The Second Conference On Antiretroviral Drug Optimization (CADO 2)

Cape Town, South Africa

16-18 April 2013

Meeting Report

Executive Summary

The second Conference on Antiretroviral Drug Optimization (CADO 2) was convened on 16-18 April 2013, in Cape Town South Africa. It was chaired by Professor Charles Flexner (Johns Hopkins University) and Dr David Ripin (the Clinton Health Access Initiative), with facilitation and logistics support from the Pangaea Global AIDS Foundation, and funding from the Bill and Melinda Gates Foundation.

CADO 2's goal was to identify an HIV research agenda for resource-limited settings over the next five-to-ten years. As well as reviewing existing compounds in early development, CADO2 identified potential novel approaches to reinvigorate first- and second-line regimens, and the role of new technologies to improve long-term durability and affordability. CADO2 built on the first CADO meeting held in 2010, which defined a short-term portfolio of research to optimize existing antiretrovirals.

Sixty experts (HIV physicians, academic researchers, policy makers and representatives of donor and funding organizations, HIV community, and the pharmaceutical industry) participated in the meeting. Recommendations and progress from the first CADO were revisited and target product profiles reviewed. Dose modifications of existing drugs and the potential of new drugs in development, novel formulations, innovative study designs and partnership opportunities were explored.

Objectives and key themes

- To develop mid- and long-term research priorities for HIV drugs and regimens in resource-limited settings.
- To identify better, more affordable and sustainable treatments and regimens, in the context of a public health approach.
- To promote minimal sequencing of maximally effective regimens.
- To identify opportunities to improve on current regimens and treatment strategies.

The meeting organizers also hoped that setting out a clear medium-term HIV treatment agenda would support efforts to incentivize research and development innovation in an environment of diminishing traditional pharmaceutical industry investment. The recommendations and deliberations outlined in this meeting report were reached collectively by meeting participants, and do not represent formal commitments of any of the organizations represented.

KEY RECOMMENDATIONS

- **First-line**
  - Studies to determine fixed-dose combination regimens that are equally or more potent and more durable and affordable than TDF/XTC (XTC here refers to either 3TC or FTC)/EFV including TAF/XTC/DTG and TAF/XTC/EFV (400 mg).
- **Post Treatment –failure**
  - Studies to identify improved second line regimens, particularly the role of fixed dose boosted, dose-optimized darunavir in replacing atazanavir or lopinavir as the protease inhibitor of choice?
  - A one pill once daily second-line regimen.
  - Studies of reduced-dose darunavir/ritonavir (DRV/r), in combination with recycled nucleosides or an integrase inhibitor.
- **Enhancing Trial Participant Criteria**
  - Studies to reflect the characteristics of people in treatment access programs, including girls and women of reproductive age, TB co-infection, and comorbidities (such as hypertension).
- **Early engagement of Private Sector Developers & Manufacturers**
  - To maximize pharmaceutical company expertise in drug development for global health priorities
  - And speed preparation for production, scale up and incorporation of new regimens into global treatment programs.
- **Longer Term Research Priorities**
  - Continued research into the potential use of oral and injectable long-acting drugs (including GSK744 and TMC278) as well as nano-formulations and implantable devices (longer term priority).

1. Introduction

Budgets for global HIV treatment and prevention in resource-limited settings will continue to be pressured, and, because the need for treatment scale-up is urgent, the emphasis on value for money has become an increasing priority.

The first CADO in 2010 focused on developing a research agenda to optimize the doses and combinations of existing approved drugs, including through role of process chemistry, and recommended a research development agenda for HIV drug optimization. The conference identified a portfolio of projects with the potential to significantly optimize treatment while achieving major cost reductions. Projects included improvements in process and formulation chemistry and dose reductions as intermediate technologies with an imperative to focus future resources on developing better regimens and formulations.

The goals and objectives of CADO2 were to identify and facilitate the development of novel, affordable, optimized drug regimens in resource-limited settings, within a public-health approach. CADO2 participants looked further into the future, to review drugs in the development pipeline, and to highlight gaps in drug development programs. Underpinning the meeting was the commitment to a single global standard for the equitable treatment of everyone, in both resource-rich and resource-poor settings. Potent, durable and affordable drug regimens are needed to sustain the contribution of universal access to HIV treatment to reversing the global AIDS epidemic.

Goals

i. To identify optimized first-line antiretroviral regimens for implementation in resource-limited settings, transitioning from existing regimens.
ii. To define a strategy for improved second-line antiretroviral regimens.
iii. To promote minimal sequencing of maximally effective regimens.
iv. To promote a medium-term drug development agenda for combinations of existing and new antiretrovirals currently in development.
v. To develop mid- and long-term HIV research priorities in resource-limited settings.
vi. To identify better, more affordable and sustainable treatments and regimens, in the context of a public health approach
vii. To incentivize research and development innovation in an environment of diminishing industry investment.

Objectives

i. Develop mid- and long-term research priorities for HIV drugs and regimens in resource-limited settings.
ii. Incentivize research and development innovation in an environment of diminishing industry investment.
iii. Identify better, more affordable and sustainable treatments and regimens, in the context of a public health approach

Meeting Structure

The conference was structured around three major questions:

i) Can we do more with what we have now?
ii) How can a research be developed that reflects global AIDS public health contexts?
iii) How will future developments alter the treatment landscape?

Expert presentations, moderated panel discussions, plenary discussions, and break out groups addressed each of the three key questions. The outcomes of small group discussions were discussed by the whole group and incorporated into meeting's key recommendations for action.

2. Can we do more with what we have now?

Background

The members of the United Nations General Assembly have committed to expanding the number of people living with HIV who are on treatment in low- and middle-income countries to 15 million by 2015 (UNAIDS). With limited resources, a public health approach needs to balance both costs and effectiveness and secure long-term program sustainability. Following the recommendations of CADO1, a portfolio of dose optimization studies and process chemistry research was begun to optimize a broad range of antiretrovirals).[1] Of note, work is on going to reformulate tenofovir to increase its bioavailability, resulting in a lower dose and reduced cost while maintaining equivalent clinical exposure. In further process chemistry work, modification of a side chain common to darunavir and atazanavir promises to reduce the cost of manufacturing these key protease inhibitors. Clinical trials of low-dose efavirenz and lamivudine have reported, and trials of low-dose zidovudine and stavudine are on going. Abacavir has resurfaced as a candidate component of first line. The relative non-availability of HLAB57-typing in resource-limited settings may be a barrier to widespread use.

The demand for options after failure of first line treatment regimens is growing – and will be an increasing priority as many of the first wave of people accessing treatment with d4T based regimens change to more effective regimens. People have been on first-line treatment longer and more are failing. The increasing use of viral load monitoring will identify first-line failures earlier. Second-line regimens still cost three to four times that of first-line regimens largely driven by high protease inhibitor costs.

Health systems are stretched in many resource limited countries, and the current model of the provision of episodic services needs to be replaced with a model more akin to chronic disease management. The keys to change are improved continuity of care across the treatment and prevention cascades, involvement of peer educators, and community support and governance. Potential weaknesses to continued successful scale up are poor linkage, engagement and retention in care, late enrolment in care, and unwillingness to initiate antiretroviral therapy, with one South African study reporting 20% refusal. Feeling well was the most common reason for refusal.[2] Drug optimization is a critical component of broader program optimization. Any attempts at drug optimization must be part of a multi-pronged approach to strengthening programs for prevention, care and treatment.

However, the current pipeline of ARVs in development (see Figure 1) contains several important drugs at late stages of development. A key challenge will be to identify their utility in public health contexts and work with manufacturers, funders and policy makers to ensure that they are rapidly made available to all who need them.

Pipeline

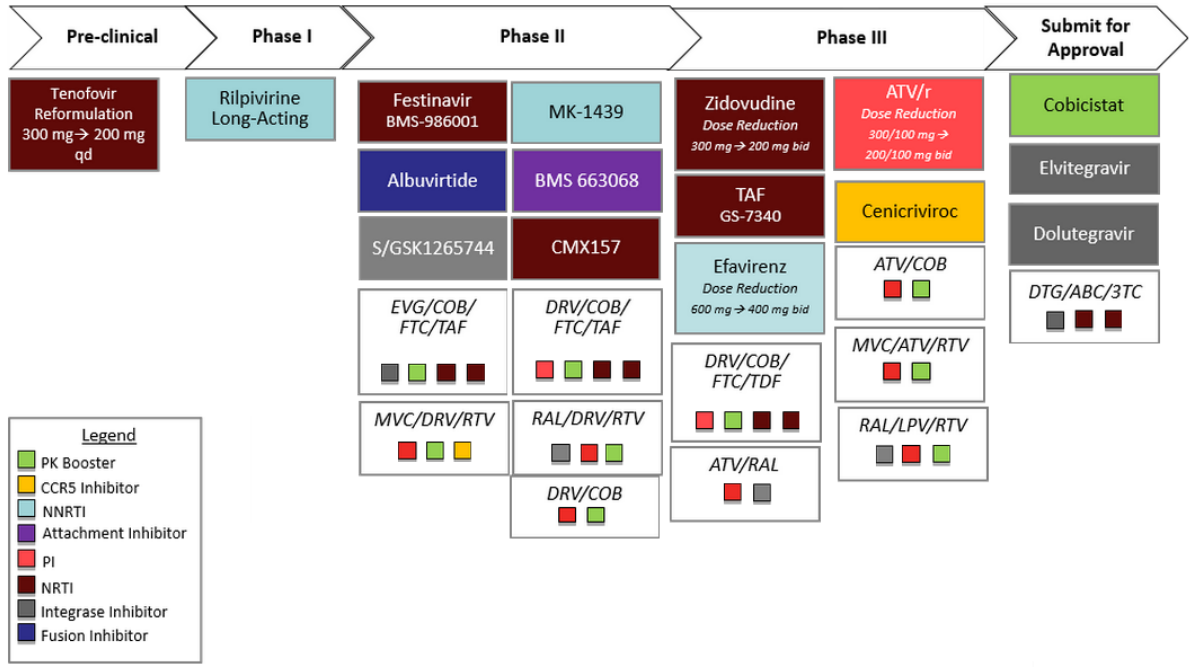

Figure 1: The ARV pipeline contains several important products at late stages of development.
(Adapted from 2012 i-Base/TAG Pipeline report (draft version) and clinical trials.gov. P. Clayden and D. Ripin)

First Line Treatment Options

KEY RECOMMENDATION: Studies to determine fixed-dose combination regimens that are equally or more potent and more durable and affordable than TDF/XTC/EFV including TAF/XTC/DTG and TAF/XTC/EFV (400 mg).

The goal sought by improving current antiretrovirals is the minimal sequencing of maximally effective regimens. The target product profile for optimal antiretroviral candidates as defined at the CADO1 meeting remains valid (see figure 2)

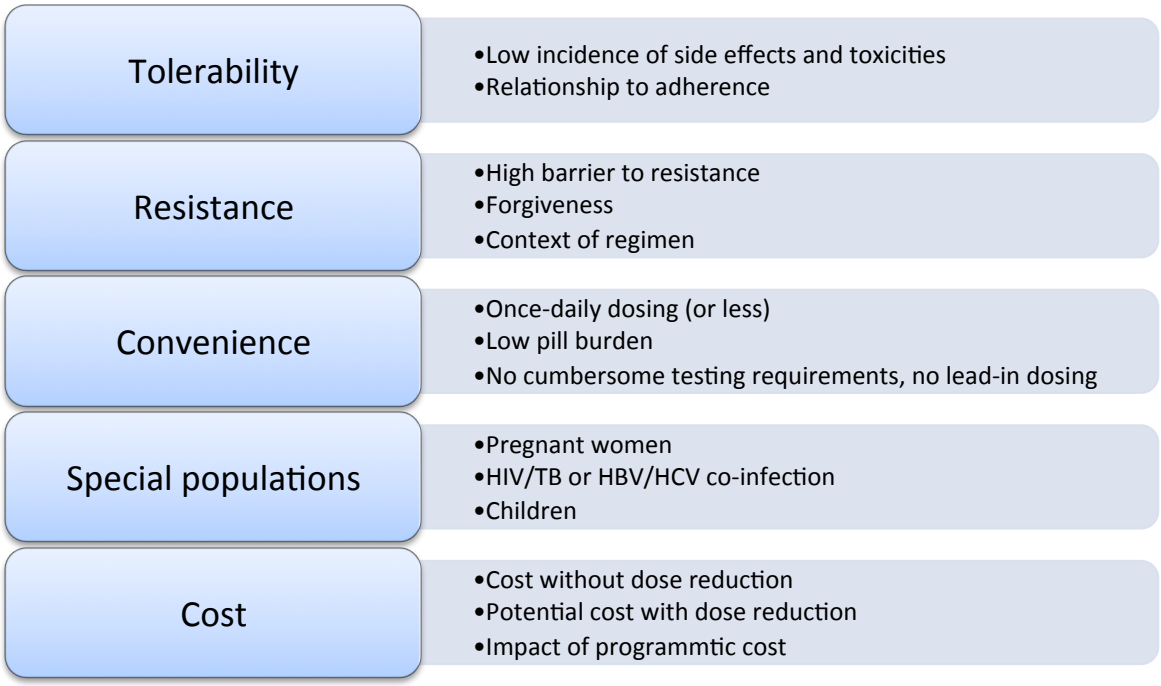

Figure 2: Target Product Profile for the ideal antiretroviral regimen as developed at CAD01

An additional consideration is that the target product profile should be defined within a public health approach. In bringing new drugs to resource-limited settings, scientific and policy challenges need to be faced and key players, major investors and researchers need to be engaged.

TDF/XTC/EFV has been demonstrated to be a highly effective first-line regimen and WHO has worked to promote this combination as the preferred one pill once a day for most populations including pregnant women. There are inherent risks in changing and it is important to understand the criteria for recommending a change.

The meeting agreed, therefore, that improving the current first line regimen of choice (as set out in the 2013 WHO Consolidated HIV Treatment Guidelines) of the fixed-dose once-daily combination of TDF/3TC/EFV should be driven not only by superior efficacy (or at least non-inferiority) but most importantly, by long term durability, tolerability and patient acceptability. This latter issue will be a major challenge for the TDF/3TC/EFV regimen given adverse effects and long-term toxicities associated with the individual components of the regimen.

Participants focused their attention on new products in development that could meet these criteria. In particular, there is a need for clinical trials in real world resource limited contexts that combine the different promising compounds in development. It was noted that combinations currently being studied (TAF + FTC + DTG /c and EVG/c [or DTG] + ABC + 3TC) appear unlikely to quickly find their way into developing market settings. The first FDA approved quad pill (TDF/FTC/EVG/c) for use in first-line for treatment naïve patients costs approximately $34,000 per patient per year in the United States.

Two tenofovir prodrugs (tenofovir alafenamide fumarate - TAF and CMX 157) have the potential to improve the delivery of tenofovir resulting in reduced cost and possibly reduced renal toxicity. Gilead's new tenofovir prodrug, TAF, has demonstrated a fivefold increase in intracellular tenofovir

diphosphate levels compared to tenofovir. With higher potency at lower doses, significant price reductions in the tenofovir active pharmaceutical ingredient are possible. In a quad formulation, TAF was non inferior to tenofovir, with lower renal exposure.[3] CMX 157 is in phase 2 studies, with potential benefits of once-weekly dosing and reduced nephrotoxicity. The novel sequencing strategy of two nucleoside reverse-transcriptase inhibitors (NRTIs) and one NNRTI in first-line followed by the boosted protease inhibitor (PI) and an integrase inhibitor in second-line was studied in the SECOND-LINE study.[4]

The replacement of EFV – and of NNRTIs generally in first line – was discussed extensively in the meeting. New integrase inhibitors, dolutegravir (DTG) and GSK744, are potential alternatives to efavirenz in first-line and would allow the NNRTI class to be an option in post-treatment failure regimens. Dolutegravir appears to be highly potent and has a long half-life and requires no boosting. It appears currently not to be associated with serious side effects or toxicities. Its low dosing suggests that it may be affordable. Studies have demonstrated superiority of dolutegravir over raltegravir and better tolerability when compared to efavirenz.[5, 6] However, the standard dose of efavirenz (600 mg) in a first-line regimen can be used safely with rifampicin-containing tuberculosis treatment but an increase in the dose of dolutegravir is required in the presence of rifampicin, complicating the management of people with HIV/tuberculosis co-infection. An approval decision for dolutegravir from the US FDA is expected in August 2013. GSK744 is currently in phase 2 studies in oral and injectable preparations.

Post Treatment Failure Options

KEY RECOMMENDATION: Studies to identify improved second line regimens, particularly the role of fixed dose boosted, dose-optimized darunavir in replacing atazanavir or lopinavir as the protease inhibitor of choice, formulation of one pill once daily second-line regimen, studies of reduced-dose darunavir/ritonavir (DRV/r), in combination with recycled nucleosides or an integrase inhibitor.

New WHO guidelines recommend boosted atazanavir or lopinavir as the preferred protease inhibitors in second-line. Atazanavir has the advantage of better tolerability, once daily dose convenience and the opportunity to save costs ($276 per patient per year for atazanavir compared to $378 per patient per year for lopinavir). Further savings from reduced active pharmaceutical ingredient prices will likely see atazanavir costing $200 per patient per year.[7]

There is a need to address simplification and cost reduction of second-line therapy. The currently recommended WHO regimen is a boosted PI plus recycled nucleosides. The WHO preferred protease inhibitors lopinavir and atazanavir have dosing (twice daily for LPV/r) and side effect (hyperbilirubinemia for ATZ/r) issues. The LASA trial is examining the lower dose of atazanavir in Thai

people.[8] Further, there is evidence that people are stopping second-line therapy after short periods of time, implying that current second-line therapy is not acceptable. There is a need to understand the reasons for this with improved post marketing surveillance.

The meeting participants considered that, taking efficacy and tolerability to define the best drug, then darunavir should be considered as standard-of-care in second-line. The Artemis study showed boosted darunavir to be clinically superior to boosted lopinavir.[9] The current cost of darunavir is higher than the WHO-recommended protease inhibitors (lopinavir and atazanavir), but that could change with increased production and purchase of darunavir. If darunavir is considered standard-of-care, dose reduction trials and co-formulation become priorities. However, it was noted that there are limited data on the use of darunavir with rifampicin.

In terms of optimal sequencing, the goal is one-pill once daily in first-line followed by one-pill once daily in second-line. The development of a single pill for second-line is a priority.

A third priority in trials of second-line antiretroviral therapy is TB co-infection. There are limited data to support appropriate management of people taking a protease inhibitor who have tuberculosis. The treatment of people who have or get tuberculosis while taking a protease inhibitor remains unclear. WHO recommends increasing the dose of the protease inhibitor but there is little evidence supporting this strategy. Rifabutin was added to the essential medicines list in 2010, to be used in combination with a protease inhibitor, but its adoption as a strategy for treating co-infected people on a protease inhibitor regimen has not happened.

3. Developing a research agenda that reflects global AIDS public health contexts

Background

Research is needed in resource-limited settings because affected populations are different and capacity exists to conduct quality research. While resources are good, there is a shortage of funds. Research networks need to be sustainable and governments, especially those with emerging economies, need to take increasing responsibility. Academic institutions are traditional partners in new drug development and local academics that understand local issues can inform government. It is important to involve communities in planning of clinical trials, to understand the needs of consumers, to disseminate findings, and to support the rollout of new regimens.

Enhancing Clinical Trial Criteria

> **KEY RECOMMENDATION: Studies to reflect the real characteristics of people in treatment programs, including girls and women of reproductive age, TB co-infection, and comorbidities (such as hypertension).**

Factors to be considered in future trial designs include simplification, real-life enrolment and follow-up, and the use of existing large cohorts in Africa, which have invested heavily in quality data collection. Rather than excluding people with tuberculosis for ART clinical trials, there needs to be stratification within trials for tuberculosis or, alternatively, separate tuberculosis studies. Efficacy should be defined by superiority rather than non-inferiority (primary endpoint of plasma viral load suppression at 48 weeks), tolerability, durability and cost. Demonstrating superiority has benefits for both patients and communities, who can lobby for the best drugs, and for program managers who can choose the best drug for their programs. Adaptive design methods in clinical research allow modifications to be made to the trial or statistical procedures of on-going clinical trials. Adaptive designs can more efficiently and quickly identify clinical benefits of the test treatment under investigation, make changes based on knowledge acquired and increase the probability of success of clinical development. The FDA snapshot algorithm uses viral load at the visit of interest and is less complicated than the previously used time to loss of virological response (TLOVR) algorithm that utilized data from every visit.

Tolerability will become increasingly important with more asymptomatic people expected to start antiretroviral therapy as the WHO threshold for initiation is reset to 500 cells/mm^3. In addition to reporting short-term toxicities within clinical trials, post-marketing surveillance for longer-term adverse events is required. Large cohorts, such as the International Epidemiologic Databases to Evaluate AIDS (IeDEA) have the capacity to conduct such pharmacovigilance. Cost and cost effectiveness are important considerations in assessing new drugs or fixed-dose combinations. With fixed-dose combinations key to long-term adherence and acceptability, rather than the traditional model of approving stand-alone drugs followed by bioequivalence studies of fixed-dose

combinations, it may be better to study fixed-dose combinations directly. Clinical trials going forward need to address what is required to obtain regulatory approval for a drug or regimen, to change normative guidelines and prepare manufacturers for production. Clinical trials need to be representative of the real world and include people with co-infections, co-morbidities (hepatitis B, diabetes, and hypertension) and pregnant women.

Early engagement of Private Sector Developers & Manufacturers

> **Key Recommendation: To maximize pharmaceutical company expertise in drug development for global health priorities, and speed preparation for production, scale up and incorporation of new regimens into global treatment programs.**

The traditional model of private sector investment in drug development is by originator pharmaceutical companies recouping research investment by marketing products and protecting investments by patent. Generic company research is focused on process chemistry and formulation aimed at high volume production at low cost. Both models have to be adapted and integrated to maximize public health benefits. Both innovator and generic companies can contribute to research studies through their relative expertise and through donation of study drug. As well as focusing on the science, development pathways are needed in which the risk is shared between the manufacturer and those who want the product. The market for antiretrovirals is robust and volumes are large, requiring substantial investment in manufacturing capacity. There are products only available in resource-limited settings due to particular demand in that setting. It is necessary to find ways that allow generic companies to invest in capacity and, at some point, sustainable pricing must be realized. Consensus on collaboration between the representatives of innovator and generic companies exists, but it is not clear how such collaboration can be advanced. There is a possibility, in resource-limited settings, to develop a new drug combination for use in those settings. However, to do this will require strong coordination amongst many partners.

Additional Priorities

In addition, meeting participants discussed other priority areas:

How to engage asymptomatic patients in long-term treatment and care

There needs to be a better understanding of the key components of the cascade of care; what are the motivators for people to enter into care (or not), why some people initially choose to delay initiation of antiretroviral therapy despite being eligible, how to improve engagement in lifelong treatment and how to retain people in care. Starting with quantification of the problem (how many people are not entering care, choosing not to start antiretroviral therapy, are poorly adherence and are lost) research is needed to understand the needs of these people and strategies to meet these needs. These include motivational interviewing to change decisions, community approaches and the role of peers in providing services. Research methods include social and behavioural science, and operational/implementation science.

Funding needs and priorities for HIV treatment and continued research

The quest for better regimens and lower cost are not necessarily mutually exclusive. First, define the best option; then, resolve how to get it to market. History has taught us that any initial increase in cost can be followed by the opportunity to recover cost over time. Research needs to be end-to-end and include product development, understanding the market and delivering the product to that market once it has been developed. While the Global Fund and PEPFAR initially focused on supporting treatment rollout and scale-up, the research community needs to work out how to engage these and other funders in developing longer-term public health driven research strategies. A roadmap to arrive at lower cost is integral to any future research agenda striving to deliver better, safer drugs in resource-limited settings. Funding new, large clinical trials will require investment by multiple partners, including governments (both in the North and South), foundations, innovator pharmaceutical companies and generic manufacturers. Both innovator and generic manufacturers need to commit to supply study products. The risk needs to be shared. Formal product development partnerships have been developed for microbicides, tuberculosis and malaria but the alternative of an informal 'virtual' product development partnership may be a more appropriate model to implement the next phase of antiretroviral therapy development. While the atmosphere seems right, how to convert enthusiasm and good will into a real-world structure will be a challenge.

3. How will future developments alter the treatment landscape?

New Approaches

Key Recommendation: Continued research into the potential use of oral and injectable long-acting drugs (including GSK744 and TMC278) as well as nano-formulations and implantable devices (longer term priority).

The meeting reviewed new technological developments to deliver HIV treatments. It was recognized that these are unlikely to transform the HIV treatment landscape in the next five to ten years, but may offer longer term benefits. Particular approaches include:

a) Nanotechnologies for pharmaceuticals: Nanotechnology is the manipulation of matter on an atomic and molecular scale. Nanotechnology can be used instead of conventional approaches to solubility and bioavailability enhancement. Such approaches include micronization (the process of reducing the average diameter of a solid material's particles to diameters of the nanometre scale) using jet mills, co-solvents and excipients to enhance bioavailability. There are various types of nanoparticle carriers of drug as well as nano-suspensions (biphasic systems consisting of pure drug particles dispersed in an aqueous vehicle, stabilized by surfactants)[10] which consist of the poorly water-soluble drug without any matrix material. Drugs are absorbed intracellularly as the nanoparticle without the need to change to a soluble state.

Drivers for nanotechnology approaches include the insolubility of active pharmaceutical ingredients, poor oral bioavailability, inter-patient variability, fed/fasting variation, pill burden, adverse drug reactions and issues with adherence. Nano-dispersions of efavirenz at a dose of 300 mg achieve the same plasma concentrations as 600 mg of standard efavirenz.[11] A nano-suspension of LPV/r is in development for use in children.

b) Injectables, devices, implants and slow-release delivery: Long-acting combination antiretrovirals offer the possibility of treatment simplification, improved convenience and adherence. Market research has shown that people who think taking pills daily is a burden are interested in an alternative. GSK744 is an analogue of dolutegravir with a long half-life and has possible applications in HIV treatment and prevention. It has been studied as a low-dose oral mono-therapy and as a nano-suspension for injection. A single injection provides detectable drug in plasma for 48 weeks. In combination with another long acting antiretroviral, rilpivirine, GSK744 is being studied as a two-drug combination antiretroviral therapy maintenance regimen with monthly dosing. The Latte study is examining an induction/maintenance strategy of GSK744 plus two NRTIs for 24 weeks followed by GSK744 plus rilpivirine as maintenance for those who are virologically suppressed at week 24 on the induction regimen.[12] In PrEP trials, GSK744 has demonstrated protection in Macaques and is being studied in humans as mono-therapy with injections every three months.

Polymeric drug delivery systems (using smart polymers for responsive drug delivery) have resulted in pilocarpine-releasing ophthalmic inserts to treat glaucoma, hormonal contraceptive implants and vaginal rings delivering oestrogen for post-menopausal symptoms and progesterone for contraception. The dapivirine ring, which releases the non-nucleoside reverse-transcriptase inhibitor dapivirine over one month to prevent HIV acquisition, is currently in phase III safety and efficacy trials. Phase I and II trials are underway for the maraviroc vaginal ring, dapivirine plus maraviroc ring and dapivirine film. Self-inserted vaginal rings have a low burden of adherence, have been shown to be acceptable by women and their partners and can deliver multiple products from one ring.

Multipurpose prevention technologies (MPTs) that simultaneously prevent sexually transmitted infections (STIs) including HIV and unintended pregnancy are a global health priority.[13] Drug-loaded nano-fiber meshes have been demonstrated to inhibit HIV infection in vitro, and physically obstructed sperm penetration.

Novel technologies

While it may be difficult to better the efficacy of current oral ARVs, long-acting injectable or implantable antiretrovirals under development offer the potential for improved acceptability and adherence. Target product profiles are needed for types of molecules, formulations and delivery methods. Adolescents and children may be candidates for better delivery system, but benefits versus risks need to be considered. While potentially more convenient, the challenges of using long acting formulations include drug interactions, unanswered safety concerns, strategies for induction/maintenance, the mix or oral and injectable formulations, the impact of long-acting treatment on clinical care engagement and how to deal with loss to follow up. For example, what to do if a person who just had an injectable gets tuberculosis. Robust post marketing surveillance for newer delivery systems is required. Other formulation opportunities should be pursued, such as long acting oral formulations, and nanotechnology to re-evaluate compounds shelved due to solubility, stability and delivery issues. In the field of contraception, injectable products historically have been preferred.

Third-line

Approaches to third-line (salvage therapy) are difficult within a public health approach. Improved durability of first- and second-line would reduce the need for third-line, which remains an individualised decision based on genotyping. One approach is to partner with industry to coordinate limited access to third-line regimens for those in need.

4. Conclusions & Next Steps

This meeting report summarizes the deliberations in Cape Town, South Africa. Key issues discussed were how to improve clinical trial design in resource-limited settings, to obtain quality results more quickly, and how to use established networks of clinical trialists in Africa to conduct the next round of research into better regimens, and for the treatment of people with HIV/TB co-infection. A key focus was how to design clinical trials that reflect the real world, that are adaptive as information becomes available, and that have simplified but robust monitoring strategies. Further focus was on tenofovir prodrugs, new integrase inhibitors and the role of newer protease inhibitors in second-line. In addition, meeting participants noted the importance of end-to-end product development that includes not only the science but also the understanding the needs of consumers, how to reduce regulatory delays, and how to prepare in advance for production at capacity to expedite rapid scale up. Novel technologies, such as oral and injectable long acting antiretrovirals, nano formulations and implantable devices, were explored as longer-term options.

CHAI, Johns Hopkins University and Pangaea agreed to continue collaborating to mobilize action on the research priorities outlined in the meeting. A range of stakeholders, from funders, community, researchers from institutes, academia and the private sector, manufacturers and policy makers will be needed to drive this agenda forward.

References

1. Crawford, K.W., et al., *Optimising the manufacture, formulation, and dose of antiretroviral drugs for more cost-efficient delivery in resource-limited settings: a consensus statement.* Lancet Infect Dis, 2012. **12**(7): p. 550-60.
2. Katz, I.T., et al., *Antiretroviral therapy refusal among newly diagnosed HIV-infected adults.* AIDS, 2011. **25**(17): p. 2177-81.
3. Zolopa, A., et al., *A Randomized Double-Blind Comparison of Coformulated Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Versus Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate for Initial Treatment of HIV-1 Infection: Analysis of Week 96 Results.* J Acquir Immune Defic Syndr, 2013. **63**(1): p. 96-100.
4. Boyd, M., *SECOND-LINE: Ritonavir-boosted Lopinavir with 2-3N(t)RTI or Raltegravir in HIV+ Subjects Virologically Failing 1st-line NNRTI/2N(t)RTI. Paper #180LB*, in *20th Conference on Retroviruses and Opportunistic infections.*2013: Atlanta, GA.
5. Pozniak, A., *Dolutegravir vs raltegravir in ART-experienced, integrase-naive subjects: 24-week interim results from SAILING (ING111762).* in *20th Conference on Retroviruses and Opportunistic Infections*2013: Atlanta.
6. van Lunzen, J., et al., *Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial.* Lancet Infect Dis, 2012. **12**(2): p. 111-8.
7. Molina, J.M., et al., *Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study.* J Acquir Immune Defic Syndr, 2010. **53**(3): p. 323-32.
8. http://clinicaltrials.gov/ct2/show/NCT01159223.
9. Estrada, V. and M. Fuster, *[Darunavir in treatment-naive patients. The ARTEMIS study].* Enferm Infecc Microbiol Clin, 2008. **26 Suppl 10**: p. 10-3.
10. Bhowmik, D., et al., *Nanosuspension -A Novel Approaches In Drug Delivery System.* THE PHARMA INNOVATION - JOURNAL, 2012. **1**(12).
11. http://britishsocietynanomedicine.org/assets/files/inaugrialMeeting/AO%20BSNM%20Oct%202012.pdf
12. http://clinicaltrials.gov/ct2/show/NCT01745289.
13. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0049792.

List of participants

Co-Chairs

Charles Flexner
Professor, Medicine, Pharmacology & Molecular Sciences, and International Health
School of Medicine and Bloomberg School of Public Health
Johns Hopkins University
Baltimore, MD United States

David Ripin
Executive Vice President, Access Programs
Chief Scientific Officer
Clinton Health Access Initiative
New York, NY United States

Participants

Martin Auton
Senior Technical Officer,
Procurement Support Services Pharmaceuticals and Health Products
The Global Fund to Fight AIDS, Tuberculosis
Geneva, Switzerland

Andrew Boulle
Director
Centre for Infectious Disease Epidemiology and Research (CIDER)
Cape Town, South Africa

Stephen Becker
Deputy Director, HIV/TB
Bill & Melinda Gates Foundation
Seattle, WA United States

Terry Blaschke
Senior Program Officer, Global Health Discovery & Translational Sciences
Bill & Melinda Gates Foundation
Seattle, WA United States

Thomas Cai
Senior Advisor and Consultant for Pangaea
AIDS Care China
Kunming, China

Polly Clayden
Director
HIV i-Base
London, UK

David Cooper
Scientia Professor and Director
Kirby Institute, University of New South Wales
Sydney, Australia

Keith Crawford
Global Director
Public Health Research for the Walter Reed Army Institute of Research (WRAIR)
Bethesda, MD United States

Tim Cressey
Lab Director
Program for HIV Prevention & Treatment
Newcastle Upon Tyne, UK

Marie-Pierre de Bethune
Vice President External Innovation
Janssen Pharmaceuticals

Meg Doherty
Coordinator, Treatment & Care
World Health Organisation
Geneva, Switzerland

Paul Domanico
Director, R&D
Clinton Health Access Initiative
New York, NY United States

Chris Duncombe
Senior Program Officer
Bill & Melinda Gates Foundation
Seattle, WA United States

Wafaa El Sadr
Professor of Epidemiology
Mailman School of Public Health, Columbia University
New York, NY United States

Sean Emery
Head, Therapeutic and Vaccine Research Program
Kirby Institute, University of New South Wales
Sydney, Australia

Shaffiq Essajee
Senior Advisor on HIV
Clinton Health Access Initiative
Boston, MA United States

David Evans
Director of Research Advocacy
Project Inform
Los Angeles, CA United States

Nathan Ford
Programme Manager
HIV/AIDS Treatment
World Health Organisation
Geneva, Switzerland

Eric Goemaere
Senior Regional HIV/TB Advisor
Médecins Sans Frontières
Honorary Lecturer, University of Cape Town
Cape Town, South Africa

Eric Goosby
Ambassador, U.S. Global AIDS Coordinator
Office of Global Health Diplomacy
State Department
Washington D.C., United States

Andrew Hill
Honorary Lecturer
Pharmacology Research Laboratories
University of Liverpool
Liverpool, UK

Tim Horn
HIV Project Director
Treatment Action Group
New York, NY United States

Sharadd Jain
Head, Global Institution Business for Formulations
Cipla
Mumbai, India

Andrew Kambugu
Head of Department
Research Program at Infectious Diseases Institute (IDI)
Makerere University College of Health Sciences
Kampala, Uganda

Arvind Kanda
Associate Vice President, Business Development
Mylan
Hyderabad, India

Bactrin Killingo
Africa Program Manager
International Treatment Preparedness Coalition (ITPC)
Nairobi, Kenya

N. Kumarasamy
Chief Medical Officer
YR Gaitonde Centre for AIDS Research and Education (YRGCARE)
Chennai, India

Geena Malhotra
Manager, Research and Development
Cipla
Mumbai, India

Simonia Mashangoane
Junior Researcher
Treatment Action Campaign
Ermelo, Mpumalanga, South Africa

Helen McIlleron
Associate Professor & Principal Investigator
Pharmacometrics Laboratory
Division of Clinical Pharmacology
University of Cape Town
Cape Town, South Africa

Meredith Moore
Director, Drug Access
Clinton Health Access Initiative
New York, NY United States

Paula Munderi
Clinical Research Fellow in Infectious Diseases
Division of Medicine of Imperial College London
London UK

Peter Ngang
Internal Medicine Department
Hôpital de la Caisse Nationale de Prévoyance Sociale
Toronto, Canada

Jeremy Nuttall
Director of Preclinical Development
International Partnership for Microbicides
Geneva, Switzerland

Rolake Odetoyinbo
Chief Executive Officer
Nigerian Positive Action for Treatment Access
Lagos, Nigeria

Andrew Owen
Professor and Researcher
Department of Pharmacology and Therapeutics
University of Liverpool
Liverpool, UK

Fernando Pascual
Medical Advisor
Medicines Patent Pool
Geneva, Switzerland

Anbar Pillay
Deputy Director
South Africa Department of Health
Pretoria, South Africa

Praphan Phanuphak
Director
Thai Red Cross AIDS Research Centre
Bangkok, Thailand

John Pottage
Chief Scientific and Medical Officer
ViiV Healthcare
Paoli, United States

Mphu Ramatlapeng
Executive Vice President, HIV/AIDS and TB
Clinton Health Access Initiative
New York, NY United States

Jim Rooney
Vice President of Clinical Affairs
Gilead Sciences
San Francisco, CA United States

Kim Shaffer
Public Health Consultant
Bill & Melinda Gates Foundation
Seattle, WA United States

Kenly Sikwese
Community Organizer
Treatment Advocacy and Literacy Campaign
Lusaka, Zambia

Anil Soni
Vice President, Healthcare Innovation Solutions
Mylan
New York, NY United States

Papa Salif Sow
Senior Program Officer in HIV Prevention and
Treatment Implementation
Bill & Melinda Gates Foundation
Seattle, WA United States

Alan Staple
Head, Originator Relations
Clinton Health Access Initiative
New York, NY United States

Nandita Sugandhi
Clinical Advisor
Clinton Health Access Initiative
New York, NY United States

Francois Venter
Deputy Executive Director
Wits Reproductive Health and HIV Institute
Johannesburg, South Africa

Marco Vitoria
HIV Expert
Department of HIV/AIDS
World Health Organisation
Geneva, Switzerland

Brenda Waning
Coordinator, Market Dynamics
UNITAID
Geneva, Switzerland

Secretariat

Ben Plumley
Chief Executive Officer
Pangaea Global AIDS Foundation
Oakland, CA United States

Benjamin Cheng
Managing Director
Pangaea Global AIDS Foundation
Oakland, CA United States

David Barr
Pangaea Senior Consultant
The Fremont Center
New York, NY United States

John Liddy
Program Manager
Public Health Consultant
Seattle, WA United States

Nikki Smith
Manager, Executive Office
Pangaea Global AIDS Foundation
Oakland, CA United States

Agenda

Conference on Antiretroviral Drug Optimization (II)
April 16 – 18, 2013, Cape Town, South Africa

Meeting Agenda

Objectives for the Meeting

- Develop mid- and long-term research priorities for HIV drugs and regimens in resource-limited settings
- Incentivize R&D innovation in an environment of diminishing industry investment
- Identify better, more affordable and sustainable treatments and regimens, in the context of a public health approach

Tuesday 16th April –*DAY 1: Can we do more with what we have now?*

Key Themes

- Goals: Promote minimal sequencing of maximally effective regimens
- Identify opportunities to improve on current regimens and treatment strategies

8:30 – 9:00	Breakfast & Registration
9:00 – 9:30	Welcome and Introductions *Charles Flexner, Johns Hopkins University* *David Ripin, Clinton Health Access Initiative (CHAI)*
9:30 – 10:00	Key Note Presentation: US Government Priorities for HIV Treatment in resource poor settings for the next decade *Ambassador Eric Goosby, PEPFAR*
10:00 - 10:30	Panel Discussion: What is the ideal target product profile for a first line regimen? *(Ben Plumley, moderator)* Overview: Charles Flexner, Johns Hopkins Medical Center Panelists: • Charles Flexner, Johns Hopkins • Papa Salif Sow, Bill and Melinda Gates Foundation • Morolake Odetoyinbo, PATA, Nigeria *Key Questions* • *What should we take for granted in a Target Product Profile?* • *What is a public health approach to defining a regimen TPP?* • *How should a Target Product Profile be affected by the current state of practice?* • *Is Atripla good enough? What will be the niche of alternative regimens using stavudine, abacavir or zidovudine?*

10:30 – 10:45 Break

10:45 – 11:15 What have we got to play with: What is in the ARV Pipeline?
Dave Ripin, CHAI

- *New compounds, pro-drugs, relevant dose optimization*
- *What are the scientific and policy challenges we face?*
- *Who are the key players, major investors, major researchers we will need to work with?*

11:15 – 11:45 Panel Discussion: What role will dose optimization play in the longer HIV Treatment Research Agenda? (*Ben Plumley and David Barr moderators*)

Panelists:

- Peter Ngang, Hôpital de la Caisse Nationale de Prévoyance Sociale (CNPS)
- Francois Venter, Wits Reproductive Health and HIV Institute (WRHI)
- Andrew Hill, Pharmacology Research Laboratories, University of Liverpool
- Sean Emery, Kirby Institute, University of New South Wales

Key questions:

- *Update on current research and expected dates for results (action)*
- *What other compounds should be prioritized?*
- *What role might dose increase play as well as reduction (e.g. rilpivirine)?*
- *Are there gaps in the R&D agenda over the medium term that can only be filled through dose optimization?*

11:45 – 13:00 Full group discussion: Developing target product profile regimens for resource limited settings: Where are opportunities for improvement?

- *What are the risks of changing from EFV/3TC/TDF? What are the criteria for recommending a change?*
- *How can the needs of special populations be addressed in the development and selection of target product profiles (e.g. pregnancy, TB, HBV/HCV)?*
- *Are there combinations that we want/need studies for prior to approval (e.g. TAF/FTC/EFV, dolutegravir combos, others?)?*

13:00 – 14:00 Lunch

14:00 – 14:30 Impact of Drug-based prevention modalities on HIV treatment approaches in resource poor settings: Balancing Pharmacologic Prevention and Treatment

Wafaa El Sadr, Columbia University

14:30 – 15:30 *Panel Discussion*: What constitutes the ideal regimen(s) after treatment failure (second & third line regimens)? (*Meg Doherty moderator*)

Panelists

- N. Kumarasamy, YRGCARE Medical Centre, Chennai
- Mphu Ramatlapeng, CHAI
- Peter Ngang, Hôpital de la Caisse Nationale de Prévoyance Sociale (CNPS)
- Helen McIlleran, Univ. of Cape Town
- David Cooper, Kirby Institute, University of New South Wales

Key questions:

- *What are the preliminary implications from the SECOND LINE study?*
- *Sequencing: Should we use our best drugs up front or save them for later?*
- *How do we make sure that increased use of monitoring tests like VL does not result in moving too many patients prematurely to 2L and beyond?*
- *What are the key concerns about potential drug interactions and how do these affect the development of a second-line TPP?*
- *How does treatment of concurrent diseases (e.g. TB, HBV, HCV) affect the development of a second-line TPP?*

15:30 – 15:45 Break

15:45 – 17:30 Full Discussion: Proposing recommendations for HIV treatment research for second-line and beyond drug and regimen development, in the contexts of treatment failure, toxicity management (*Nathan Ford and Meredith Moore moderators)*

- *What work is needed now after the results of ERNEST and SECONDLINE studies?*
- *How do we define treatment failure in public health treatment programs in resource poor settings?*
- *Should integrase inhibitors be protected for use in treatment failure?*
- *Which PI to prioritise – LPV, DRV or ATV?*
- *To boost or not to boost – is there still a role for ritonavir (dose reduced, generically produced…)*

17:30 – 17:45 Wrap Up Day 1: Co-Chairs

Reception & Dinner

Wednesday 17th April – *How will future developments alter the treatment landscape?*

9:00 – 9:05	Opening Remarks for Day 2: Co-Chairs: Factors affecting long-term prospects for HIV drug and regimen development
9:05 – 9:30	Presentation: Implementing and informing normative guidance for HIV treatment over the next five years: What does WHO see as research and development priorities? *Meg Doherty, WHO*
9:30 - 10:30	Panel and Full Group Discussion: Funding needs and priorities for HIV treatment and continued research. (*Charles Flexner and David Ripin moderators)* Panelists: • Christopher Duncombe , Bill and Melinda Gates Foundation • Martin Auton, Global Fund for AIDS, TB and Malaria • Anban Pillay, Ministry of Health, South Africa • Brenda Waning, UNITAID • Eric Goemere, Médecins Sans Frontières (MSF) *Key Questions* • *What do funders see as research priorities?* • *Lowering drug costs vs. better, longer-lasting regimens: what are donor priorities?* • *Do the resources currently exist to invest in the next phase of HIV treatment development? If not, how we do we mobilize them?* • *Do we have adequate resources to fund full treatment scale up?* • *What parties are missing from this discussion that might contribute resources / funding for this type of work?*
10:30 – 10:45	BREAK
10:45 – 11:15	Presentation: What potential role will novel formulations (nano-formulations and nanotechnology) play in HIV drug development designed for resource-limited settings? *Andrew Owen – Univ. of Liverpool*
11:15 – 11:45	Presentation: Injectables, devices, implants, slow-release delivery – what have we learned? What can we learn from other disease areas for new delivery mechanisms in resource-limited settings? *John Pottage, ViiV Healthcare* *Jeremy Nuttall, IPM*
11:45 – 13:00	Full Group Discussion: Novel formulations: What are the potentials and the problems? (*Ben Cheng and Paul Domanico moderators)* • *Are there any long acting formulations in the pipeline that could be relevant for resource limited settings? Would they be affordable?* • *How will potential novel HIV drug formulations affect treatment for concurrent diseases like TB, HBV, and HCV?*

- *What is known about the potential toxicities from long-acting and other novel formulations? How can these be managed?*

13:00 – 14:00 Lunch

14:00 - 15:00 Panel Discussion: Drug Development in Resource Limited Settings (*David Barr and Francois Venter moderators)*

Panelists:

- Bactrin Killingo, ITPC
- Paula Munderi, MRC Uganda
- Serge Eholie, Univ. of Abidjan
- Praphan Phanuphak, Thai Red Cross AIDS Research Center

Key Questions

- *How does development strategy for resource poor settings differ from traditional legacy pharmaceutical development?*
- *How should trials be designed and monitored in the era of treatment scale up?*
- *As treatment landscape changes and grows, how will we be reaching hard-to-reach populations?*
- *Can we save ourselves trouble/expense of doing studies through better post-approval surveillance?*

15:00 – 17:00 Full Group Discussion: Proposing the Key Components of future HIV clinical research in resource-poor settings

- How will we monitor success and toxicity?
- What information about current regimens is lacking because of inadequate monitoring?
- What data should we collect going forward to better answer these questions in the future?

17:00 – 17:15 Wrap-up Day Two (Co-Chairs)

Participants have evening off

Thursday 18th April – Public Health Contexts and Finalizing Research Agenda

9:00 – 9:05 Opening Remarks (Co-Chairs)

9:05 – 10:15 Panel Discussion: What partnership opportunities are there with the private pharmaceutical sector? (Ben Plumley, Dave Ripin moderators)

Panelists:

- Roger Pomerantz, Merck
- Marie-Pierre de Bethune, Janssen
- Jim Rooney, Gilead
- John Pottage, ViiV
- Anil Soni, Mylan
- Sharadd Jain, Cipla

Key Questions

- *Does the industry see the need for further R&D in HIV treatment?*
- *How can industry be incentivized to participate in HIV treatment R&D designed for resource poor settings?*
- *If Industry doesn't lead future HIV treatment research, what can it contribute? "Shelved" compounds? Know how?*
- *Can the generics industry expand its role in R&D as well as manufacture?*
- *What is the role of the public and NGO sector future drug development? Is there a future of not-for-profit drug development?*

10:15 – 10:45 Discussion

10:45 – 11:00 Break

11:00 – 12:00 Breakout Groups: Revisit and finalize recommendations developed from the last two days for the mid- to long-term HIV treatment research agenda

- Optimization of existing technologies
- Role of novel technologies in treatment optimization
- Addressing significant logistical and operational obstacles in drug optimization research in resource limited settings
- Strategies for implementing the treatment research agenda

12:15 – 13:00 Report Backs & Discussion (*Charles Flexner and David Ripin, moderators*)

13:00 – 13:30 Conclusions & Next Steps (Co-Chairs)

13:30 Lunch