCs.	UNITAID recently created a patent pool for ARVs and other medicines and diagnostics that could be useful for low resource settings (UNITAID, 2010).
Tax-credits	A large tax credit could be given to companies that invest in R&D, registration, or other costs related to making more ideal ARV combinations available in low-resource settings. The credit might be proportional to estimated savings by the public over time through these improved combinations. To motivate investment into ARVs, the credit should exceed already existing R&D tax credits.	More than twenty countries offer general tax credits for R&D. The amount of credit varies greatly between countries.
Regulatory fast-tracking	Affluent countries expedite the review of a new medicine application for companies that make available a new ARV with utility for low-resource settings at a low price. This fast-track status might be applied to the particular ARV or as a credit to another medicine which might have more of a market in affluent countries.	The FDA and EMEA have expedited review processes in place for drugs that address a critical unmet need such as multi-drug resistant HIV and cancer.
IP extensions	Extensions of either patent term or exclusivity might be offered by governments of affluent countries for companies that make available medicines for HIV in low-resource settings at low cost.	Current laws extend exclusivity for “orphan drugs” and patent-term for developing pediatric formulations.
“Prizes”	A financial “prize” is offered for the first party to develop and make available in low-resource settings a regimen that meets certain pre-set specified criteria, including thresholds for efficacy, tolerability, and price. Provision of benchmarks along the way toward the prize could allow organizations to receive needed incremental funding.	No examples yet exist of how a prize has led to drug development, but the concept has been extensively described elsewhere (Love and Hubbard, 2007).
Risk-sharing and non-profit pharmaceutical companies	Public and private partners share the costs and risks of drug development through a competitive and transparent process. Activities might be limited to supporting clinical trials or go beyond to include in-country registration and supporting manufacturing and distribution of better ARV regimens for low-income countries.	The International AIDS Vaccine Initiative, the TB alliance, the Medicines for Malaria Venture, and the Institute for One World Health all focus on other key unmet needs.

bottlenecks, including in-country registration and scale-up of manufacturing and distribution.

If companies collaborate to develop improved combinations that are inexpensive to manufacture, they may also benefit from a competitive advantage both in lucrative high-income country markets and in middle-income countries where they could sell their drugs at a lower price than their competitors. Ideally, a “win-win” situation will occur in which better regimens for affluent countries become available which also meet the needs of LMICs. Hopefully, through exercising enlightened self-interest stakeholders will agree on a pricing approach that encourages innovation without “breaking the bank” and crowding out other global health priorities.

Fortunately, dramatic reductions in the cost and complexity of treating HIV should be within reach and do not necessarily require a “quantum leap”, such as a cure that eradicates the latent reservoir in resting T-cells or an immunotherapy that sustainably suppresses virus. An investment could pay for itself many times over through improving patient outcomes and access, saving many millions of lives and billions of dollars over the long term.

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