TasP ANRS 12249 trial
Science proposal

To be submitted by Group Facilitators for approval
To F. Dabis, M-L. Newell and D. Pillay
Copy to C Iwuji and J Orne-Gliemann

1. Proposal	
Title of the proposal	Outcomes on PI-based second line HIV-1 treatment in the TasP study
Date	12th of August 2015
2. Working group	
Name (select one)	Clinical and Virology
Has this proposal been discussed already and agreed with the relevant Group Facilitators?	Yes
3. Study team	
Lead investigator	Dami Collier
Collaborators within the TasP study team (Protocol 2.0)	Collin Iwuji, Anne Derache, Deenan Pillay
Collaborators outside the TasP study team	Ravi Gupta
Statistician / Where will the statistical analysis be performed?	Dami Collier & Kathy Baisley- Africa Centre
Associated PhD?	*No*
4. Background	
An estimated quarter of all HIV infected individuals treated with antiretroviral therapy (ART)	

are failing treatment on first line non-nucleoside reverse transcriptase inhibitor (NNRTI) based treatment and qualify for protease inhibitor based (bPI) second line treatment[i]. It has been observed that up to 32% of those on second line bPI treatment do not suppress the virus[ii, iii, iv]. This has implications for third line therapy in resource limited settings.

Although the published studies are limited, there is a suggestion that the prevalence of PI drug resistance mutation at second line failure in South Africa is very low, up to 7% whereas drug resistance in other drug classes remain high, up to 78% [iv, v, vi, vii]. All but one of these studies measured the contribution of non-adherence to second line failure. The contribution of non-adherence, drug toxicity, pharmacokinetics eg concomitant rifampicin use and pharmacodynamics eg lack of refrigerator for soft gel lopinavir tablets to second line failure have been insufficiently studied.

This study aims to estimate the incidence rate of second line failure, the prevalence of antiretroviral drug resistance and to investigate factors associated with second line failure including but not limited to non-adherence, the duration on failing first line regimen, retention in care, drug tolerance, concomitant rifampicin use and lack of refrigeration of lopinavir amongst the TasP second line failing HIV-1 patients.

Reference:

[i] UNAIDS (2013) Global update on HIV treatment 2013. Geneva: UNAIDS.
[ii] Fox MP, Ive P, Long L, Maskew M, Sanne I (2010) High rates of survival, immune reconstitution, and virologic suppression on second-line antiretroviral therapy in South Africa. J Acquir Immune Defic Syndr 53: 500-506.
[iii] Ajose O, Mookerjee S, Mills EJ, Boulle A, Ford N (2012) Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis. AIDS 26: 929-938.
[iv] Johnston V, Cohen K, Wiesner L, Morris L, Ledwaba J, et al. (2014) Viral Suppression Following Switch to Second-line Antiretroviral Therapy: Associations With Nucleoside Reverse Transcriptase Inhibitor Resistance and Subtherapeutic Drug Concentrations Prior to Switch. J Infect Dis 209: 711-720.
[v] Levison JH, Orrell C, Gallien S, et al. Virologic Failure of Protease Inhibitor-Based Second-Line Antiretroviral Therapy without Resistance in a Large HIV Treatment Program in South Africa. Fox MP, ed. *PLoS ONE*. 2012;7(3):e32144. doi:10.1371/journal.pone.0032144.
[vi] Wallis CL, Mellors JW, Venter WDF, Sanne I, Stevens W. Protease Inhibitor Resistance Is Uncommon in HIV-1 Subtype C Infected Patients on Failing Second-Line Lopinavir/r-Containing Antiretroviral Therapy in South Africa. *AIDS Research and Treatment*. 2011;2011:769627. doi:10.1155/2011/769627.
[vii] El-Khatib Z, Ekström AM, Ledwaba J, et al. nViremia and drug resistance among HIV-1 patients on antiretroviral treatment – a cross-sectional study in Soweto, South Africa. *AIDS (London, England)*. 2010;24(11):1679-1687. doi:10.1097/QAD.0b013e32833a097b.

5. Overview of proposed methodology

Summarise the proposed study design (if this proposal requires additional interventions/data

collection) or the proposed analysis plan (if this proposal is based on available data), relating it to the Background section.

Please include all necessary methodological details including how the new intervention will be delivered if any.

This should normally cover no more than one page of A4 (Sections 6 to 8 will allow you to provide further details)

This will involve a retrospective analysis of prospectively collected data.

All patients on PI-based second line treatment (lopinavir) in TasP will be included.

The outcome of interest is a composite outcome of virological failure, defined as viral load greater than1000 copies/ml within 6 months of commencing bPI therapy, death within 6 months without evidence of suppression (VL<1000), lost to follow up within 6 months without evidence of suppression and death within 12 months if no viral load was done following switch to second line.

The exposures of interest include a measure of adherence, the duration on failing first line regimen, retention in care (measured by number of clinic visits), drug intolerance to lopinavir, TB treatment with rifampicin and lopinavir refrigeration, PI resistant genotype at switch.

The analysis will involve a determination of the rate of PI failure in person-years. Characteristics of the cohort will be described. The association between the exposures and virological failure will be analysed using a competing risk regression analysis, with death after attaining viral suppression or death after 12 months as a competing risk.

The effect of the following covariates will be analysed in the regression model; sex, age, socioeconomic status, education, marital status, dwelling (urban, peri-urban, rural), other ART patient in household, distance from clinic, distance from national highway, residence status in community, the presence of another HIV infected individual in the household, CD4 at switch and viral load at switch.

6. New data required (if sub-study proposal)

Outline the scope and content of the additional data collection tools planned.

N/A

7. Variables required (if analysis proposal)

Please list all variables required from TasP datasets (form name and questions number and/or variable name).

TasP ID

Date of Birth

Sex

All first line regimens

All first line regimen start and stop dates

Second line regimen

Second line regimen start date

Second line regimen stop date

All clinic visit dates

All Viral loads will dates

All CD4 with dates

All genotypes with dates

All TB history with dates

Treatment regimen for TB

Adherence measurements- pill count, self-reported, prescription frequency

Adverse drug reactions on second line and date

Reported drug intolerance on second line and date

Socioeconomic status index

Refridgerator asset ownership

Education level

Employment type

Marital status

Dwelling- urban, rural, peri-urban

Distance from clinic

Distance from n2 highway

Residence status in community (ie non-resident household member- does the patient live outside the Hlabisa sub-district for work for example?)

The presence of another HIV infected individual in the household

8. Bio-bank access requirements

Which samples are proposed for additional analyses (over and above the TasP parameters, the results of which are stored in the database)?

What kind of sample, volume and on what group of subjects?

Samples of log5 PBMC and 2x 1ml of plasma samples from pre and post PI failure in order to do the NGS and single genome work.

9. Feasibility assessment

Please state the results of any preliminary assessment to establish whether this proposal is feasible, particularly in terms of sample size, or explain why this has not been undertaken and if/when it is planned.

The TasP trial has been running for 3 years now and currently has 109 individuals on second line PI- based therapy. Of these 11 have been identified to have VL in excess of 1000 at least 6 months after initiation of bPI. Detailed clinical and demographic data has been collected on the participants and it is feasible to investigate the outcome on bPI therapy and factors associated with failing bPI therapy.

10. Communications Strategy

Targeted conferences and journals.

11. Milestones

Intended start date of the proposal	1st October 2015
Targeted date for submission of results to PIs	1st March 2016
Targeted manuscript submission date	31st March 2016

12. Funding

Please state if operational, laboratory, statistical or other scientific support or other resources are required to conduct this proposal.

Outline plan for securing such resource e.g. grant fund.

Funding for laboratory services has been granted for the TasP ANRS 12249 trial.

Scientific and statistical services will be funded by a BIA research fellowship grant.

[i] UNAIDS (2013) Global update on HIV treatment 2013. Geneva: UNAIDS.
[ii] Fox MP, Ive P, Long L, Maskew M, Sanne I (2010) High rates of survival, immune reconstitution, and virologic suppression on second-line antiretroviral therapy in South Africa. J Acquir Immune Defic Syndr 53: 500-506.
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[vi] Wallis CL, Mellors JW, Venter WDF, Sanne I, Stevens W. Protease Inhibitor Resistance Is Uncommon in HIV-1 Subtype C Infected Patients on Failing Second-Line Lopinavir/r-Containing Antiretroviral Therapy in South Africa. *AIDS Research and Treatment*. 2011;2011:769627. doi:10.1155/2011/769627.
[vii] El-Khatib Z, Ekström AM, Ledwaba J, et al. nViremia and drug resistance among HIV-1 patients on antiretroviral treatment – a cross-sectional study in Soweto, South Africa. *AIDS (London, England)*. 2010;24(11):1679-1687. doi:10.1097/QAD.0b013e32833a097b.