

# OPTIMIZE

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*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.*

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## MAJOR ACHIEVEMENTS FROM FEBRUARY 2017

### LOW-DOSE DARUNAVIR STUDY, Wits RHI

- As of end February, there were 276 participants screened and 224 enrolled in the low-dose DRV (WRHI052) study
- Recruitment strategies continue to be reviewed and amended where necessary to improve participant numbers. We aim to add a new high-volume recruitment site in March.
- Retention to date:
  - Visit 1 Completed = 210 expected/208 completed (99%)
  - Visit 2 Completed = 154 expected/153 completed (99%)
  - Visit 3 Completed = 77 expected/76 completed (99%)

### ADVANCE STUDY, Wits RHI

- ADVANCE has rapidly taken off in February, with the first participant enrolled on 1 February.
- As of the last week of February (3 March), we had screened 98 participants, of which 90 are eligible for study entry, and 53 have been enrolled. This has exceeded the monthly accrual projections. Because of this, the human resource needs have escalated significantly.
- Site 03 (Shandukani) was activated on 8 February 2017. The recruitment team is actively screening for adolescents, and will also manage the care of participants who become pregnant after enrolment, and opt to remain in the study.
- The recruitment activities for ADVANCE will be further supplemented by the existing relationships created by the Wits RHI Health System Strengthening team, and other local projects, through a referral process.
- Forward planning and procurement for the next 6-monthly batch of study drugs has been executed, with deliveries of some (those procured) estimated in late March 2017.



### Upcoming Events

13-17 March: TAC training and update of treatment literacy materials (TAC and HIV i-Base)

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- Site 01 (Yeoville) had their first monitoring visit from the CRO (Triclinium) from 15-16 February; site personnel effectively managed to accommodate 3 clinical research associates (CRAs) during this visit, and the monitoring visit report has been submitted.

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

- Recruitment is on track. The study has recruited half of the participants, and still aim to have the last participant first visit in May. To date 15 participants have been screened, 11 enrolled, and 1 withdrawal.
- A protocol steering committee will have a call on 13 April
- Preliminary data will be submitted for WHO in late May/early June
- Abstract will be submitted for CROI 2018 (deadline is 1 October 2017)

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

- The study is on track, with a start-up meeting planned for 13 April.

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

- Still finalising the protocol

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

- Recruitment:
  - 20 participants have been enrolled
    - UK: 7 participants enrolled, 1 screened and due in clinic next week for baseline
    - Uganda: 13 participants enrolled, 2 are due in clinic for screening next week
  - The study needs to recruit 4 participants – 2 if the potential participants from Uganda are eligible
- Analysis:
  - Abstract has been planned for IAS. Submission deadline is 15 May 2017.

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

- *In vivo* work was completed on three formulations of DRV/r at different ratios
- Processing of tissue and plasma samples from these *in vivo* studies will show the plasma profile over time, and tissue distribution of drug
- *In vitro* testing of ATV formulations has been completed and results will show which formulations to take forward for *in vivo* testing
- A pre-IND has been written and is in the review stages
- Awaiting quotations for GLP toxicology studies on EFV-SDN to move this work forwards
- Final UNKNOWN draft sent and awaiting UNKNOWN feedback

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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

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

### *Country-level Activities:*

- Mozambique: USAID met with USAID Mission and MZ MOH at CROI to discuss the potential for conducting a needs assessment in MZ. ICAP Country Director had a number of meetings with the MZ MOH resulting in their support for the needs assessment. Initial plans made with the ICAP country team to arrange interviews with key stakeholders for the needs assessment next month. The process was started to translate all needs assessment tools to be translated to Portuguese.
- Kenya: Initiated conversations with NASCOP regarding introduction planning, as well as around the CHAI DTG pilot. Attempted to engage the USAID Mission regarding the enhanced monitoring concept.
- Zimbabwe: Met with USAID to develop a strategy for introducing the project to the Mission in Zimbabwe. ICAP Country Director in Zimbabwe liaised with USAID Mission to arrange a meeting.

### *Documents and Tools Development*

- SA Needs Assessment finalized and circulated for review among key South Africa stakeholders (Francois, Jorge, and Yogan).
- Impact Overview finalized with review from USAID, MPP, and Mylan and is currently with graphic designer.
- USAID CII developed the Stakeholder Landscape Analysis into a short report.
- ICAP developed a concept to respond to the PAC recommendation to compile evidence regarding integrase inhibitor and PI/r use in pregnancy.
- Continued the development of a web-based landing page where WS3 documents will be showcased and accessed by relevant stakeholders.

### *Collaborations*

- ICAP and CII developed a concept to present OPTIMIZE, relevant findings from the landscape analysis, and source information on NDRA registration, multi-month scripting, and visibility of procurer, provider, and patient preferences at the upcoming supplier-buyer summit.
- Women Care Global presented to ICAP and CII about their work regarding regional harmonization process across Africa; the Gates Foundation presented to ICAP and CII on the WHO Collaborative registration process.

### *Enhanced Monitoring*

- ICAP received approval from USAID to move ahead with the development of an enhanced monitoring project in alignment with the CHAI/NASCOP DTG pilot in Kenya.
- ICAP briefed its Kenya team on key questions to review with NASCOP and CHAI's Kenya team. ICAP initiated development of the enhanced monitoring project protocol.
- Representatives from ICAP attended calls hosted by WHO to discuss mother and baby toxicity monitoring and agreed to continue collaborating with WHO to coordinate enhanced monitoring activities.

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

- No new filings to report

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

- UNITAID-funded activities
  - *Fit for Purpose 2017* distributed at the WHO Think Tank meeting at CROI 2017 (printed version and with background materials by WHO). Further copies distributed at UNITAID event and other key meetings. Available online at <http://i-base.info/fit-for-purpose-feb-2017/>
  - *HTB South* printed for distribution as an insert with the South African Journal of HIV Medicine (journal of the Southern African HIV Clinicians Society).
  - Planned session on ART optimisation for TAC training 13-17 March. HIV i-Base will also help to facilitate a workshop on materials development during the training.
- USAID-funded activities
  - Planned upcoming activist ART optimisations meetings at INTEREST 2017 (May, Malawi) and IAS2017 (July, France). 10 activists from AfroCAB and 6 activists from TAC will be attending.

## **COMMUNITY ENGAGEMENT, TAC**

- Monitoring and Evaluation
  - The TAC is revamping its M&E system – a consultant will be engaged to assist with this
  - The TAC is currently assessing datasets and data tools across all structures. This will qualify and authenticate the reporting source documents, and strengthen TAC information management
  - The master trainers will be oriented on all donor-funded reporting requirements during the March training
- Project Management
  - The TAC was invited to form part of the Wits RHI treatment CAB – two members from TAC will be seconded to this. In addition, the TAC was also invited to join the CHAI Optimised ARVs CAB
  - TAC is formalising a working relationship with the clinics in Region F of Johannesburg to assist Wits RHI with the recruitment for ADVANCE
  - Several workshops and trainings with TAC branches in Gauteng were held in February, with the main purpose being introducing ADVANCE. The branches will further cascade this information down to communities

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

- Started establishing the expert HCW committee to guide the activities
- Commenced gathering materials for the health worker training, and have scheduled the first training (with doctors) in early April
- SAHCS will be reviewing its programmes to determine how to include treatment optimisation
- Planning an article on treatment optimisation for the *HIV Nursing Matters* journal – to be written by the Wits RHI team

## **OTHER**

- Wits RHI advised the Gauteng Department of Health's Pharmacy and Therapeutics Committee on the role of DTG within programmes, prior to their broader recommendation within the national programme. Gauteng is the largest province by population, home to over a quarter of the country's population.
- USAID provided an additional \$1.5 million of funding in Year 2. Funding will go towards nanotechnology work on Efavirenz (University of Liverpool), early adopter work in Kenya of patients switching to DTG-based regimens (ICAP), with 3 proposals from Wits RHI and University of Cape Town still under consideration.

## **MAJOR PLANS FOR MARCH 2017**

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

- Start preparing for presenting the first interim analysis of the WRHI052 data to the DSMB in April 2017 (first statistical review).
- Review the current recruitment plan and addition of the Themba Lethu clinic at Helen Joseph Hospital as an additional recruitment site to meet the enrolment target before May 2017.

### ***ADVANCE, Wits RHI***

- Submission of an adolescent pamphlet to Ethics for approval – this pamphlet has been developed as a recruitment tool to generate study awareness and interest.
- Submission of a waiver request of parental/caregiver consent for 16-18 year olds to Ethics for approval.

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

- DRV/r formulations will be assessed reference *in vivo* data and optimal formulations chosen to take forwards
- Analysis of *in vitro* ATV formulation data, including ATV/r formulations to be completed to choose formulations for *in vivo* testing

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

### ***Country-level activities***

- Mozambique: Continue to liaise with the MOH and organize, schedule, and conduct all interviews for the Mozambique needs assessment.
- Kenya: Engage with the USAID Mission and NASCOP to discuss the project broadly. Hold meetings with the CHAI Kenya team in order to discuss introduction planning roles and responsibilities.
- Zimbabwe: Meet with the USAID Mission to discuss moving forward with a needs assessment; initiate planning for needs assessment if relevant

### ***Documents and Tools Development***

- Receive stakeholder feedback on SA needs assessment and finalize the document.

- Initiate review of integrase inhibitor and PI/r use in pregnancy.
- Continue the development of a web-based landing page where WS3 documents will be showcased and accessed by relevant stakeholders.
- Conduct data for and develop case study on Lessons Learned from Past First-line Transitions.
- Initiate development of a guidance document on the WHO CRP and regional harmonized registration.

### Enhanced Monitoring

- Facilitate meetings with USAID, NASCOP, and CHAI to gain an understanding of the details around the DTG pilot.
- Draft enhanced monitoring protocol and develop plan for database development based on information obtained about existing data systems in Kenya.

### COMMUNITY ENGAGEMENT, TAC

- Develop advocacy strategy for civil society
  - TAC will collaborate with HIV i-Base and update treatment literacy materials (including new posters) to strengthen the TAC campaign and advocacy strategy. This will happen during the TAC training happening 13-17 March 2017.
  - Training of master trainers from 7 provinces on ART optimisation and new drugs (TAF, DTG) during the TAC training

### STAFFING CHANGES

- ICAP identified a Regional Technical Specialist to coordinate product introduction activities in sub-Saharan Africa.
- ICAP identified a Product Introduction Coordinator to oversee product introduction activities based in NYC.
- ICAP conducted interviews to identify a Program Coordinator for the Kenya program.

### 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 Technical Steering Committee/Calendar+Events](https://www.dropbox.com/home/OPTIMIZE%20TechnicalSteeringCommittee/Calendar+Events))

- 14 February 2017: Andrew Owen, University of Liverpool: Human confirmation of oral dose reduction potential of nanoparticle antiretroviral formulations (abstract attached at end of document, and presentation uploaded in Dropbox)

### MEDIA COVERAGE

- 21 February 2017: University of Liverpool website: New nano approach could cut dose of leading HIV treatment in half (<https://news.liverpool.ac.uk/2017/02/17/new-nano-approach-to-hiv-therapy-presented-at-leading-conference/>)
- 22 February 2017: USAID website: First-in-human trials demonstrate nanoformulations' ability to transform HIV treatment (<https://www.usaid.gov/what-we-do/global-health/hiv-and-aids/resources/news-and-updates/first-human-trials-demonstrate>)

**HUMAN CONFIRMATION OF ORAL DOSE REDUCTION POTENTIAL OF NANOPARTICLE ARV FORMULATIONS**

Andrew Owen<sup>1</sup>, Steve Rannard<sup>1</sup>, Akil Jackson<sup>2</sup>, Laura Dickinson<sup>1</sup>, Marco Giardiello<sup>1</sup>, Marco Siccardi<sup>1</sup>, Paul Domanico<sup>3</sup>, Melynda Watkins<sup>3</sup>, Yao Cheng<sup>4</sup>, Marta Boffito<sup>5</sup>

1 Univ of Liverpool, Liverpool, UK, 2 Chelsea and Westminster Hosp, London, UK, 3 Clinton Health Access Initiative, Boston, MA, USA, 4 Medicines Patent Pool, Geneva, Switzerland, 5 Chelsea and Westminster NHS Fndn Trust, London, UK

*Background:* Emulsion-templated spray drying to form solid drug nanoparticle (SDN) formulations of efavirenz (EFV) and lopinavir (LPV) previously showed preclinical potential for dose reduction while maintaining pharmacokinetics (PK). This study sought to confirm this in healthy volunteers after single dose and at steady state.

*Methods:* Healthy volunteers (n=4) were consented and screened before receiving 50mg NANO-EFV OD over 21 days. A 72-hour PK profile was generated after the first dose, followed by steady-state PK profile after the final dose with 228-hour plasma decay. Single plasma concentration measurements were also made on days 7, 14, and 17. Safety (including physical examination with vital signs, ECG, urinalysis, laboratory testing) occurred at screening, day 1, 2, 14, 21 and at completion. Five volunteers were consented and screened before receiving 200mg NANO-LPV (boosted with 100mg Norvir) BID over 7 days. A 12-hour PK profile was generated after the first dose, followed by steady-state PK after the final dose with 56-hour decay. A single plasma concentration measurement was also made on day 3. Safety assessments occurred at screening, day 1 (pre morning and afternoon dose and 4 hours post afternoon dose), day 7, and at completion. PK was analysed through population-PK models, with the resulting models used to simulate (n=1000) bioequivalence with previously published clinical data.

*Results:* Both nanoformulations proved to be well tolerated at the studied doses, with no grade 3-4 adverse events. For NANO-EFV, simulations predicted 300mg OD would provide bioequivalence to 600mg OD Sustiva for AUC<sub>0-24</sub>, C<sub>max</sub>, C<sub>12</sub>, but not C<sub>24</sub> (see table). Importantly, bioequivalence was missed at C<sub>24</sub> because concentrations were predicted to be higher than those for Sustiva. Similar simulations were made for 200mg NANO-EFV versus 400mg of the conventional formulation. For NANO-LPV, simulations predicted 200mg BID (with 100mg Norvir) would provide bioequivalence to BID Kaletra for AUC<sub>0-12</sub>, C<sub>max</sub>, and C<sub>12</sub>.

*Conclusion:* These data confirm the potential for a 50% dose reduction while maintaining therapeutic exposure, using a novel approach to formation of SDNs. If confirmed in larger future studies, the approach has the potential for savings up to 243 million USD per year while also freeing up manufacturing capacity up to 930 tons per year.

<b>EFAVIRENZ</b>	<b>Geometric mean</b>		<b>Geometric Mean Ratio</b>
	<b>NANO-EFV 300 mg</b>	<b>Sustiva 600 mg</b>	<b>GMR (90% CI)*</b>
AUC <sub>0-24</sub> (mg.h/L)	51.56	58.61	0.88 (0.86-0.90)
C <sub>12</sub> (mg/L)	2.03	2.51	0.81 (0.78-0.83)
C <sub>24</sub> (mg/L)	1.90	1.44	1.32 (1.26-1.37)
C <sub>max</sub> (mg/L)	2.99	3.36	0.89 (0.87-0.91)
<b>LOPINAVIR</b>	<b>NANO-LPV 200 mg<sup>#</sup></b>	<b>Kaletra 400 mg</b>	<b>GMR (90% CI)*</b>
C <sub>12</sub> (mg/L)	4.16	4.02	1.04 (0.99-1.08)
AUC <sub>0-12</sub> (mg.h/L)	72.35	79.07	0.92 (0.89-0.94)
C <sub>max</sub> (mg/L)	10.69	9.97	1.07 (1.05-1.10)

\*Nanoformulation as reference, <sup>#</sup>boosted with 100mg Norvir