Current and future priorities for the development of optimal HIV drugs

Marco Vitoria, Ajay Rangaraj, Nathan Ford, and Meg Doherty

Purpose of review
To summarize global efforts to accelerate access to simpler, safer and more affordable antiretroviral drugs and how this has shaped HIV treatment policy over the last decade, and outline future priorities. Several expert consultations aimed at aligning opportunities for optimization of antiretroviral drugs have been convened by WHO in partnership with academic institutions, international agencies, innovators and manufacturers. The increased access to lifelong treatment for people living with HIV also brings about new challenges in the long-term use of antiretrovirals (ARVs).

Recent findings
The article describes the evolution of global research agenda on ARV optimization ascribing the characteristics of a target product profile, the importance of sequencing of first-line and second-line regimens, the role of programmatic data when looking at policy transition for new ARVs, inclusion of more subpopulations living with HIV, as well as the challenges in identifying what improvements can be made in an era where drugs are already safe, tolerable and efficacious.

Summary
Within a framework of evolving treatment harmonization and simplification, future therapeutic options in development must take into consideration safety and efficacy across a range of patient populations as well the mode of administration in the context of lifelong therapy.

Keywords
antiretroviral therapy, fixed-dose combinations, integrase inhibitors, long-acting formulations, tenofovir alafenamide

INTRODUCTION
Since the approval of zidovudine monotherapy for treatment of AIDS in 1987 [1], remarkable progress has been made in developing antiretroviral drugs that are more effective against HIV infection. In the last three decades, the standard of care evolved from less potent and more toxic mono and dual therapies used in early 90s to highly active and better tolerated triple drug regimens, including the adoption of fixed-dose combinations (FDCs), harmonization of treatment regimens among different populations. This improved therapeutic and safety profile is supportive of the current policy of treating all HIV positive individuals as soon as diagnosis is confirmed (‘Treat-All’) [2*], and consequent reductions in mortality, and improvement in life expectancy and quality of care of patients with HIV on antiretroviral therapy (ART), even in low-income settings [3].

In the last three decades, at least 30 individuals and more than 20 dual and triple combined antiretroviral (ARV) medications were approved for treatment, and one dual combination for prevention of HIV infection, many of which are available as generic formulations (Fig. 1) [4,5].

The expansion of therapeutic options has been facilitated by a joint collaborative effort between international organizations, academic institutions, innovator and generic manufacturers, and other stakeholders, particularly over the last decade [6,7,8*,9*]. This collective work has resulted in a number of initiatives in support of ARV drug optimization, including at least three major international conferences held, respectively, in 2010, 2012 and 2015 [10].

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KEY POINTS

- A joint collaborative effort between international organizations, stakeholders and countries produces innovative solutions, which is necessary to reach 90/90/90 targets by 2020.

- A global ARV optimization framework was established to improve access to ART, with transition to new drugs and formulations with better efficacy, lower toxicity and higher durability, with reduction of treatment complexity, cost and the risk of HIV transmission at population level.

- Sequencing of optimized first-line, second-line and third-line regimens will allow for better planning, ensure optimal use of different ARV regimens and prevent stock outs.

- Integration of approaches for HIV, viral hepatitis, noncommunicable diseases and sexually transmitted infections is expected and its due consideration in the development of new HIV drugs.

- Future therapeutic options must take into consideration safety and efficacy across a range of patient populations as well the mode of administration in the context of lifelong therapy.

2013 and 2017 [6,10,11**] that aimed to proactively shape the research and policy agenda [9*].

THE EVOLUTION OF THE GLOBAL RESEARCH AGENDA ON ARV OPTIMIZATION

A first international conference on drug optimization (CADO-1) held in 2010. At that time, approximately 7 million people were on ART [21% of all people living with HIV (PLHIV)] and the estimated number of AIDS-related deaths was almost 1.8 million/year. Transition from stavudine/lamivudine/nevirapine to zidovudine/lamivudine/nevirapine was in course in the majority of low-income and middle-income countries (LMICs) and the median price of a first-line regimen was 160 USD per patient per year [12]. CADO-1 established the principles of drug optimization to facilitate increased harmonization of adult (including pregnant and lactating women) and paediatric ARV regimens, and defined the target product profiles, which included safety, efficacy, tolerability, durability, stability, convenience, accounting for special populations and achieving lower costs for treatment (Table 1) [6].

A key focus of the discussions at that time was on potential strategies to reduction in drug costs centred around the simplification of the process chemistry, reformulation, dose reduction as well as negotiated prices for more cost-efficient delivery of ARVs in countries with limited resources.

To further promote and refine these principles, subsequent ARV optimization meetings were set out to identify an overarching HIV treatment agenda for resource-limited settings, focusing on first-line and second-line treatments and understanding new technologies that may help to give long-term durability and affordability to ARV regimens [13].

This shift in focus was reflected with a new set of recommendations established in the second conference on drug optimization (CADO-2) held in 2013 [10]. In that year, the number of people on ART increased to almost 10 million (28% of all PLHIV), but the number of AIDS deaths had only slightly decreased to 1.6 million per year. Transition from zidovudine/lamivudine/nevirapine to tenofovir/lamivudine/efavirenz (EFV) as the preferred first-line regimen already had started in LMICs [14]. The CADO-2 main objective was to establish an HIV-treatment research agenda for resource-limited settings over the next 5–10 years, identifying a priority list of affordable first-line and second-line ART regimens, increasing the focus on development of once daily generic FDCs, ideally as one tablet a day, the intersection of HIV with concurrent illnesses/comorbidities, particularly TB and hepatitis B, as well as incentivizing novel treatment regimens and strategies at a time when there was declining investment in HIV treatment research. Two investigational drugs of high interest at that time were the dolutegravir (DTG) and a new tenofovir produg-tenofovir alafenamide (TAF). There was also a perception that optimizing the safety, convenience and availability of ART would help prevent more HIV infections.

At the end of 2017, a third global conference on ARV optimization (CADO-3) was convened with an objective to better define the critical research necessary to optimize second-line and third-line treatment regiments and also promote adequate sequencing and recycling of key antiretroviral agents in the context of public health [11**]. The global number of people on ART reached 21 million (57% of all PLHIV), the number of AIDS deaths declined to less than 1 million per year and transition from EFV to DTG containing regimens has started in many countries. The median price of first-line regimens per patient has reduced to 85 USD/year [15]. At CADO-3, there was an emphasis on ensuring that optimal products elected as preferred options for HIV treatment should be well tolerated, safe and effective across specific populations – namely pregnancy and breastfeeding women, TB/HIV coinfection as well as other comorbidities. Specific emphasis was also placed on the emergence of HIV drug resistance, particularly in
the context of service delivery models that reduced contact with health services.

At CADO-3, a prioritized list of research questions (Table 2) and a list of priority products (Fig. 2) were established. ARV regimens containing DTG and TAF were defined as the major short-term and medium-term priorities, respectively. Clinical studies on sequencing and recycling of TDF and TAF as well as on the role of DTG in patients who previously failed to regimens containing nonnucleoside reverse transcriptase inhibitors (NNRTIs) were defined as key priorities. The availability of darunavir/ritonavir (DRV/r) as a heat stable formulation and at a price similar to lopinavir/ritonavir was viewed as an opportunity to transition towards DRV/r as the preferred option for second line in the near future. Dose optimization studies on the use of low-dose DRV/r in second-line patients were also elected as a key medium-term priority. The use of oral and injecting long-acting drugs as well as nanoformulations and implantable devices was viewed as longer term priorities. Furthermore, emphasis was placed on the need to consider regulatory/intellectual property issues from the outset. A DTG-based FDC was identified as a potential candidate for second- and third- line regimens in order to facilitate the sequencing of regimens in patients who fail on an NNRTI-based regimen.

In summary, the global ARV optimization framework was initially focused on improving

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**Table 1. Target product profile for an ideal antiretroviral**

<table>
<thead>
<tr>
<th>Category</th>
<th>Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolerability</td>
<td>Low incidence of side-effects and toxicities</td>
</tr>
<tr>
<td>Resistance</td>
<td>High barrier to resistance</td>
</tr>
<tr>
<td>Convenience</td>
<td>Once-daily dosing (or less)</td>
</tr>
<tr>
<td>Special populations</td>
<td>Pregnant women, HIV/TB or HBV/HCV coinfection, Children</td>
</tr>
<tr>
<td>Cost</td>
<td>Cost without dose reduction, Potential cost with dose reduction, Impact of programmatic cost</td>
</tr>
</tbody>
</table>
global access to key ARV drugs available at that time by reducing cost and simplifying manufacturing processes, aiming the rapid reduction in mortality from HIV, preservation of life and prevention of progression to AIDS and the risk of HIV transmission at the population level. With the evolving science of HIV treatment in the last decade, new steps were taken to ensure a transition to new drugs and formulations with better efficacy, lower toxicity, limited contraindications and higher durability against drug resistance, to reduce the need to switch to more complex and expensive regimens and also to reduce the risk of HIV transmission at population level.

**POLICY TRANSITION TO NEW ARV OPTIONS: OPPORTUNITIES AND CHALLENGES**

The most recent drug optimization meetings have emphasized the importance of programmatic data

### Table 2. CADO-3 list of research questions

<table>
<thead>
<tr>
<th><strong>CADO 3: Priority research questions</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical studies on sequencing and recycling of TDF and TAF</strong></td>
</tr>
<tr>
<td>Switching from TDF to AZT (SoC) vs. maintaining TDF in 2L after failing a TDF regimen in 1L</td>
</tr>
<tr>
<td>Retrospective resistance testing</td>
</tr>
<tr>
<td><strong>Clinical studies on use of DTG in 2L patients who failed to EFV vs. 2 NRTI + PI (SoC)</strong></td>
</tr>
<tr>
<td>Consider factorial on NRTIs use</td>
</tr>
<tr>
<td>Clinical data to support whether DTG boosting is necessary for rifampicin containing coadministration (in HIV/TB patients)</td>
</tr>
<tr>
<td>If programmes implementation before RCT results: enhanced monitoring protocol and only proceed if good access to VL monitoring; organize result monitoring to gather real data</td>
</tr>
<tr>
<td><strong>Dose optimization study on the use of low-dose DRVr in 2L patients</strong></td>
</tr>
<tr>
<td>DRV/r 400/100 mg OD vs. DRV 800/100 mg OD (SoC)</td>
</tr>
<tr>
<td>Consider factorial on NRTIs used</td>
</tr>
<tr>
<td><strong>All studies should reflect real characteristics of people in treatment programs (e.g.: pregnant and women of child-bearing age, TB coinfection and other comorbidities)</strong></td>
</tr>
<tr>
<td>Consider to include community participation and regulatory/IP incentives</td>
</tr>
</tbody>
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**CADO 3: short, medium and long term priorities**

**Short-term**  
1-2 years
- TDF/3TC/EFV
- TDF/3TC/EFV$_{400}$
- DRV/r (400/50mg)

**Medium-term**  
2-5 years
- TAF/XTC
- TAF/XTC/DTG
- new DRV/r formulations §

**Long-term**  
+5 years
- Long acting formulations (entry inhibitors and INSTIs)
- maturation & capsid inhibitors
- bNAb

* Other lower priority products can be consider if new data become available in the future (bictegravir, doravirine, DTG/3TC, DRV/3TC, DTG/DRV/r)  
§ Low dose standard formulation (400/100mg) or standard dose nanoformulation (800/100 mg)

**FIGURE 2.** CADO-3 list of optimized products and formulations.
to inform benefits and challenges in introducing and scaling up DTG as the preferred first-line regimen [7,10]. There was discussion on low-dose EFV (EFV 400mg) as an alternative first-line option in the event that DTG is unavailable or patients face tolerability issues. Several fixed-dose DTG dual therapy regimens have recently been developed, notably DTG combined with rilpivirine and DTG with DRV/r. These were not given a priority at that time, as existing clinical trial data with these regimens were limited, particularly with respect to populations of concern in resource-limited settings.

Medium-term opportunities include the role of regimens including the new tenofovir prodrug (TAF) and new DRV formulations, with critical research focusing on the efficacy/safety, switch regimens, dose-reduction and/or the use of nanoformulations, particularly for DRV. Long-term goals include long-acting formulations of new compounds, maturation and capsid inhibitors and biologicals. Key research is also needed to evaluate the efficacy and safety of different second-line ART options [8*].

Furthermore, harmonization of adult and pediatric and key populations has been a goal for HIV treatment, ideally as FDCs. DTG offers great potential as a first-line regimen options, particularly as a generic fixed dose combination – requires less quantity of active pharmaceutical ingredient, once daily dosing, favourable side-effect profile compared to EFV [16].

In the future, however, it may be useful to expand the idea of target populations, particularly in the further scale-up of HIV treatment to reach the 90-90-90 targets by 2020 [3]. Upon reaching the global 90-90-90 target, a large number of individuals will be on life-long therapy. Developing a robust, cross applicable treatment regimen having evaluated an expanded safety requirement in addition to efficacy at the level of clinical trials will be of great utility and the importance of such pragmatic clinical trials, particularly when considering pregnancy, TB/HIV co-infection, teratogenicity, early birth defects as well as the effects of polypharmacy in aging populations [9*,17].

**LOOKING TO THE FUTURE: HOW TREATMENT OPTIMIZATION WILL LOOK LIKE?**

Given the high efficacy, safety, tolerability and convenience of current ARV therapy, it can be challenging to identify where and to what extent further improvements can be made. New agents under investigation are challenging the current treatment paradigm of three active antiretroviral medications taken orally every day to maintain viral suppression [18]. Several two-drug therapy options are under study and may simplify treatment and reduce cost [19,20]. Long-acting medications dosed every week or month, or longer, may be easier for some patients, improve medication adherence and increase cost-effectiveness [21]. A few longer acting ARVs in development will provide additional oral therapy options, but the majority of novel regimens will likely be delivered via alternative drug delivery systems. This includes the potential delivery of some new agents such as cabotegravir and rilpivirine as long-acting injectable formulations or as a subdermal implant [22]. These methods of drug, while new for HIV treatment, are common in other therapeutic areas such as hormonal contraception and psychiatry and may represent an additional way to improve medication adherence and effective treatment. These agents, along with the recent approval of ibaluzumab (a novel anti-CD4 monoclonal antibody), may provide future therapeutic options, particularly for those with heavy treatment experience [23] (Table 3).

Future ARV optimization will move towards inclusion of new drugs classes, new technologies in process chemistry and formulations and new therapeutic strategies. How to retain the public health approach and guarantee equitable access to these innovations in all settings remains an important challenge.

Additional patient populations should also be considered in the future development of optimal ARVs. With the significant decrease in the mortality and establishment of HIV as a chronic disease, aging populations with HIV will form a significant proportion of the people on ART in the near future, and is already know that they at an elevated risk of cardiovascular disease, type 2 diabetes and other comorbidities when compared with general population [24]. Greater integration is expected in the future between HIV, TB, hepatitis, sexual/Reproductive health and noncommunicable diseases [25–27]. Close coordination between the innovators and these disease areas will further enhance considerations for safety and applicability.

In this context, enhanced pharmacovigilance is a critical component to ensuring patient safety. Clinical trials have limited scope to discover rare but important adverse/side-effects – the recent example of a potential safety issue with DTG is a difficult lesson demonstrating the importance of having established networks for outcome surveillance [28]. In the absence of the ongoing study, such a signal would be unlikely to have been detected, with potential serious consequences. Surveillance systems should also be in place when considering drug–drug interactions, pregnancy and elderly/geriatric populations on ARVs.
Finally, treatment optimization goes beyond of pharmacological/patient adherence interventions. Improvement in the efficiency and quality of treatment programs and the promotion of innovative, comprehensive strategies and actions to eliminate HIV-related stigma and discrimination are essential to improve the outcomes and reach global HIV elimination targets. Several challenges need to be overcome. These include increased testing uptake, and sustained high levels of treatment coverage, adherence and retention in care. Cost implications at the regional and country levels will also vary and need to be further explored. Additional ARV drug costs may be at least partially offset by increased efficiencies, such as implementation of the differentiated care approach, task shifting and integration of HIV and related services.

**CONCLUSION**

The optimization of ARV drugs in the last decades has dramatically improved both treatment and prevention outcomes of HIV infection globally. Continued development of compounds and formulations that improve the efficacy, safety and tolerability of HIV drugs will provide additional progress in this area. Notwithstanding, these extraordinary achievements, important challenges to consolidate the treatment optimization agenda still remain, considering that as of the end of 2017, still some 15 million HIV positive individuals were not receiving treatment [29]. Therefore, drug innovations should be combined with innovative care delivery models to ensure durable, efficacious and safe treatment for all PLHIV. Innovators should consider the ease of administration and scale-up of a new ARV in low/middle-income settings in addition to the framework laid down by the CADO process. Sequencing of first-line, second-line and third-line regimens will also allow better planning, rationalize the number of regimen that programmes need to procure and minimize the risk of ARV stock outs.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest


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**Table 3. Major new ARVs in phase III studies**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug</th>
<th>Formulation</th>
<th>Dose</th>
<th>Rationale for use and ongoing main studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI</td>
<td>RILPIVIRINE-LA</td>
<td>IM injection long-acting solution (combined with cabotegravir)</td>
<td>600 mg</td>
<td>Long-acting ARV [monthly administration]. LATTE 2 study</td>
</tr>
<tr>
<td>INSTI</td>
<td>CABOTEGRAVIR</td>
<td>Tablet (single) and IM injection long-acting solution (combined with rilpivirine-LA)</td>
<td>30 mg 400 mg</td>
<td>Long-acting ARV [oral induction + monthly administration] LATTE 2 study</td>
</tr>
<tr>
<td>ENTRY BLOCKER</td>
<td>ABLUVIRITDE</td>
<td>IV injection solution</td>
<td>160–320 mg</td>
<td>Long-acting fusion inhibitor. Subcutaneous formulation under development TAVENT study</td>
</tr>
<tr>
<td>ENTRY BLOCKER</td>
<td>FOSTEMSAVIR</td>
<td>Tablet</td>
<td>600–1200 mg</td>
<td>Oral attachment inhibitor, which blocks CD4 receptor (once daily). BRIGHTTE study</td>
</tr>
<tr>
<td>ENTRY BLOCKER</td>
<td>UB-421</td>
<td>IV injection long-acting solution</td>
<td>25 mg/kg</td>
<td>Humanized monoclonal immunoglobulin that blocks CD4 receptor (every 2 weeks). UBP-A304 study</td>
</tr>
<tr>
<td>ENTRY BLOCKER</td>
<td>PRO-140</td>
<td>SC injection long-acting solution</td>
<td>350–700 mg</td>
<td>Humanized monoclonal immunoglobulin that blocks CD4 receptor (every week). CD03 study</td>
</tr>
</tbody>
</table>
8. Vitoria M, Hill A, Ford N, et al. The transition to dolutegravir and other new antiretrovirals in first-line and second-line regimens, as well as in emerging ART strategies as dual therapy. It also listed the research priorities for DTG and the implications for other emerging ARVs.