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An improvement in antiretroviral medication would expand access to AIDS treatment globally.

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ABSTRACT

Better antiretroviral (ARV) regimens that are less expensive and easier to administer than the current standard of care are desperately needed, as 5.2 million people in low- and middle-income countries are already receiving antiretroviral therapy (ART) and 33.4 million people are estimated to be living with HIV worldwide. We describe several illustrative examples of how novel ARVs and treatment simplification approaches can simultaneously improve outcomes and significantly lower costs, and we believe that such improved regimens can be developed in the near future. These regimens would: 1) contain new ARVs that are more affordable, durable, and palatable; 2) contain less ARVs; and/or 3) allow for weekly or monthly dose that is directly observed.

But in order for this to be successful, there will also need to be procedures to promote international collaboration and good will in addition to technical solutions. As a result, we also recommend a few crucial steps that interested parties should do to hasten the general release of improved ARV regimens.

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

INTRODUCTION

The need for antiretroviral medication (ART) is enormous, even if it has been miraculously successful in reaching 5.2 million of the 33.4 million HIV-positive individuals worldwide who live in low- and middle-income countries (LMICs). (WHO, 2010; UNAIDS et al., 2009). Ten million individuals who are now in need are still unreachable because of new WHO guidelines that suggest starting sooner at a CD4 count of 350. Additionally, nations are shifting towards more expensive but superior ART regimens that are less hazardous. Therefore, due to its low annual cost of $79 for the medications alone, a generic fixed-dose combination (FDC) of three ARVs known as "triomune" (nevirapine, stavudine, and lamivudine) was the most popular regimen in LMICs at first, but it is currently being changed due to toxicity (CHAI, 2010). By contrast, a generic version of the tripla (efavirenz, tenofovir disoproxil fumarate, emtricitabine), the most widely prescribed first-line regimen in wealthy nations, costs $200 per patient year when taken once daily. Unfortunately, some patients will eventually need to move to second-line regimens that contain the much more expensive boosted protease inhibitors (bPIs) due to the relatively modest resistance barrier of both regimens. UNAIDS has already predicted that the yearly expenses of ART in LMICs in 2010 will be $9 billion, with the great majority of patients still on first-line treatment.

Additionally, it looks like we're heading towards giving ART even earlier in the course of an infection, in part for primary prevention purposes like preventing infection in discordant couples and PMTCT (Thompson et al., 2010; Donnell et al., 2010; Shapiro et al., 2010).

While this is going on, the number of new HIV infections continues to greatly exceed the number of people starting treatment, and other critical health needs are rightfully requiring attention from the limited resources that the global economic slump is threatening. Maintaining the current momentum to treat the tens of millions of individuals who will require therapy in the next decades will be challenging, especially as overburdened health systems are already starting to falter under the weight of ART implementation.

We believe that an achievable "game-changer"—a better state of ART, that is, ARV regimens that are less expensive and easier to implement—is desperately needed (UNAIDS, 2010a). ART would be most effective if it were close to 100% effective, easy to administer, and had low costs associated with service delivery,

which accounts for the majority of ART's present expenditures. Additionally, there should be very little toxicity, no need for laboratory monitoring, good heat stability, and a high barrier to resistance development in the regimen. The burden on the healthcare system might potentially be lessened by gradually implementing ART services at the community level. Moreover, youngsters, pregnant people, and those suffering from hepatitis B or tuberculosis should all follow the ideal regimens.

Finally, the production cost of the perfect regimen must be quite low. If all 33.4 million HIV-positive individuals were to receive it, the production expenditures alone would only come to roughly $1 billion a year, based on a fictitious manufacturing cost of about $30 per patient year.

Is a substantially better ART regimen on the horizon? We think so, and we outline three possibly complementary ways that novel ARV regimens could simultaneously lead to significant cost savings and improved results. These entail following regimens that: 1) contain novel ARVs with improved qualities; 2) have fewer ARVs; and/or 3) allow for directly observed dosing on a weekly or even monthly basis, potentially reducing resistance and the need for treatment failure monitoring.

But in order for this to be successful, there will also need to be procedures to promote international collaboration and good will in addition to technical solutions. We therefore offer our top priorities for immediate dissemination of improved regimens.

THREE APPROACHES TO IMPROVE OUTCOMES AND REDUCE COSTS

For context, first-line regimens in low- and middle-income countries usually have three elements:1) a cytidine analogue, typically lamivudine; 2) a non-nucleoside reverse transcriptase inhibitor (NNRTI), either nevirapine or efavirenz; and 3) a second nucleoside or nucleotide (N(t)RTI), either stavudine, zidovudine, or increasingly TDF. Typically, second-line regimens combine a bPI with two additional N(t)RTIs. Receptor blockers and integrase inhibitors are two other medication groups that aren't being used extensively in LMICs. A number of significant disadvantages of the ARVs and regimens that are currently in use are listed in Table 1.

Employing more affordable, robust, and palatable methods to produce ARVs

There are a number of novel ARVs that are either in clinical research or have already received approval that may be useful for LMICs in comparison to ARVs with more perfect qualities. We present the following four examples as examples. We selected these because to their low daily doses, which suggests that they would be economical to manufacture, in addition to their promising clinical qualities.

In a pooled analysis of two phase III trials involving patients who were not yet on therapy, rilpivirine—an NNRTI—given at a dose of 25 mg per day was found to be non-inferior to efavirenz at a dose of 600 mg per day. Compared to efavirenz, rilpivirine caused fewer discontinuations owing to adverse events and abnormal lab results, but virologic failure was more common. According to Azijn et al. (2009), rilpivirine also has IN VITRO efficacy against viruses that are resistant to nevirapine and efavirenz. Regrettably, it is incompatible with rifampicin, a drug used frequently to treat tuberculosis.

At doses of 10 to 50 mg daily, this integrase inhibitor, which is now in phase III studies, was extremely effective and well tolerated in patients who were new to treatment. In phase IIa trials, its backup chemical, S/GSK1265744, was similarly very effective at 30 mg daily (Min et al., 2009). With a far stronger IN VITRO barrier to resistance than both the integrase inhibitor raltegravir, which is now licenced, and the investigational integrase inhibitor elvitegravir, which is undergoing phase III studies, S/GSK1349572 appears to be preferable. Only 4.1 fold changes in susceptibility were seen after a prolonged IN VITRO passage of the wild-type virus in the presence of S/GSK1349572, compared to >100 fold changes for both raltegravir and elvitegravir during the same period (Kobayashi et al., 2011). In the event that clinical investigations likewise reveal this strong resistance profile, S/GSK1349572 may prove to be a more economical option for second-line treatment than bPIs, which necessitate daily dosages ranging from 400 mg (atazanavir/ritonavir) to 1000 mg. Elvucitabine, also known as Achillion, is a cytidine analogue that, in phase II trials, demonstrated comparable safety and efficacy to lamivudine at a dose of 10 mg per day. Alternatively, lamivudine at 150 mg twice-day has a similar potency at 25 mg daily to emtricitabine, another cytidine analogue that is already licenced at 200 mg daily.

Additional powerful pro-tenofovir medications: GS 7340 (Gilead) and HDP-tenofovir (Chimerix): In phase I trials, hexadecycloxypropyl (HDP)-tenofovir is a prodrug of tenofovir. Comparably, GS 7340 is a different tenofovir prodrug that similarly results in much greater intracelullar tenofovir IN VIVO levels.

It's interesting to note that Gilead put a stop to this drug's development in 2004 because it didn't think GS 7340 had a unique profile that would justify further research and development (Gilead, 2004). Gilead, however, recently released findings from a phase Ib trial suggesting the medicine is once again in active development, following a more than 6-year sabbatical. After 14 days of monotherapy, doses of 50 or 150 mg of GS 7340 were well tolerated and much more powerful than 300 mg TDF (Markowitz et al., 2011).

It is evident that the cost of producing a medicine depends on both the manufacturing technique and the necessary dose. Nonetheless, the costs of the ten adult generic ARVs listed on the 2010 Clinton Health Access Initiative Nevirapine costs the least per day at 0.025 cents per mg, while ritonavir costs the highest at 0.25 cents per mg. The price list varies by around ten times per mg. Thus, it is possible to approximate the price of generic versions of the majority of single-low dose medications given at a dosage of 25 mg/day to be between $2 and $23 per patient year1, however not all medications will fall into this range. Any potential cost savings could be limited since compounds with complex prodrug patterns, including HDP-tenofovir and GS 7340, might be more expensive to manufacture per milligramme than TDF.

Reducing the number of ARVs in a regimen

This is a second strategy that may reduce toxicity, expense, and the extent of cross-resistance to many antiretroviral classes. 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), despite the fact that no dual-therapy first-line regimens have yet been shown to be equivalent to NNRTI-based triple regimens (Riddler et al., 2008). Newer, lower-dose ARVs may offer better opportunities. An oral combination of rilpivirine and S/GSK1349572, for instance, should be given priority for development if drug-drug interactions are found to be acceptable. This is because the combination may be highly effective in both treatment-naïve and experienced patients, require no laboratory monitoring, and be relatively inexpensive to manufacture. This might allow for the majority of patients on first- and second-line regimens to be switched to the same regimen, streamlining clinical care, monitoring, and the supply chain.

Furthermore, in some situations, even monotherapy may be helpful. When used as maintenance monotherapy, bPIs work reasonably well for patients whose virus load was undetectable on multi-drug regimens prior to simplification (Arribas et al., 2010b; Wilkin et al., 2009; Nunes et al., 2009). Despite the fact that these studies have not shown any resistance to bPIs, their high cost is concerning. With its strong resistance IN VITRO profile, S/GSK1349572 may someday provide a significantly less expensive substitute for such an induction-maintenance strategy. But these kinds of investigations would have to be done carefully only if and when more information became available.

Once-monthly or once-weekly ART

One potential strategy to enhance results and minimise expenses is to administer injections once a month, once-weekly oral regimens, or a combination of the two under direct observation. This could increase compliance in some situations and decrease resistance as a result. In certain patients who have previously reached an undetectable viral load, an intermittent treatment regimen of five days on and two days off has been demonstrated to be successful (Reynolds et al., 2010; Cohen et al., 2008). Thus, if at least two of the three medications in a regimen maintain therapeutic levels for a week, it might be possible to simplify to once-weekly dosage. Because the key metabolites of elvucitabine and HDP-tenofovir have very long half-lives, once-weekly dosage may be possible.

Furthermore, Tibotec is creating an injectable version of rilpivirine that will be administered once a month. Phase I trials found that intramuscular injections were well tolerated in humans up to a dose of 600 mg. Models predicted that a 600 mg injection in a month would result in troughs comparable to those caused by a 25 mg daily dose (van t' Klooster et al., 2008; Verloes et al., 2008). Tibotec is searching for additional low-dose medications for a long-acting combo injectable. It's interesting to note that ViiV just started phase 1 clinical studies for its experimental integrase inhibitor S/GSK1265744 at injectable dosages ranging from 100 to 800 mg.

Once-weekly or once-monthly routines, however, could have drawbacks. For instance, these regimens may result in a prolonged exposure of the virus to sub-therapeutic concentrations of ARVs in patients who are lost to follow-up (LTFU), potentially raising the risk of resistance development, especially if agents with a weak barrier to resistance were used. Furthermore, once-monthly injections could not be as acceptable to other clients and would have different programme requirements. Although these are significant factors, we believe that long-acting ART strategies—especially monthly (or even less frequent) ART injections that could be administered directly—deserve more

research and development because they may improve adherence in patients who are kept in care. This could reduce the requirement for laboratory testing, such as monitoring viral load, testing for resistance, and possibly even CD4.

Prioritizing better regimens for pediatric HIV and PMTCT

It is crucial to remember that, unlike in the past, women's and children's unique requirements should be given priority when new ARV regimens and treatment modalities are tried. In PMTCT, the World Health Organisation now advises a bPI for newborns with HIV who are exposed to nevirapine. Nevertheless, the liquid bPI formulations that are now available for young children lack palatability, necessitate a cold chain, and cannot be used with other ARVs that are easily divided and dissolved in water or breastmilk in formula. For children and carers, once-daily, lower-dose FDCs with strong resistance barriers would be preferable. Since option B of the new guidelines currently advises ART for all pregnant and lactating HIV+ women, less expensive, simpler regimens would also be helpful for PMTCT.

CATALYZING COLLABORATION TOWARD AN ATTAINABLE "GAME-CHANGER"

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

The pursuit of strategies to lower the cost of combinations of antiretroviral drugs that have already received approval should be prioritised in future research. These strategies may include dose-optimization (Hill et al., 2010), formulations with improved bioavailability, improved manufacturing processes, and negotiating lower prices for drugs and active pharmaceutical ingredients. ART's non-drug expenses, however, are currently nearly twice as high as the ARVs themselves. Because of this, cutting the price of ARVs by themselves won't significantly lower the overall cost of administering ART—at least not for the next few years, when the great majority of patients will still be on first-line regimens.

Longer term research may potentially lead to the development of a viable cure for HIV, maybe through therapeutic vaccination strategies that successfully suppress viral replication or better pharmacological therapy that eradicate the latent HIV reservoir. These methods are undoubtedly deserving of more study, and their prospects have already received a thorough analysis elsewhere. As of right now, there isn't even proof-of-concept in

We estimate that it would take ten years or more for such methods to be proven to be successful and widely scaled up, even with the exception of one patient who underwent a genetically engineered bone marrow transplant (Hutter et al., 2009).

On the other hand, we believe that there are good opportunities in the near future to significantly improve upon an already-proven concept—ART. It may be possible to significantly lower service-delivery costs with improved ART regimens that are easier to administer in the community and do not require laboratory monitoring for toxicity and resistance. Future research should prioritise developing an affordable ARV regimen with a strong resistance to medication in order to streamline treatment and lower the cost of second-line treatment for ART-eligible individuals in the future.

Approaches to increase investment into better ARV regimens for LMIC

Realistically, a variety of parties, particularly pharmaceutical corporations, must work together to see a product through development, especially a combination product. With its recent commitment to provide voluntary licences for all of its present and future HIV medications for generic production to supply least developed nations, ViiV, a collaboration between GSK and Pfizer, made a significant first step. It would be wise for other big pharmaceutical companies, like Johnson and Johnson's Tibotec and Gilead, to do the same with their promising new HIV medications. However, performing clinical trials of combinations that have more favourable qualities for LMICs—such as being relatively affordable to produce—remains the most immediate obstacle on the essential pathway to making improved regimens available. This will necessitate businesses proactively collaborating with one another.

Parties with an interest should examine which combinations, in theory, would be most beneficial for LMICs, publish a thorough analysis, and periodically distribute a report outlining developments. Next, companies should be held responsible by clients and shareholders to show that testing these combinations is a top priority. Even if the unprecedented global display of social responsibility should be a strong incentive in and of itself, there should be other —carrots to encourage firms as well. Table 2 provides a summary of several potential strategies. We believe that a particularly practical and effective measure that could be swiftly adopted would be to provide a large tax credit for research and development of ARV combinations that are anticipated to be more suitable for low resource situations.

In order to adequately incentivize firms, the benefit ought to surpass any current general R&D tax credits. These credits might also be used for later important pathway segments that have shown to be bottlenecks, like in-country registration and expanding production and distribution. Companies may gain a competitive edge in both lucrative high-income country markets and middle-income countries where they may offer their pharmaceuticals at a cheaper price than their rivals if they work together to discover better combinations that are less expensive to make. Better routines for wealthy nations that also satisfy the needs of LMICs will ideally become available in a "win-win" scenario.

Through the exercise of enlightened self-interest, parties should be able to come to an agreement on a pricing strategy that promotes innovation without going over budget or displacing other global health goals.

CONCLUSION

Thankfully, significant drops in the expense and intricacy of HIV treatment need to be achievable and don't always necessitate a —quantum leap, like a treatment that eliminates the latent reservoir in quiescent T-cells or an immunotherapy that suppresses the virus throughout time. By enhancing patient outcomes and access, an investment might pay for itself many times over, ultimately saving billions of dollars and millions of lives.

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