



Pangaea Global AIDS

2015 Treatment Optimization Meeting Report

Vancouver July 17-18, 2015

Meeting Objectives

Chaired by Dr Tsi Tsi Apollo (Zimbabwe) and Dr Andrew Kambugu (Uganda) Pangaea, the Amsterdam Institute for Global Health and Development (AIGHD), Clinton Health Access (CHAI) and the International AIDS Society (IAS) convened an expert meeting to review the progress, gaps and future plans for HIV drug optimization since the second Conference on Antiretroviral Drug Optimization (CADO2) held in 2013. In particular, the perspectives of country implementers, researchers from the North and the South, innovator and generic pharmaceutical companies, funders, community and global normative guideline agencies were sought.

The meeting prioritized key actions that participants considered essential to bringing to people living with HIV in resource limited settings, effective, tolerable new drugs, formulations and timelines, and how to operationalize these as rapidly as possible. Participants also prioritized recommendations to optimize service delivery as part of the whole treatment optimization package. The recommendations of this meeting were presented at a formal conference session on treatment optimization during the 2015 IAS conference in Vancouver

As a key outcome of the meeting, Pangaea reiterated its ongoing commitment to continue monitoring and disseminating progress on all aspects of the treatment optimization agenda, including convening relevant experts where appropriate. In the light of the START and TEMPRANO results, growing global advocacy for treatment for all, significantly increased global and national resources to fund treatment will be needed. In this context, treatment optimization is an even more critical contributor to expanding the scope and quality of long-term HIV treatment.

Key recommendations

FIRST-LINE TREATMENT RESEARCH PRIORITIES

- The availability of a limited formulary of antiretrovirals (ARVs) will facilitate optimization of first-line therapy
- There should be two first-line choices: efavirenz (EFV) or dolutegravir (DTG) paired with tenofovir (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide fumarate [TAF]) plus

emtricitabine or lamivudine (FTC or 3TC, referred interchangeably as XTC).

SECOND LINE TREATMENT RESEARCH PRIORITIES

- CADO2 recommended that second-line therapy should include boosted darunavir (DRV) as the preferred protease inhibitor. There is a need to identify which booster (ritonavir [RTV] or cobicistat [COBI]) should be prioritized for use in a fixed dose combination.
- There is a need to clarify the optimal doses of DRV and RTV in a FDC.
- Potential manufacturers and purchasing agencies need to define volume needs to maximize further opportunities for cost reduction in the manufacturing of DRV.
- Research into fixed dose combination of DTG and boosted DRV as a key second-line option needs prioritization.
- Sequencing should be from an EFV-based first line to a boosted DRV plus DTG or recycled nucleosides in second line.
- Sequencing should be from a DTG-based first-line to a boosted DRV plus two nucleosides in second-line.
- Research is needed to evaluate if it is feasible for normative guideline agencies to recommend that RTV and cobicistat (COBI) are interchangeable.

DELIVERY and IMPLEMENTATION SCIENCE RESEARCH PRIORITIES

- Treatment optimization means optimization of drugs and service delivery to maximize retention in care.
- There is a need to incorporate research into improvements in delivery implementation and retention in care into the treatment optimization agenda, particularly as it relates to efficiencies and improvements through “differentiated care” models.
- The meeting participants called on WHO to clearly articulate what research is needed to make guideline recommendations.

First-line

We have efficacious first-line drugs now and better drugs becoming available, which have the potential for improved tolerability and reduced cost. While a single EFV-based fixed dose combination for almost everybody with HIV has been a remarkable public health achievement, it needs to be rethought based on the data that we currently have available. The concept of a limited formulary of first-line drugs with two choices, either DTG or EFV (at whatever dose is finally decided), paired with TDF and either FTC or 3TC was supported by meeting participants. TDF and TAF were considered interchangeable for this formulary exercise. The limited formulary was thought to be programmatically feasible even as we move to more decentralization and task shifting. A simple algorithm could guide providers in the choice of regimen. The appropriateness of switching from EFV to DTG was discussed. The scale down of stavudine (d4T) was driven by side effects and any possible scale down of EFV does not have the same level of urgency, as millions of people around the world are stable on an EFV-containing regimen. How to potentially switch people from ERFV to DTG is therefore an open question. A possible scenario is that all those who are stable on the EFV could remain on that regimen, those with tolerability issues be switched and those initiating antiretroviral therapy (ART) for the first time could start the DTG

(especially those with high CD4 counts and no HIV-related symptoms) who may benefit from the benefit from the better tolerability of DTG.

In terms of first-line drug optimization, there are three bodies of work around DTG, EFV 400 mg and TAF. Studies are ongoing to examine the efficacy and tolerability of DTG in access markets with a particular focus on its use in pregnancy and HIV/TB coinfection. It was predicted that the cost of DTG would be the same or less than currently available regimens. A study is ongoing to examine the use of EFV 400 mg in pregnancy and funding is needed to study it in HIV/TB coinfection. The group decided it would be important to discuss further with Gilead its development plans for TAF in both the commercial and access markets. Boosted versus unboosted TAF, access to PK/PD data and use of TAF in pregnancy and people with HIV/TB co-infection were highlighted by the group as issues relevant to resource limited settings.

Second line

While currently only 5% of people in low- and middle-income countries (LMIC) are on second-line, this will increase as more treatment failure is diagnosed especially as viral load monitoring is rolled out. DRV was approved in the US in 2006 but is still not widely available in LMIC. Reasons include that DRV was registered as a third line drug only in some LMICs and the lack of an FDC, which is expected to change at the beginning of 2016. Approximately 17 LMICs have now filed for DRV approval. The group heard that the science of the superior efficacy and tolerability of DRV over lopinavir (LPV) and atazanavir (ATV) was not reflected in 2013 WHO guidelines, which do not list DRV as a preferred protease inhibitor because of cost. The group called on WHO recommend DRV as the preferred protease inhibitor. The use of RTV and COBI for DRV was discussed. RTV is widely used in LMICs but COBI is not. Formulating a DRV/RTV single tablet is difficult. Even though the dose of RTV is 100mg milligrams the addition of excipients brings the total milligrams closer 500-600 mg tablet, which is too large to swallow. The group called for research is to evaluate if it is feasible for normative guideline agencies to recommend that RTV and COBI are interchangeable. COBI can only be used in once daily regimens and RTV needs to be the booster in pediatric formulations of DRV. A new second-line regimen of DTG plus boosted DRV is in development. In addition to improved tolerability, this regimen simplifies sequencing from two ARV classes in first-line to two new classes in second-line with improved efficacy compared to the current standard of care of recycling nucleosides from first line into second line. DTG has a clear role in both first- and second-line regimens.

Sequencing

Whatever regimens are used, sequencing within the public health approach requires that first- and second- line be considered as sets of treatment. If a DTG-based regimen is used in first-line, a boosted protease inhibitor plus two nucleosides would be used in second-line. If an EFV-based regimen is used in first-line, second-line would be a boosted protease inhibitor plus DTG.

Randomized Clinical Trials and Implementation Science

There are two options in the introduction of a new first line regimen; conduct a randomized clinical trial (RCT) of a DTG-containing regimen versus standard of care in LMICs or to monitor the global population rollout in the same settings. The group favoured the latter. There are programs such as MaxART in Swaziland, the programs of MSF, AMPATH and others that may have the capacity to monitor the efficacy of the new regimen and conduct the necessary pharmacovigilance in these settings.

Delivery

Treatment optimization needs to go beyond the optimization of drugs and include the optimization of service delivery and the strengthening of health systems and community systems to accommodate the continuing scale up of ART in an environment of treatment for all those who are ready to start lifelong ART irrespective of this CD4 count. Less than 30% of people diagnosed with HIV infection in resource limited settings navigate the full cascade of care. [Rosen, Mugglin] The delivery of HIV care in the initial rapid scale-up of HIV care and treatment was based on existing clinic-based models, which are common in highly resourced settings and largely undifferentiated for individual needs. A new framework for treatment based on the specific needs of different groups of individuals across the cascade of care is needed. Differentiating the service needs of those who are unwell and those who are stable on ART and where and how those services are delivered is key to maximizing treatment outcomes. Based on consultations with countries and experts, UNAIDS estimates that 95% of HIV service delivery is currently facility based. Further, UNAIDS projects that increasing community-based service delivery to at least 30% of total service delivery will not only reduce costs but, by bringing services closer to the people who need them, improve service uptake and retention in care.

Addendum

CADO2 recommendations

- Conduct studies of first-line combinations that are equally or more potent and more durable and affordable than current standard of care
- Conduct studies to identify improved second-line regimens, particularly dose-optimized DRV to replace ATV and LPV
- Develop a one pill once daily second-line regimen
- Study reduced dose DRV/r
- Clinical trials should reflect the characteristics of people in treatment access programs, including girls and women of reproductive age, TB co-infection, and comorbidities
- Engage private sector developers and manufacturers to use their expertise in drug development and large-scale manufacture.
- Continue research into the use of oral and injectable long-acting drugs

Progress since CADO 2

First line:

ENCORE study results demonstrate benefits of EFV(400) over EFV(600)

- FDA has indicated willingness to review based on ENCORE
- 1st FDC filing anticipated beginning of 2016
- Studies to demonstrate EFV(400) in pregnancy and TB co-infection being organized

DTG approved as superior alternative to EFV(600)

- First generic filed April 2015, others to follow
- FDA has indicated willingness to approve FDC formulations of DLG with TDF/XTC as per FDC guidance
- FDCs under commercial development

TAF filed with FDA as boosted and unboosted dosages

- Some question as to whether there will be sufficient evidence to support WHO guidelines inclusion at unboosted dose at time of approval

Second line:

DRV/r/DLG studies under discussion (participants to update us)

- FDA has indicated willingness to approve FDC formulations of DLG with ATV/r, DRV/r as per FDC guidance

Dose optimization of DRV/r under discussion (participants to update us)

1st DRV/r (800/100) FDC filing anticipated beginning of 2016 (as 400/50 tablet)

Process chemistry work to demonstrate potential for price parity of DRV/r (800/100) with LPV/r (800/200)

Around the room

On day 1, participants representing their institutions were asked to report on progress they had made on treatment optimization since CADO2, their perspective on gaps and barriers to continue treatment optimization and their future plans.

AFROCAB

AFOCAB advocates for both treatment access and treatment optimization, including the importance of including social research in clinical research. Pangaea supported AFROCAB members in implementation science training. i-Base and CHAI have provided training to AFROCAB on treatment optimization.

Gilead

Gilead has supported the rollout of WHO recommended first-line ART by working with regional business partners to provide ARVs at discounted prices in access markets and working with generic licensing partners in India and South Africa to produce generic ARVs for sale in LMIC.

In 2014, 7.3 million LMIC were receiving Gilead ARVs, more than 98% of which were made by generic partners. Gilead reported that their global access program for ARVs has been a success and could be used as a model for other ARVs in the future. The company's development plans for new ones are summarized in figure 1.



Bill and Melinda Gates foundation

Bill and Melinda Gates foundation has focused on optimizing product manufacture and reformulation process and manufacturing chemistry. Work has been conducted on the efficiencies of flow chemistry compared to batch chemistry and efforts to reduce the cost of synthesis of TDF, DRV and TAF. The foundation stressed the need for better understanding of HIV drug resistance, models of service delivery, qualitative rather than quantitative thinking in clinical trial design and development, the optimum use of diagnostics, and how to improve adherence and data systems.

ViiV

DTG was approved for use in developed countries two years ago and is now available in 48 markets. A FDC of DTG and abacavir was approved one year ago. ViiV is currently conducting studies of DTG in pregnant women and people with HIV/TB co-infection, a switch study of LPV to DTG in second line therapy and is working on long-acting injectable versions of DTG and rilpivirine (RPV). ViiV is also developing a new integrase inhibitor, Cabotegravir (GSK1265744) and is conducting a phase III trial, in partnership with Janssen, of the two-drug regimen (DTG and RPV) for maintenance therapy for those who have already achieved viral suppression.

Zimbabwe National HIV Program

Zimbabwe has a HIV prevalence of 15% and 820,000 people are receiving ART. The country has almost completed a phased three-year introduction of the 2013 WHO guidelines with most people receiving TDF/3TC/EFV and d4T phased out. Zimbabwe currently has a \$70 million funding gap for its HIV program and, with the numbers of people on treatment are expected to increase to 1.4 million if the world

moves to treating everyone with HIV, costs need to be reduced. Newer ARVs models of service delivery would be welcomed in the national program if they can improve tolerability and reduce cost. Studies of new drugs are needed in populations in LMICs especially where there is a high incidence of tuberculosis. High quality programs are the key to keeping people in care need and treatment optimization must include drug optimization treatment and systems and delivery optimization.

Infectious Diseases Institute and Uganda National HIV Program

Uganda is implementing 2013 guideline changes in addition to the national rollout of viral load monitoring using specimen transport and central laboratories. A priority for the country is implementation science research, especially related to retention and adherence for people starting ART early and the importance of disclosure to partners and family in improving adherence and retention. A substantial investment is needed in data systems, which are currently weak, to measure the impact of ART scale up.

Clinton Health Access Initiative (CHAI)

CHAI has continued development of TDF (xb), a potentially more bioavailable formulation of TDF that would provide equivalent exposure to TDF with a lower mg loading of the tablet. Data from the study should be available in August. CHAI has provided support to several partner organizations progressing drug optimization research and development including support for approval and commercialization of an EFV (400) containing FDC, generic submission of DTG, and commercialization of a DRV/r FDC.

The Wits Reproductive Health and HIV Institute (Wits RHI)

Wits RHI is conducting the controversial low-dose d4T treatment optimization study, which is scheduled to finish in December 2015. With half of the approximate 1,000 participants in the study are receiving TDF and being monitored for renal and bone toxicity, the study will provide unique data on the use of TDF in an African population. South Africa plans to replace LPV in second-line therapy with DRV and the South African government is sponsoring a study of people who are undetectable on a LPV-containing regimen switching to low-dose DRV (600mg boosted). 48-week data for this study should be available by the end of 2016. An important challenge has been the recent stock outs of all ARVs in South Africa with the exception of generic TDF/3TC/EFV underscoring the importance of FDCs not only for adherence but also for supply chain management.

HIV i-base

i-Base published “Fit for purpose: antiretroviral treatment optimization” in 2014 and 2015. In partnership with the University of Liverpool, Makerere University and ViiV, i-Base supported the *DOLphin* trial of DTG in pregnant HIV mothers and neonates. The trial is examining pharmacokinetics of DTG in pregnant women in the third trimester and post-partum during breastfeeding. Sites in Uganda in the phase II investigator-led study are in the final stages of preparation. i-Base also supported CHAI in the TDF reformulation work stream and SSAT ‘s EFV 400 mg PK study in pregnant women.

St. Stevens AIDS trust (SSAT)

SSAT acknowledges that the 90/90/90 targets are audit targets of the quality of HIV care and has been working on health systems strengthening to assist countries in African to meet the targets. SSAT is conducting a pharmacokinetic study of EFV in pregnancy in collaboration with Mylan.

Treatment Action Group (TAG)

TAG focuses on the epidemic in the USA. It has identified unboosted TAF as a potential gap in the development of the drug. TAG has worked with Gilead and US regulators to prioritize unboosted TAF for use in LMICs. TAG is a member of the community advisory board for the TDF reformulation work with CHAI funded by Bill and Melinda Gates Foundation.

Mylan

Mylan produces ARVs for access markets process chemistry. The company is using process chemistry of to lower the cost of FTC, which now has price parity with 3TC. Mylan has invested \$250 million in generic ARV manufacturing plants. Mylan worked with Bill and Melinda Gates foundation on the distribution point-of-care CD4 technology but that work has now stopped. The company is funding the PK study of low-dose EFV in pregnancy and plans to file for approval of low dose EFV in 2016. Mylan called for a limited formulary of first line ARVs so the manufactures can produce high volumes at the lowest cost.

Janssen

In January 2015, the US FDA approved a fixed-dose combination of DRV 800 mg and COBI 150 mg. Janssen is developing a co-formulation of DRV/r for children. The company is also supporting a trial of DRF/cobicistat/FTC/TAF as single-tablet regimen, the use of long acting RPV for prevention and treatment, studies of a 2 drug ARV regimen for maintenance therapy, the use of DRV with rifampicin and ways of reducing the cost of DRV. Janssen supports disease management platforms designed to make databases available to local researchers and to ensure that viral load results are returned to clinics.

Merck

Merck is exploring the use of raltegravir (RAL) in different populations, including coinfection with TB and HCV, aging populations and women. RAL has been approved for use in children over four weeks of age. Merck has signed agreement with the Medicines Patent Pool (MPP) to facilitate access to RAL for children. The company is developing a new NNRTI, doravirine, active against EFV and nevirapine (NVP) resistant viruses.

International Center for AIDS Care and Treatment Programs at Columbia University (ICAP)

ICAP acknowledges that the keys to achieving impact are high coverage and high quality program and is working to enhance coverage and quality of programs across the cascade through quality improvement activities with Ministry of health partners. ICAP is conducting population based impact assessment in 12 countries with US CDC using household sampling of HIV incidence, prevalence, CD4 count and viral load. The survey has been completed in Swaziland and is ongoing in Malawi and Zimbabwe. ICAP stresses the importance of implementation science to examine multiple interventions across the cascade of care and identify pockets of substandard care. It is also working with PEPFAR to scale up viral load monitoring and to understand the current underutilization of second line ART.

International Treatment Preparedness Coalition (ITPC)

ITPC works to ensure that the consumers of products (ARVs) have enough the knowledge to contribute to treatment optimization discussions and that civil society is actively involved in the development of

the research agenda through treatment education and literacy. ITPC participates in policy decisions around stock outs, human rights, price reduction and intellectual property.

Botswana National Program

The national HIV prevalence rate among adults aged 15 to 49 in Botswana is 21.9%, the second highest in the world, after Swaziland. As a middle-income country, Botswana faces funding challenges with increasing national funds required for its HIV response. 40% of patients are receiving AZT/3TC based ART, not a WHO preferred regimen. The country has integrated HIV into primary care, but more than 20% of the population having to visit a clinic every month for HIV care is not sustainable and there is an urgent need to scale up community-based care. Botswana would welcome the introduction of newer better ARVs.

INSERM International Research Center

Founded in 1964, the French National Institute of Health and Medical Research (INSERM) is a public scientific and technological institute, which operates under the joint authority of the French Ministry of Health and French Ministry of Research. INSERM conducted the ground breaking *TEMPRANO* study that found that starting HIV treatment at a CD4 cell count > 500 cells/mm³ reduced the risk of serious illness including tuberculosis and death by 44% when compared to starting treatment CD4 cell count < 500 cells/mm³. It is also conducting studies of HIV-2 infection. With weak health care systems in much of West Africa, INSERM is focused on program and monitoring optimization. Still most people are late presenters and there is a need to differentiate treatment optimization for early presenters, late presenters and people who are stable on treatment.

WHO

There are now 15 million people on treatment globally but still 2 million new infections per year. We have a single first-line FDC available in every country in the world, which can be taken by all those infected with HIV above the age of 10 years including pregnant women and people co-infected with TB. This is an ideal regimen for the WHO public health approach to the delivery of care. Individualized approaches and choices have some risks as we learned from pediatric world which has multiple and fragmented regimen choices. With moves to introduce choices into adult ART, there is a need to continue to harmonize adult and paediatric regimens. There is an urgent need to rethink how services are delivered as continued to scale up occurs and WHO supports differentiated/adaptive care which provides care in clinics for those who needed and care in communities for those who are stable on treatment. The meeting participants discussed the need for WHO to clearly articulate what research is needed to make guideline recommendations.

Gaps and Actions needed for Optimization of Key ARVs

(Source i-Base/TAG 2014 Pipeline Report, adapted from Marco Vitoria. Global Access to New HIV Therapies WHO June 2014)

OPTIMISED STRATEGY	TOLERABILITY	RESISTANCE	CONVENIENCE	PW, TB, CHILDREN	COST REDUCTION	ACTION NEEDED	ESTIMATED TIMELINE (YEARS)
Low dose EFV	√	?	√	?	√	PK studies (PW and TB)	1-2
Low dose DRV/r	√	?	√	?	√	PK studies (titration of best DRV:RTV ratio) RCT (comparative studies standard vs low dose)	2-5
Use of DTG	√	√	√	?	√	Studies in PW, TB and children Comparative trials (TDF/TAF) first line RCT (DRV/r+DTG second line)	2-5
Use of TAF	√	?	√	?	√	Comparative trials using DTG Studies in PW, TB and children	2-5
Long-acting formulations	√	?	√	?	√	Phase II/III studies (treatment and preventative)	>5

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The meeting and this report were funded by Pangaea. We are enormously grateful to all our supporters who provide unrestricted funding, particularly the Chevron Corporation, who enable us to carry out our work