

# OPTIMIZE

This is a monthly update shared with all members involved in OPTIMIZE, and is meant to provide a short update of major achievements, challenges, and plans for the future. Please submit any inputs to Celia Serenata before the 1<sup>st</sup> Wednesday of every month.

## MAJOR ACHIEVEMENTS FROM MARCH 2017

### LOW-DOSE DARUNAVIR STUDY, Wits RHI

- As of end March, there were 316 participants screened and 258 enrolled in the low-dose DRV (WRHI052) study
- Retention to date:
  - Visit 1 completed = 225 expected/ 224 completed (100%)
  - Visit 2 completed = 163 expected/ 163 completed (100%)
  - Visit 3 completed = 96 expected/ 94 completed (98%)
  - Visit 4 completed = 12 expected/ 12 completed (100%)
- Upon review of the recruitment plan and discussions to achieve the enrolment target by May 2017, Themba Lethu (a high-volume ART clinic) was identified as an additional recruitment site. Institutional approval was granted on 15 March to enable recruitment of participants from this clinic. A presentation of the study was provided to participants in the pharmacy waiting area within the clinic and general levels of interest and enthusiasm were created by this effort.
- Wits RHI has been working with Dr. Andy Hill (an independent biostatistician) to prepare the data for first interim analysis, which will be presented to the DSMB on 26 April. The data tables have been finalised and reviewed; only minor edits were required.

### ADVANCE STUDY, Wits RHI

- As of 31 March, we had screened 148 participants, of which 131 were eligible for study entry, and 113 have been enrolled.
- Due to the increase in the participant accrual rate, 2 additional clinicians have been recruited and have received regulatory approval; the 3<sup>rd</sup> clinician is awaiting approval.
- The statistical analysis plan has been reviewed and will be finalised by mid-April for submission to DSMB.



## Upcoming Events

8 April: Southern African HIV Clinicians Society session on ART Optimisation – Prof Venter will present on OPTIMIZE

26 April: DSMB meeting (presenting ADVANCE, WRHI052 and SSAT062)

## Important Contacts

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- The ADVANCE pamphlet received regulatory approval on 22 March. The pamphlet was designed as a tool to aid in recruitment of adolescents, due to the challenges in recruitment of this vulnerable population, particularly around the legal age of consent to participate in a clinical study.
- The CRO performed the second monitoring visit from 27 – 31 March; monitoring findings will be addressed within the month of April.
- Protocol Clarification Memo #2 was submitted for regulatory approval on 24 March. The memo clarified details regarding mental health, sleep questionnaires, neuropathy screen, actigraphy, assessment of PK levels on participants who fall pregnant and consent to remain in the study, assessment of PK levels on TB-infected participants, and the window period for performing DEXA scans.

#### ***EFAVIRENZ 400mg TB PK STUDY (SSAT062), Mylan (St. Stephen's AIDS Trust)***

- Study has recruited half of all participants: 14 enrolled and 2 withdrawals. An additional 2 participants have baseline visits planned, with another 3 screening visits booked (all in UK).
- Recruiting for this study is challenging.
- Preliminary UK data to be analysed in April 2017.
- April data and revised version of protocol will then be submitted to Uganda authorities.
- Aim is to submit abstract for CROI 2018.

#### ***TAF-RIF TB PK STUDY (RIFT), St. Stephen's AIDS Trust<sup>1</sup>***

- Site initiation visit booked for 13 April
- Approvals:
  - Medicines and Healthcare Products Regulatory Agency (MHRA) approval received
  - Research Ethics Committee (REC) conditional approval received, revised protocol and updated informed consent form submitted in response
  - Health Research Authority (HRA) approval still pending

#### ***DTG-RIF TB PK STUDY (RADIO), St. Stephen's AIDS Trust***

- SSAT team kick-off meeting completed
- Protocol in development and essential documents being drafted
- The SSAT Project Manager role is transitioning to Charlotte Alcock, who is also the current manager for the RIFT study

#### ***EFAVIRENZ 400mg PREGNANCY PK STUDY (SSAT063), Mylan (St. Stephen's AIDS Trust)<sup>2</sup>***

- 23 participants have been enrolled – 15 in Uganda and 8 in the UK.
- Recruitment has now officially closed in the UK. Currently screening additional women in Uganda to reach the target of 25 participants.
- Late-breaker abstract is being planned for IAS 2017.

#### ***NANOTECHNOLOGY, University of Liverpool***

- *In vivo* work completed on Darunavir, but requires further optimization of the data

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<sup>1</sup> Funded by Gilead, not OPTIMIZE

<sup>2</sup> This study is not funded through OPTIMIZE, but is included here as a point of interest

- Atazanavir experiments both *in vitro* and *in vivo* planned and cell lines growing

## **MARKET ACCESS AND PRODUCT INTRODUCTION, ICAP**

### *Country-level Activities:*

- South Africa: Needs assessment completed. Final version to be formatted and shared.
  - Mozambique: Interviews for needs assessment are ongoing. ICAP met with USAID and conducted an interview for the needs assessment.
  - Kenya: Conversations are ongoing with NASCOP and other stakeholders regarding the plan for phasing-in DTG-based regimens. Discussions took place around the specific patients who would be eligible for DTG-based regimens and the counties where initial phase-in would take place. ICAP drafted version 1 of the circular that will be shared with facilities when the DTG transition starts. The plan is to introduce DTG at high-burden facilities in high-burden counties. The current plan is for the following patient groups to be prioritized:
    - Current patients on TDF/3TC +NVP prioritized
    - Current patients on PI-based 1<sup>st</sup> line ART
    - Patients with neuropsychiatric illness and not able to tolerate EFV-based regimens
    - New patients with contraindication to EFV
    - Use in 3<sup>rd</sup> line and other non-standard regimens
- A 'Situation analysis' (needs assessment) is ongoing in Kenya. An initial draft is being developed based on desk research and existing knowledge as we wait for interviews to be conducted after as non-human subjects designation received from KEMRI.
- Zimbabwe: Meetings with USAID ongoing to get formal approval to conduct the needs assessment.

### *Enhanced Monitoring*

- ICAP met with NASCOP, USAID, and CHAI in Kenya to introduce Optimize, specifically the activities related to enhanced monitoring in the context of the ongoing DTG phase-in.
- Initial planning conducted on how enhanced monitoring can be done using existing M&E systems.
- Internal draft of a protocol has been developed for the enhanced monitoring project and is currently undergoing review at ICAP.

## **MARKET ACCESS, Medicines Patent Pool (MPP) and Mylan**

- Mylan received tentative FDA approval for its TLE product (TDF/Lamivudine/Efavirenz) on 10 March 2017. (See more information in the CHAI update below).

## **DEMAND CREATION AND COMMUNITY ENGAGEMENT, HIV i-Base**

- *HTB South* printed and distributed with the *Southern African Journal of HIV Medicine*
- Conducted treatment training with the TAC in Johannesburg, including briefing on ADVANCE and other ART optimisation studies
- Held a planning workshop with the TAC to develop new materials for the TAC trainers, including: a community guide to the ADVANCE study (including FAQs); and update of *HIV in Our Lives*, and a less technical version of *Fit for Purpose*
- Updated the organisation GroundUp on ADVANCE and ART optimisation studies

- Held planning meetings with TAC, Wits RHI, and SAHCS in Johannesburg
- Researched flights and hotel accommodation for the community advocates for the training linked to INTEREST and IAS (May and July 2017) – booking as soon as funds are received

## **COMMUNITY ENGAGEMENT, TAC**

### *Update Treatment Literacy Materials*

- HIV i-Base was instrumental in assisting TAC in updating its HIV treatment literacy materials, including training the 7 TAC provincial trainers on ART optimisation, including the future of DTG and TAF. The training also included in overview of OPTIMIZE, including the different clinical trials underway. Other topics included:
  - Project deliverables, tools and responsibilities
  - Communication strategy and protocol
- The provincial trainers now have to develop provincial training plans (to be finalised before Q3).
- During the TAC training HIV i-Base shared the *Fit for Purpose 2017* distributed during CROI 2017. The TAC provincial trainers made some suggestions for edits to make it a document that could also be used by TAC at provincial and lower structures.
- TAC and HIV i-Base is also collaborating on developing FAQ sheets and manuals for the community based on the inputs during the March training.
- The *HIV in Our Lives* training materials was reviewed for its relevancy in 2017 and the future. Polly Clayden is working with TAC on updating these materials.
- A follow-up meeting between TAC and Polly Clayden on 23 March will finalise plans for:
  - Training of the Wits RHI Treatment CAB – contents
  - Aligning the TAC and HIV i-Base calendar on project deliverables
  - Confirming project activities and schedules

### *ADVANCE recruitment in Region F*

- The TAC engaged in building a working relationship with the different facilities in Region F (Johannesburg) from which ADVANCE is recruiting, through engagement with Wits RHI staff to facilitate introduction to clinics. Working through the Wits RHI liaisons is the best way to engage with the Region F facilities.

### *Operations*

- TAC and SAHCS are meeting soon to discuss the HCW activities that were planned for Q1 and Q2.

## **CLINICIAN/HEALTH WORKER ENGAGEMENT, Southern African HIV Clinicians Society**

- The Clinicians Society Expert Committee is now in place.
- Continuous medical education (CME) training modules designed, dates set, and venues booked. The first CME training is set for 8 April in Johannesburg (to date 82 people confirmed attendance). Cape Town and Durban are booked for May. [Prof Venter from Wits RHI will talk about ART optimisation at the Johannesburg session].
- SAHCS met with Polly Clayden on 21 March to finalise the healthcare worker (HCW) materials and FAQs.

- SAHCS to schedule a meeting in April 2017 (through Vusi Sibeko) to begin training the Wits RHI Treatment CAB
- Existing SAHCS trainings are being updated to include ART optimisation.
- *HIV Nursing Matters* articles are being collected and reviewed for print in April.

## **OPTIMAL ARV PROJECT, CHAI**

CHAI receives a complementary grant from UNITAID focused on ARV optimisation, called OPTIMAL. CHAI will share a quarterly update on their activities. CHAI already collaborates with ICAP on enhanced monitoring, and with Wits RHI in South Africa on DTG introduction.

### ***Demand Side Updates***

#### **CHAI-UNITAID Optimal ARV Community Advisory Board (CAB)**

- CHAI is collaborating with the African Community Advisory Board (AfroCAB) and HIV i-Base to establish the Optimal ARV CAB, which will inform CHAI's demand-generation and community engagement strategy for new products.
- Representatives from each of the seven focal countries and regional representatives from West Africa have been selected. An official kick-off of the board will take place in Senegal on April 11-12.

### **Catalytic DTG Procurement**

- To accelerate uptake of DTG and build a market in anticipation of the launch of TLD, in late 2016 CHAI and UNITAID partnered with country governments in Kenya, Nigeria, and Uganda as well as global procurement partners to develop a limited, catalytic procurement initiative.
- CHAI is supporting the rollout strategy and transition planning for the catalytic DTG procurement in Kenya, Nigeria, and Uganda.
  - Kenya: NASCOP is preparing to roll out the initial shipment of 5,000 packs from ViiV, set to arrive in early April, with an initial focus on a small number of sites where enhanced implementation monitoring will take place. With the 150,000 pack order from Aurobindo expected in May, broader scale-up is expected to begin then. The official launch of the catalytic DTG initiative in Kenya will only take place once this next, significant tranche of DTG has been delivered and is ready for use in the designated sites. NASCOP is preparing a communiqué on new products phase-in planning, including DTG, as a supplement to the guidelines. Patient literacy materials on DTG will be developed, and there are plans to sensitize facility staff on pharmacovigilance and tools.
  - Uganda: CHAI supported the MOH to develop a protocol for enhanced monitoring of patient and provider acceptability of DTG. The protocol is in ethics review and the studies are expected to start in mid-2017. The 2017 ART Guidelines were formally launched in January and regional meetings to disseminate the new guidelines were held in February. National Training of Trainers is ongoing, regional trainings will commence in April and facility level trainings are scheduled to start in May.
  - Nigeria: CHAI supported the MOH to develop a protocol for enhanced monitoring of patient and provider acceptability of DTG. The protocol is in ethics review and expected to start in mid-2017. The product introduction roadmap for new products in

the 2016 National Guidelines was developed and will be formally adopted at the next National Quantification meeting. CHAI developed job aides for the new guidelines rollout that will double as DTG product introduction materials for health workers.

### **Product Uptake and Demand Generation**

- CHAI continued the demand generation and new product introduction rollout work in early 2017 with a focus on new first-line adult products DTG and TLE400, due to their upcoming availability, and paediatric products ABC/3TC 120/60 mg and LPV/r pellet introduction and rollout.

### **South Africa Tender**

- CHAI is continuing to work with the NDoH in South Africa to support product adoption decisions to ensure rapid access to optimal products for patients, and provide cost savings for the NDoH and supply security for the national ART program. CHAI supported NDoH in assessing their product priorities for the upcoming tender process as well as an assessment of tender extension scenarios to maximize new product registrations.

### **Supply Side Updates**

#### **DCGI Update**

- On March 6<sup>th</sup>, 2017, a stakeholder meeting was hosted in India by the Department of Commerce and Indian drug regulatory body to discuss the fast-track regulatory approval process for combination products for HIV, and other key infectious diseases. This was a follow-up meeting to the FDC meeting held in May 2016. In the follow-up meeting it was announced that there is now an approved a fast-track process to review and grant BE-NOCs & CT waivers for priority FDCs of HIV and other infectious diseases. The determination of priority status for FDCs will be based on input provided by the WHO, which will be updated on a frequent basis. The approval of this fast-track process has received green light from the various committees within the Indian regulatory system.
- As a next step, Indian generic manufacturers were requested to expedite submission of their regulatory dossiers for review. Another key topic discussed during the March 6<sup>th</sup> meeting was the need for clarity on Phase IV trials for products that receive approval through CT waiver. While no recommendation was made on Phase IV studies, industry representatives were requested to develop a brief note on issues related to Phase IV studies and the potential solutions. Since the stakeholder meeting on March 6<sup>th</sup>, CHAI has developed a TLD clinical waiver justification document and shared it with suppliers. This is to ensure there is a coordinated and common approach to CT waiver for TLD.

#### **TLE 400 FDA Approval**

- On Friday March 10<sup>th</sup>, the US FDA tentatively approved Mylan's TDF/3TC/EFV (300/300/400 mg) product, making it the first generic SRA approval for TLE400 through an innovative regulatory pathway resulting from collaboration between the FDA, the Kirby Institute, and CHAI. TLE400 offers some clinical benefits and cost savings in relation to TLE600 and its approval is an exciting step-forward. Clinical data on use in pregnancy and TB is not yet available, with pregnancy data anticipated in Q2 2017 and TB data in 2018.

CHAI is working with governments to consider product priorities and phase-in strategies in the context of TLD availability in late 2017.

## **OTHER**

- Prof Francois Venter was invited to participate in the Mylan South Africa HIV Advisory Board meeting held on 18 March in Johannesburg. During the meeting he provided an update on ADVANCE.
- Dr Michelle Moorhouse from Wits RHI provided the text for 16 text messages on treatment optimisation. These are sent out weekly to the members of the Southern African HIV Clinicians Society. [An example from the message on 3 April: HIV treatment optimisation is a process intended to enhance the long-term efficacy, adherence, tolerability, safety, convenience and affordability of combination ART with the goal of expanding access to well tolerated and effective lifetime treatment to all those in need.]

## **MAJOR PLANS FOR APRIL 2017**

### **LOW-DOSE DARUNAVIR STUDY, Wits RHI**

- Submission of the first interim data analysis to DSMB on 26 April

### **ADVANCE, Wits RHI**

- Recruitment of additional site support staff, and a research nurse
- Receipt and inventory of 6-monthly batch of TDF/FTC 300/200mg into the pharmacy
- Expecting feedback from the ethics committee (HREC) regarding the request for waiver of parental consent of adolescents 16-18 years old
- The age stratification has been clarified and the Nukleus participant management database will be updated to align participant randomisation at the 3 research sites
- Expecting regulatory approval for Protocol Clarification Memo #2 submitted on 24 March

### **NANOTECHNOLOGY, University of Liverpool**

- Completion of Darunavir optimisation and selection.
- Completion of Atazanavir *in vitro* experiments with a view for *in vivo* experiments being carried out end of April and throughout May.

### **MARKET ACCESS AND PRODUCT INTRODUCTION, ICAP**

#### *Country-level activities*

- Mozambique: Complete interviews for needs assessment. Draft needs assessment and share with stakeholders for review. Plan meeting with USAID and MOH post-needs assessment to discuss findings and role of OPTIMIZE going forward.
- Kenya: Continue to attend meetings around the planning for DTG phase-in, including refining plans for patients and location of initial phase-in, brainstorming around supply and demand information sharing platform (led by CHAI), commodity security meetings etc. Receive KEMIR designation of non-human subjects research for the needs assessment and initiate interviews for the assessment.

- Zimbabwe: Obtain USAID formal approval for needs assessment. Initiate desk research, interview planning, and ethics review for needs assessment if applicable.

### Enhanced Monitoring

- Meet with NASCOP's SI unit and the Pharmacy and Poisons Board to learn more about existing data systems which can be integrated into the protocol development; also integrate developments re: location and number of patients who will be eligible for DTG-based regimens into protocol.
- Continue internal review of protocol; share draft protocol with NASCOP for review, then USAID Mission and DC.
- Initiate development of tools to implement enhanced monitoring protocol.

### COMMUNITY ENGAGEMENT, TAC

- Develop advocacy strategy for civil society
- Provincial Head (Ms M Magagula) will formally introduce TAC's partnership with Wits RHI in connection with ADVANCE; a date for the introduction to be finalised. This is to assist with recruitment and information sharing at the facility level, and through patients disseminate this to the community level

### STAFFING CHANGES

- Dr. Maureen Syowai has been hired as the ICAP Regional Technical Coordinator for OPTIMIZE. She is based in Kenya and can be reached at: [msyowai@icapkenya.org](mailto:msyowai@icapkenya.org)
- Dr. Shobha Vakil has been hired as the ICAP Country Program Officer for OPTIMIZE in Kenya. She can be reached at: [svakil@icapkenya.org](mailto:svakil@icapkenya.org)
- ICAP identified a Product Introduction Coordinator to oversee product introduction activities. She will start next month.
- Dr. Firdaus Nabeemeeah and Dr. Tiego Masemola have been hired as clinicians on ADVANCE based at the CMJAH/Yeoville research sites, and have received regulatory approval as study clinicians.

### OUTPUTS

List any articles, manuscripts submitted for review; abstracts submitted; presentations given. (Also provide electronic version of such products for the Dropbox – see

[https://www.dropbox.com/home/OPTIMIZE/TechnicalSteeringCommittee/Calendar+Events](https://www.dropbox.com/home/OPTIMIZE%20TechnicalSteeringCommittee/Calendar+Events))

- 11 March: Dr Michelle Moorhouse gave a talk on TAF for CIPLA
- 22 March: Dr Michelle Moorhouse gave a lecture to medical students at the Wits Medical School which included a section on treatment optimisation
- 24 March: Prof Francois Venter presented on ADVANCE and the future of 1<sup>st</sup> line ART at the Themba Lethu Clinic (Right to Care) HIV Masterclass

### Papers in process

- Venter WDF. A Complex but Exciting Future: New Options for Second-Line Antiretroviral Therapy. Current Tropical Medicine Reports. In press.

- Venter WDF, Clayden P, Serenata C. The ADVANCE Study: A Groundbreaking Trial to Evaluate a Candidate Universal Antiretroviral Regimen. Current Opinion in HIV and AIDS. Estimated publishing date end June/early July.
- Serenata CM, Gouws H, Grab J, Moorhouse M, Maharaj E. Optimising ART in the 21<sup>st</sup> Century. HIV Nursing Matters. Estimated publishing date May.

## **MEDIA COVERAGE**

- None since the last update

## **USEFUL WEBSITES**

USAID page on ART optimisation: <https://www.usaid.gov/what-we-do/global-health/hiv-and-aids/technical-areas/antiretroviral-therapy-optimization>

UNITAID page on ART optimisation: In process