Antiretroviral Treatment as Prevention • ANRS 12249
Ukuphila kwami, ukuphila kwethu (my health for our health)

A cluster-randomised trial comparing the impact of immediate versus South African recommendations guided ART initiation on HIV incidence
The ANRS 12249 TasP (Treatment as Prevention) trial
in Hlabisa sub-district, Kwazulu-Natal, South Africa

ANRS 12249 TasP Protocol

Version 2.0 • 09/01/2014
Phase 1 (2011-2013) and Phase 2 (2013-2016)

Modification from the Version 1.2 dated March 8th, 2012, signed 14/01/2013. Amendment 1 approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BREC) on 02/08/2012. Expedited application approved by BREC on 26/09/2012. Amendment 2 approved by BREC on 20/09/2012. Amendment 3 approved by BREC on 14/12/2012. Amendment 4&5 approved by BREC on 15/03/2013. Amendment 6 approved by BREC on 13/08/2013. Amendment 7 approved by BREC on 10/10/2013. Amendment 8 approved by BREC on 12/11/2013. Amendment 9 approved by BREC on 12/03/2014.

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Atripla® to be used in the trial will be provided by Merck & Co. and Gilead

Abstract

Title: A cluster-randomised trial comparing the impact of immediate versus South African recommendations guided ART initiation on HIV incidence. The ANRS 12249 TasP (Treatment as Prevention) trial in Hlabisa sub-district, Kwazulu-Natal, South Africa

Background: Thirty years after the discovery of the human immunodeficiency virus (HIV), prevention is difficult to achieve and the pandemic does not show any sign of abating. Antiretroviral therapy (ART) is now rolled out at a large scale in lower-income countries. ART with fully suppressive antiretroviral (ARV) drugs combinations lowers HIV viral load (VL) in all body compartments and decreases the risk of transmission to a low level. It is thus legitimate to raise the following question: Could ART contribute to reducing transmission at individual and population level? Not only may earlier treatment reduce HIV incidence (acquisition of new cases of HIV infection through sexual or mother-to-child transmission), it may also benefit the individual. The long-term benefits of starting ART earlier would likely be of particular importance in settings where the incidence of life-threatening HIV-related diseases occurring at relatively high CD4 levels (tuberculosis, invasive bacterial diseases, and possibly malaria) is substantial, a typical situation in most sub-Saharan Africa including South Africa.

Research hypothesis: HIV testing of all adult members of a community, followed by immediate ART initiation of all, or nearly all, HIV-infected participants regardless of immunological or clinical staging will prevent onward transmission and reduce HIV incidence in this population.

Objectives: To estimate the effect of ART initiated immediately after HIV diagnosis, irrespective of CD4 count criteria, on the reduction in incidence of new HIV infections in the general population in the same setting.

Setting: The trial will be conducted in Hlabisa sub-district, Umkhanyakude district, Northern KwaZulu-Natal, South Africa. This rural setting of 1430 km^2 in size has a population of approximately 220 000 Zulu-speaking people. In this sub-district, the Africa Centre for Health and Population studies, a research institute at the University of KwaZulu-Natal (http://www.africacentre.com) carries out socio-demographic and HIV surveillance and clinical research. The KwaZulu-Natal Department of Health and the Africa Centre established in 2004 the Hlabisa HIV Treatment and Care Programme, devolved to all 17 primary health care clinics in the sub-district. By mid-2013, over 28 000 HIV-infected people eligible for treatment had been initiated on ART; patients' treatment eligibility is determined by South African guidelines.

Design: A cluster-randomised trial with 22 (2×11) clusters will be conducted within the Hlabisa sub-district, covering a total population of approximately 22 000 inhabitants aged 16 years and above, of whom an estimated 17 600 will be HIV-negative. A full prevention and HIV testing strategy will be provided in both the intervention and control arms, consisting of the current range of community and clinic testing options plus the implementation of 6-monthly rounds of home-based HIV testing. The adult HIV-infected population residing in the intervention clusters will be offered immediate ART initiation upon HIV diagnosis whereas the HIV-infected population in the control clusters will be offered ART according to national guidelines (CD4 less than 350 cells/ml, WHO stage 3 or 4 disease or MDR/XDR TB). The protocol outlines the overall trial design, which has HIV incidence as primary outcome. The first phase of the trial (24 months) will take place in ten (2×5) clusters, with three rounds of home-based HIV testing and surveillance according to the trial protocol, and has as main outcome

acceptability and feasibility rather than HIV incidence. If results from the first phase indicate acceptability and feasibility, the trial will be rolled-out to the other 12 clusters during the second phase. Possible amendments to the trial for phase 2 will be based on the advice from the Data Safety Monitoring Board and the Scientific Advisory Board.

Trial eligibility criteria: To be aged 16 years and above and a member of a household in the designated cluster (head of household defines membership status in KwaZulu culture).

Treatment eligibility criteria: Those already on ART from the Hlabisa HIV Treatment and Care Programme may opt to transfer their care to the trial; the few (if any) people already on ART from private/other HIV treatment providers will be encouraged to take part in the trial monitoring procedures, and be given the opportunity to change ART provider to the Hlabisa HIV Treatment and Care Programme trial.

Trial treatment: The standard first-line drug regimen will be the combination of tenofovir (TDF) + emtricitabine (FTC) + efavirenz (EFV) once daily, i.e. Atripla®. This will also be applicable to pregnant women irrespective of the trimester of pregnancy.

Follow-up: The treatment and follow up of HIV-infected patients in the first phase will be for a maximum of 24 months (March 2012-March 2014) and this will continue for another 24 months with the additional 12 clusters from 2014.

Data collection: Quantitative data will be collected from participants during each round of HIV counselling and testing in the community to build a comprehensive individual, household and, ultimately, population picture of key social, demographic, behavioural, partnership and economic issues (Individual home-based questionnaire). Clinical, biological and social data will be collected from HIV-infected participants on ART or not attending the trial clinics during routine follow-up appointments (Clinic-based survey). In addition, activity measures will be collected from each of the trial clinics (Structure questionnaire).

Trial primary outcome: HIV incidence, measured at the end of the trial, that is 48 months in the 10 phase 1 clusters and 24 months in the 12 additional clusters in phase 2, using two approaches: 1) using dried blood spots (DBS), with longitudinal follow-up and 2) using a locally validated test for recent infection: capture BED enzyme-linked immunoassay (cBED assay). The latter will be used to validate recent infections in material collected in the first round of testing to confirm assumptions used in sample size calculations.

Trial secondary outcomes Behavioural and socio-economic outcomes (such as acceptability of HIV counselling and testing, sexual partnerships, quality of life, household expenditures, cost-effectiveness) and clinical outcomes (programme retention, mortality, incidence of severe morbidity including tuberculosis, adherence to ART measured by self-report and virological response on treatment, new cases of vertically-acquired HIV infections and MTCT rates in the area, acquired HIV drug resistance) measured after 24 months of follow-up.

First phase outcomes: The first phase will specifically focus on the trial secondary outcomes in order to: 1) assess the acceptability and feasibility of the intervention; and 2) validate and update the parameters of the model used to estimate the trial sample size and HIV incidence, in terms of: uptake of HIV testing, linkage to care upon HIV diagnosis, internal migration and ART initiation.

Timing: The entire trial, including planning, will take place over six years (2011-2016). The first phase will take 24 months. Data analysis and review of results

will be performed during 2013 to inform decision-making regarding process and procedures for phase 2.

Sample size: A fully parameterised, deterministic mathematical model demonstrates that a 34% reduction in cumulative HIV incidence (4.5% versus 2.98%) in HIV-negative participants over two years should be feasible across a wide range of parameter space. Sample size calculations indicate that 22 clusters (11 in each arm), with 1 000 consenting participants >15 years of age in each cluster (N=22 000; 17 600 HIV-negative), are required to achieve this objective. The first phase will be conducted on 10 000 participants in 10 clusters, which allows the measurement of the proportion agreeing to test over three rounds of testing within 1% (95% CI) and uptake of testing in the intervention communities of all HIV-positive participants within 4% (95% CI).

Expected results: We aim to provide proof-of-principle evidence regarding the effectiveness of Treatment-as-Prevention in reducing HIV incidence at the population level. We will collect data from the participants to inform the generalizability of the results, and thus inform policy resulting in wide implementation.

Résumé

Titre : Un essai randomisé en cluster comparant l'impact d'une mise sous traitement ARV immédiate versus les recommandations sud-africaines sur l'incidence du VIH. L'essai ANRS 12249 TASP (traitement par la prévention) dans le sous-district de Hlabisa, Kwazulu-Natal, Afrique du Sud.

Contexte : Trente ans après la découverte du virus de l'immunodéficience humaine (VIH), la question de la prévention du VIH est encore non résolue. Les traitements antirétroviraux (ARV) sont désormais mis en place à large échelle dans les pays à ressources limitées. Or il a été montré qu'un traitement ARV combinant des molécules ayant une forte capacité de suppression virale permettait de réduire la charge virale (CV) dans tous les compartiments corporels et de réduire le risque de transmission du VIH à de très faibles niveaux. Il semble donc légitime de se poser la question suivante : les traitements ARV pourraient-ils contribuer à réduire la transmission du VIH aux niveaux individuels et populationnels ? Non seulement le traitement précoce pourrait réduire l'incidence du VIH (les nouveaux cas d'infection par transmission sexuelle et transmission mère-enfant), mais il pourrait également offrir des bénéfices individuels. Les bénéfices à long terme du traitement précoce seraient d'autant plus grands que l'incidence des maladies opportunistes graves liées au VIH (tuberculose, infections bactériennes invasives et probablement le paludisme) survenant à des taux élevés de CD4 est élevée, comme c'est le cas dans la plus grande partie de l'Afrique sub-saharienne et notamment l'Afrique du Sud.

Hypothèses de recherche : Le dépistage VIH de tous les membres d'une communauté, suivi de la mise sous traitement immédiat de tous, ou quasiment tous, les individus infectés par le VIH, quel que soit leur statut immunologique ou clinique, préviendrait la transmission du VIH et réduirait l'incidence du VIH dans cette population.

Objectifs : Estimer directement l'impact du traitement ARV initié immédiatement après le diagnostic de l'infection par le VIH et quel que soit le niveau de CD4 des patients non encore éligibles au traitement ARV, sur l'incidence de nouvelles infections VIH dans la population générale de la même région.

Environnement : L'essai sera conduit dans le sous-district de Hlabisa, district de Umkhanyakude dans la province du KwaZulu Natal en Afrique du Sud. Cette zone rurale de 1 430km² compte approximativement 220 000 habitants, l'incidence du VIH y est estimée à 3,4%. L'Africa Centre for Health and Population Studies, un institut de recherche de l'Université du KwaZulu Natal (http://www.africacentre.com), y conduit des activités de surveillance démographique et des questions de santé dont l'infection à VIH/Sida. Le Département pour la Santé de la province du KwaZulu Natal et l'Africa Centre ont lancé en 2004 le Programme de Traitement et de Prise en Charge de Hlabisa, décentralisé à l'ensemble des 17 centre de santé primaires du sous-district. Mi-2013, plus de 28 000 individus infectés par le VIH et éligibles au traitement ARV, selon les recommandations actuellement en vigueur en Afrique du Sud, en bénéficiaient.

Méthodologie : Un essai randomisé en grappes (« clusters ») sera conduit dans le sous-district de Hlabisa au sein de 22 (2x11) grappes comprenant un total de 22 000 individus âgés de plus de 15 ans, 17 600 étant séronégatifs au début du programme. Un paquet global et le plus complet possible de services de prévention et de dépistage du VIH sera mis en place dans les deux groupes de grappes. Il s'agira notamment de combiner les services existants de dépistage à la

clinique et au sein de la communauté, et la mise en place de cycles de six puis de quatre mois permettant d'offrir le dépistage du VIH à domicile. La population adulte infectée par le VIH et résidant dans les grappes tirées au sort pour constituer le bras « intervention » pourra être mise sous traitement ARV immédiatement tandis que la mise sous traitement de la population des grappes constituant le groupe de comparaison se fera selon les procédures actuelles recommandées par le gouvernement sud-africain, en incluant les individus présentant avec un taux de lymphocytes CD4 <350 cellules/ml. L'essai sera conduit en deux phases. Le présent protocole décrit le schéma d'étude dans son ensemble, étude dont le critère de jugement principal sera l'incidence du VIH. La première phase de l'étude (24 mois) sera conduite dans 10 (2×5) grappes : trois cycles de dépistage VIH à domicile seront conduits, toutes les procédures du protocole seront mises en œuvre et les critères de jugement principaux seront l'acceptabilité et la faisabilité de l'intervention et non pas l'incidence du VIH. Si les résultats de la première phase montrent l'acceptabilité et la faisabilité de l'intervention, l'essai sera mis en place dans l'ensemble des 12 autres grappes en phase 2. Des amendements possibles au protocole de l'essai pourront être envisagés suivant les recommandations du Comité Indépendant de Surveillance et du Conseil Scientifique.

Critères d'éligibilité pour l'essai : Être âgé de 16 ans ou plus et être un membre d'un ménage de la grappe sélectionnée (dans la culture KwaZulu, le chef de ménage identifie les membres du ménage)

Critères d'éligibilité pour le traitement TasP : Les personnes déjà sous traitement ARV au sein du Programme de Traitement et Prise en Charge de Hlabisa seront recrutés dans l'étude ; le faible nombre de ceux déjà sous traitement ARV et suivis dans le secteur privé ou par d'autres professionnels de santé seront encouragés à participer à l'essai et pourront intégrer le Programme de Traitement et Prise en Charge de Hlabisa s'ils le désirent.

Intervention ARV de l'essai : Le régime ARV de première ligne combinera le tenofovir (TDF) + l'emtricitabine (FTC) + l'efavirenz (EFV) en une prise par jour. Ce régime s'appliquera aussi aux femmes enceintes, quelque soit leur âge gestationnel.

Suivi : La durée de traitement et de suivi pour les patients infectés par le VIH est d'un maximum de 24 mois durant la première phase (Mars 2012-Mars 2014) et continuera pendant 24 supplémentaires dans les 12 clusters additionnels de la phase 2.

Collecte des données : Des questionnaires seront administrés à chaque cycle de dépistage à domicile, afin de décrire au niveau individuel, du ménage et de la communauté les données sociales, démographiques, comportementales et économiques des participants et les paramètres cliniques et biologiques des patients sous traitement ARV. Des données quantitatives seront également collectées auprès des patients suivis au sein des cliniques de l'essai au cours de leurs visites de routine. Enfin, des donnés d'activité et de processus seront collectées au sein de chaque clinique de l'essai.

Critère de jugement principal de l'essai : L'incidence du VIH, mesurée à la fin de l'essai (48 mois dans les clusters de phase 1 et 24 mois dans les 12 clusters additionnels de la phase 2), 1) en utilisant les échantillons collectés sur papier buvard au cours du suivi à long terme et 2) en utilisant un test validé en Afrique du Sud pour estimer l'infection récente, le capture BED enzyme-linked immunoassay (cBED assay)

Critères de jugement secondaires de l'essai : Des indicateurs comportementaux et socio-économiques tels que l'acceptabilité du conseil et du

dépistage du VIH, les partenaires sexuels, la qualité de vie, les dépenses des ménages, le rapport coût-efficacité et des indicateurs cliniques (rétention dans l'essai, la mortalité, l'incidence d'évènements morbides sévères dont la tuberculose, l'adhérence au traitement ARV, les cas d'infections pédiatriques et les cas de résistance virale acquise).

Critères de jugement de la première phase : La première phase de l'essai répondre en particulier aux objectifs secondaires de l'essai pour 1) évaluer l'acceptabilité et la faisabilité de l'intervention et 2) valider et mettre à jour les paramètres du modèle utilisé pour estimer la taille de l'échantillon et l'incidence du VIH, en termes de: dépistage du VIH, accès aux soins de liaison après diagnostic du VIH, les migrations internes et les critères d'initiation ART.

Calendrier prévisionnel : L'essai, y compris la période de mise en place, est prévu sur six ans (2011-2016). La première phase est prévue sur 24 mois. L'analyse des données réalisée en 2013 permettra de se prononcer sur la suite de l'essai et/ou la modification de certaines procédures en phase 2.

Taille de l'échantillon : Un modèle mathématique déterministe et entièrement paramétré a montré la faisabilité sur deux ans d'une réduction de 34% de l'incidence cumulée du VIH (4,5% vs. 2.98%) au sein de participants séronégatifs. Les calculs de taille d'échantillon suggèrent que 22 grappes (11 dans chaque bras) comprenant 1 000 participants de plus de 15 ans dans chaque grappe (N=22 000, 17 600 personnes séronégatives au début de l'essai) sont nécessaires pour répondre à cet objectif. La première phase portera sur 10 000 personnes dans 10 grappes, ce qui permet de documenter à 1% près la proportion de personnes acceptant le test au cours des trois cycles de dépistage (IC 95%) et à 4% près la couverture du dépistage dans les communautés des grappes du bras « intervention » de tous les individus infectés par le VIH

Résultats attendus : Nous espérons montrer que la stratégie du Traitement comme moyen de Prévention de la transmission du VIH peut être mise en place au sein d'une population à forte incidence du VIH, quel que soit le stade de l'infection et les caractéristiques du dépistage des individus de cette population, et que cette approche novatrice contribue à réduire l'incidence du VIH et offre des bénéfices individuels et populationnels. Les résultats documentés dans cet essai devraient être suffisamment forts pour encourager la réplication de cette stratégie dans d'autres pays à ressources limitées et avoir des implications politiques permettant sa mise en place à large échelle.

List of abbreviations and definitions

3TC	Lamivudine
AE	Adverse Event
ANRS	Agence Nationale de Recherches sur le SIDA et les hépatites virales
ART	AntiRetroviral Treatment
ARV	AntiRetroViral (drug)
bd	Twice daily
BIA	Budget Impact Analysis
BMI	Body Mass Index
CAB	Community Advisory Board
CAR	Clinic Activity Report
CAP	Consumer Advisory Panel
CBC	Clinic Baseline Visit (Counsellor) questionnaire
CEA	Cost-Effectiveness Evaluation
CFU	Clinic Follow-Up (Counsellor) questionnaire
CHE	Clinic History and Examination questionnaire
CRF	Case Report Form
d4T	Stavudine
DBS	Dried Blood Spot
DoH	Department of Health
DSA	Demographic Surveillance Area
DSMB	Data Safety Monitoring Board
EFV	Efavirenz
FDC	Fixed-Dose Combination
FTC	Emtricitabine
GCP	Good Clinical Practices
GIS	Geographical Information System

HAART	Highly Active AntiRetroviral Therapy
HASI-P	HIV/AIDS stigma instrument for people living with HIV/AIDS
HAT-QOL	HIV/AIDS-Targeted Quality of Life (scale)
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HHI	TasP Household Information Assets questionnaire
HIV	Human Immunodeficiency Virus
HSV2	Herpes Simplex Virus
ICH	International Conference on Harmonisation
IEC	Information, Education, Communication
IQ	TasP Home-based Individual Questionnaires
IT	Information Technology
LPV/r	Lopinavir/ritonavir (boosted)
MCC	Medicines Control Council of South Africa
MDR TB	Multi-Drug Resistant Tuberculosis
NGO	Non-Governmental Organisation
Nocte	Every night
NVP	Nevirapine
od	Once daily
PEP	Post-Exposure Prophylaxis
PIT	Pill Identification Test
PITC	Provider-Initiated Testing and Counselling
PLWHA	Person Living With HIV/AIDS
PMTCT	Prevention of Mother-To-Child Transmission of HIV
ppy	person per year
PROQOL	Patient Reported Outcomes Quality Of Life
QALY	Quality-Adjusted Life Years
RCT	Randomised Clinical Trial

SAB	Scientific Advisory Board
SAE	Serious Adverse Event
SC	Steering Committee
SCB	Social Science Clinic-based Baseline questionnaire
SCC	Social Science Clinic-based Counsellor-administered questionnaire
SCI	Social Science Clinic-based Interviewer-administered questionnaire
SCS	Social Science Clinic-based Survey (SCB + SCC + SCI)
SOP	Standard Operating Procedure
STI	Sexually Transmitted Infection
TB	Tuberculosis
TDF	Tenofovir disoproxyl fumarate
THR	TasP Household registration questionnaire
VAS	Visual Analogue Scale
VCT	Voluntary Counselling and Testing (HIV)
VL	Viral Load (HIV plasma RNA measurement)
WHO	World Health Organization (Switzerland)
XDR TB	Extensively Drug-Resistant Tuberculosis
ZDV	Zidovudine

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1. Rationale

1.1 State of knowledge

1.1.1 The challenges of prevention of sexual transmission of HIV

Twenty-five years after the discovery of the human immunodeficiency virus (HIV), successful prevention remains challenging and the pandemic continues unabated (1). A vaccine remains elusive despite recent advances in the past two years (1, 2). Vaginal microbicides without antiretroviral (ARV) drugs have failed to show significant long-term benefit (3); the recent results from the Tenofovir (TDF) - containing microbicide are promising but need confirmation in a further trial (4). Treatment of sexually transmitted infections, including herpes simplex has no measurable effect on HIV transmission (5). Male circumcision halves the risk of HIV transmission from females to males but is not (yet) a widely-used public health measure, although the South African government has started implementing a programme, focussing on young men in April 2010. As a consequence, effective prevention continues to rely on behavioural change and condom use, but these methods have their limitations, as evidenced by the resurgence of unsafe sex in homosexual males in Western Europe and the USA (6), and limited uptake and more importantly sustainability in lower-income countries (7, 8). At their current or anticipated level of use none of these methods is effective enough to contain the pandemic in countries with high incidence and prevalence of HIV infection such as South Africa.

1.1.2 Antiretroviral therapy can reduce sexual transmission

HIV plasma viral load (VL) in the index HIV-infected individual is the dominant determinant of transmission, documented in heterosexual couples and mother/child pairs (9, 10). Antiretroviral therapy (ART) with fully suppressive ARV drugs combinations lowers VL in all body compartments and decreases the risk of transmission to a very low level. It is thus legitimate to raise the following question: **Could ART contribute to reducing transmission at individual and population levels?** Head-to-head comparisons are not available and are unlikely to be promoted, but in cohort studies where routine use of condoms was encouraged in sero-discordant couples, results differed substantially depending on whether index patients were on ART (0.46 case of HIV acquisition per 100 person-years [ppy]) or not (5.64 ppy) (11). In the same meta-analysis, Attia et al estimated a zero (97.5% upper confidence limit of 1.27 ppy) transmission risk for those on ART and with successful viral suppression (VL <400 copies/ml). The HPTN 052 study showed that ART reduces HIV transmission by 96% in stable couples where one partner is HIV-infected and the other is not (12). This NIH trial has not addressed the question of the reduction of HIV transmission at the population level.

1.1.3 Can ART be provided at earlier stages of HIV infection than currently recommended?

Until 2009 international recommendations for initiating ART were generally conservative everywhere in the world, especially in resource-limited settings where ART initiation was recommended only at a CD4+ (CD4) count of 200 cells/mm^3 or less or for end-stage HIV disease. However, recently two pieces of evidence considerably changed this approach: analyses of observational data from the USA and Europe (13, 14) and a randomized clinical trial conducted in

Haiti (15). Further, there is some evidence of benefit of earlier treatment from trials of structured treatment interruption. For instance, the ANRS 1269 TRIVACAN trial conducted in Côte d'Ivoire showed that patients interrupting ART at intermediate CD4 levels had higher risks of morbidity and mortality than patients remaining on ART (16). Finally, observational cohort data from Zimbabwe have shown that the risk of death of untreated HIV-infected women was 6.2 times higher for those with more than 600 CD4 when compared with HIV-negative women (17).

In November 2009, WHO recommended to substantially broaden eligibility for ART, with treatment of all HIV infected people with CD4 <350 cells/mm^3 irrespective of clinical symptoms or at WHO clinical stage 3 or 4 irrespective of CD4 count. Treatment should also be provided for those with a diagnosis of active tuberculosis (TB) irrespective of CD4 cell count, those who have a co-infection with hepatitis B virus (HBV) if the latter requires treatment and for pregnant women fulfilling treatment criteria (18). Two clinical trials are currently investigating whether ART initiated well above 350 cells/mm^3 provides sufficient additional individual benefits in terms of mortality and severe morbidity: the NIH-sponsored START trial (clinicaltrials.gov identifier NCT00867048) and the ANRS-sponsored TEMPRANO trial (clinicaltrials.gov identifier NCT00495651). Although the results of these trials are not expected before the end of 2015, evidence and programmatic experience have continued to shift the risk-benefit ratio towards starting ART earlier. Thus in June 2013, the revised WHO guidelines promoted "expanded eligibility for ART with a CD4 threshold for treatment initiation of 500 cells/mm^3 or less for adults, adolescents and older children. Priority should be given to individuals with severe or advanced HIV disease and those with CD4 count of 350 cells/mm^3 or less. ART is recommended to be initiated regardless of CD4 count for certain populations, including people with active tuberculosis (TB) disease who are living with HIV, people with both HIV and hepatitis B virus (HBV) infection with severe chronic liver disease, HIV-positive partners in serodiscordant couples, pregnant and breastfeeding women and children younger than five years of age" (19).

1.1.4 Strengthening HIV testing approaches

Without HIV testing, bio-medical interventions cannot target HIV-infected individuals. Motivations for testing vary, but many people test to obtain treatment, often when they feel unwell. Restricting treatment to those who have already developed symptoms and meet CD4 count criteria as discussed in the previous section may actually serve as a serious, if unintentional, barrier to the uptake of HIV testing.

Over the past two decades, HIV counselling and testing services have primarily been promoted and provided in the context of Voluntary HIV Counselling and Testing (VCT). However, the limits of VCT approaches in resource-limited settings, particularly regarding achieving early diagnosis, high levels of population coverage and access to "hard-to-reach" groups (20, 21), have led to the development of other innovative forms of HIV testing such as Provider-Initiated Testing and Counselling (HIV testing and counselling recommended by health care providers for any persons attending health care facilities as a standard component of medical care, such as HIV testing in TB clinics, door-to-door testing, partner notification), home-based or mobile HIV testing that take testing services to people (22).

Defining a feasible, acceptable, and efficient strategy to obtain very high rates of testing (e.g. near universal HIV testing repeated bi-annually) may necessitate further development of both existing VCT services available and extension of

PITC. The South African government strongly supports a coherent, consistent HIV services' approach, encouraging all public health facilities – fixed and mobile – to offer HIV testing. Successfully testing the numbers needed to achieve the coverage required for implementation of treatment for all or nearly all infected people is quite different to simply promoting VCT, and will certainly necessitate a more intensive approach to provider-initiated services, taking into account the needs and attitudes of different population groups and considering the relevance of different modes of HIV testing in different populations.

1.1.5 Could combination antiretroviral therapy be used universally to reduce sexual transmission of HIV at population level? If yes, which combination?

In 2009 a mathematical modelling exercise using a hypothetical population and assumptions relating to the South African setting concluded that *"Universal voluntary HIV testing and immediate ART (regardless of CD4 count) combined with present prevention approaches, could have a major effect on severe generalised HIV/AIDS epidemics"* (23). Two accompanying commentaries addressed how and whether this was feasible to deliver in the 'real world' (24, 25). The modelling exercise showed that HIV transmission could be substantially reduced within a few years. The authors argued that current clinical practice, which in nearly every setting, relies on CD4 counts and advanced HIV disease as the trigger to introduce ART, limits its preventive efficacy by leaving key points in HIV's natural history to go unchecked by effective VL-reducing treatment (these key points are the peak VL at seroconversion and the sustained period of somewhat elevated VL set point during the asymptomatic period). Dodd et al developed a deterministic mathematical model to investigate the impact of test-and-treat interventions under a variety of assumptions about the epidemic (26). They showed that such an intervention could substantially reduce HIV transmission, but that the impact might depend on the epidemiological context (notably determined by the sexual partner network, such as heterogeneity, concurrency and mixing).

Providing that a universal test and treat approach is appropriate, the question of the choice of ARV drug combination for wider and prolonged use becomes central. This ARV regimen should fulfil the following criteria: 1) Appropriateness for all CD4-cell strata to simplify its use; 2) Minimal side effects in otherwise "healthy" patients to avoid treatment drop-outs; 3) High potency to maximize effect on transmission; 4) High genetic barrier to minimize acquisition of viral resistance; 5) Sustainability for many years to limit and delay switches to second-line ARV regimens; 6) Low pill burden to facilitate treatment adherence; 7) Minimal laboratory requirements for follow-up; 8) Safety; 9) Affordability and 10) Coverage of special populations (TB co-infection, hepatitis B co-infection, pregnant women). A fixed-dose-combination (FDC) of (efavirenz [EFZ 600mg / tenofovir disoproxil fumarate [TDF] 300mg / emtricitabine [FTC] 300mg) available in South Africa as Atripla® or other generic forms administered once daily fulfils most of these criteria.

Not only may earlier treatment reduce HIV incidence at a population level, it may also benefit the individual. The long-term benefits of starting ART earlier would likely be even more important in settings where the incidence of life-threatening HIV-related diseases occurring at relatively high CD4 levels (tuberculosis, invasive bacterial diseases, and possibly malaria) is substantial, a typical situation in most sub-Saharan Africa including South Africa. Two randomised clinical trials have been designed or are in progress to address the "when to start" question in different settings and at different CD4 levels. The TasP trial addresses

the same issue but expands it further, although prevention of new infections is its "raison d'être" (26).

1.2 Study hypothesis

HIV testing of all members of a community, followed by immediate ART initiation of all HIV-infected individuals regardless of immunological or clinical staging will prevent onward sexual transmission and reduce HIV incidence in this population.

1.3 Study design

TasP will be **a population-based cluster-randomised trial (RCT), with small communities used as the units for randomisation. It aims at evaluating whether ART delivered at an earlier stage of HIV infection than currently recommended can prevent onward transmission of HIV.** This effect on HIV incidence among HIV-negative subjects will be the direct consequence of the treatment initiation among those non-eligible for ART according to the current standards. TasP aims to address this very important question and **produce such evidence, from a rural area in KwaZulu-Natal, the province with the highest HIV incidence and antenatal prevalence in South Africa, the country with one of the highest HIV burdens in sub-Saharan Africa, the continent where 70% of new HIV infections occur**.

1.4 Trial phases

The TasP trial will be implemented in **a two-phase approach**:

- The **first phase** will be conducted in a selected number of clusters (see section 8). All trial procedures to be implemented in this first phase will be as planned in this full trial protocol.
- If in the first phase the procedures and approach are shown to be feasible and acceptable and if the aims of the trial are still deemed relevant within the context of international research advances and the research strategy of the Africa Centre and partner institutions, and in agreement with the Steering Committee (SC), recommendation of the Scientific Advisory Board (SAB) and the Data Safety Monitoring Board (DSMB), the protocol will be implemented in the remaining clusters (see section 8) in the **second phase.**

1.5 Expected results of the trial

We aim to contribute to the evidence-base that a Treatment as Prevention approach can be applied to an entire population with a high incidence of HIV infection, irrespective of the stage of HIV disease and circumstances of HIV testing of participants in that population, and that Treatment as Prevention contributes to a reduction in HIV incidence while yielding further population and individual benefits.

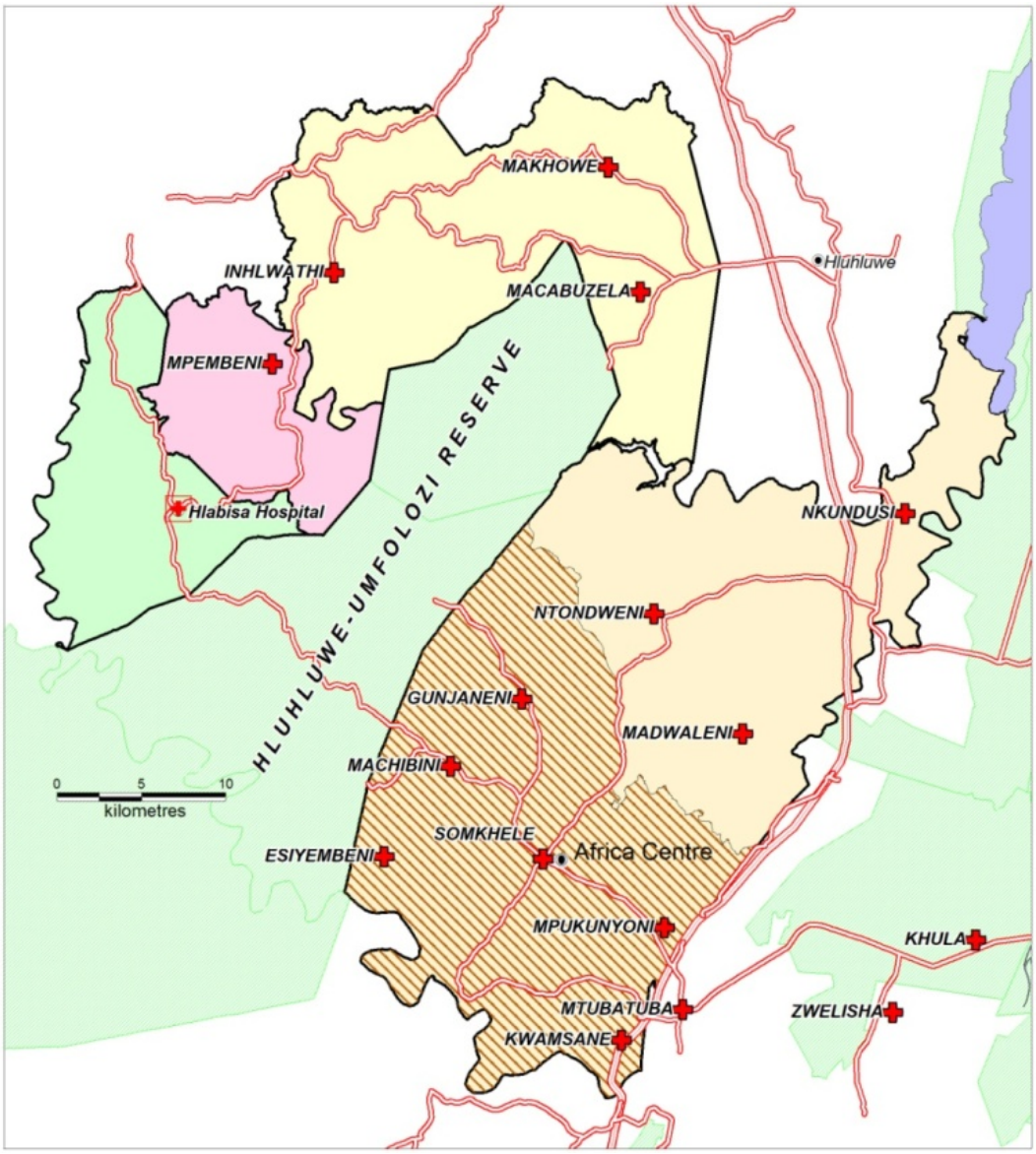
The evidence obtained should be strong enough for this approach to be replicated in a wide range of resource-limited settings, to have policy implications to result in wide implementation.

2. Trial setting

2.1 Hlabisa sub-district

The trial will be conducted in Hlabisa sub-district, Umkhanyakude district, Northern KwaZulu-Natal, South Africa (Figure 1). The Hlabisa health sub-district is a rural setting of 1 430 km^2 in size, with a population of approximately 220 000 Zulu-speaking people of whom 3.3% are located in a formal urban township (KwaMsane), 19.9% in peri-urban areas and the remainder (76.8%) classified as living in a rural area. The rural population lives in scattered homesteads that are not concentrated into villages or compounds (as would be the case in many other parts of Africa).

Figure 1
Hlabisa sub-district, uMkhanyakude district, Northern KwaZulu-Natal, South Africa (shaded area is the area of the Africa Centre surveillance)



Health facilities in the Hlabisa sub-district are provided by one central community hospital (300 beds) and 17 fixed primary health care clinics

(Department of Health clinics), which provide the bulk of the health care for the population of the sub-district. All clinics provide care for minor ailments, family planning services, antenatal and postnatal care, conduct deliveries, treat sexually transmitted diseases, provide child immunisations, diagnose and manage TB, and care for chronic illnesses such as diabetes and hypertension (and HIV treatment and care, see below section 2.3). In addition to the 17 fixed clinics, 31 mobile clinic points are provided twice monthly, mainly for childhood immunisations and maternal and child health care. The sub-district is also serviced by approximately 130 community health workers, each of whom is expected to regularly visit a group of assigned homesteads.

2.2 The South Africa HIV treatment programme

The HIV treatment programme in South Africa is the largest in the world, with 2 million individuals estimated to have been receiving HAART in mid-2012 (27) (HSRC July 2013). One key aim of the current National Strategic Plan for HIV is to provide access to treatment, care and support to 80% of HIV-infected people and there has been significant scale-up of activity in the past few years (28). There remains, however, a large unmet need for treatment, with an estimated coverage in 2009/2010 of approximately 58% of those eligible for treatment, although this varies across districts (28).

The national response to HIV and the development of implementation plans is informed by the national strategic plan on HIV, STIs and TB (28) (ref) and the delivery of ART is guided by the recently updated National Antiretroviral Treatment (29). Until early 2010, HIV-infected adults were eligible for ART if CD4 cell count <200 cells/mm^3 or WHO stage IV condition. In April 2010, new guidelines were implemented where pregnant females and individuals with TB disease became eligible for ART if CD4 cell count <350 cells/mm^3, and in August 2011 these guidelines were further extended to eligibility starting at 350 for all HIV infected people in addition to all those with WHO stage 3 or 4 disease or anyone with MDR or XDR TB. The 2013 South African revised antiretroviral treatment guidelines also include all pregnant women to be eligible for ART for the duration of pregnancy and breastfeeding (29) (see Appendix 15.1). The current first-line drug regimens in use in South Africa are TDF + 3TC/FTC + EFV/NVP (see Appendix 15.1).

2.3 Hlabisa HIV Treatment and Care Programme

The Hlabisa HIV Treatment and Care Programme is a partnership between the KwaZulu-Natal Department of Health (DoH) and the Africa Centre, aiming to provide an accessible, equitable and comprehensive service to all people living with HIV infection (30). Established in 2004, the service is decentralized to all 17 primary health care clinics in the sub-district, and is nurse- and counsellor-driven, with scheduled physician visits to initiate patients on treatment and manage clinical problems. Recently, agreement was reached regarding nurse-led initiation and a number of nurses within the programme are enrolled on training programmes to allow this to happen. By September 2011, over 18,000 HIV-infected people eligible for treatment had started HAART; patients' eligibility is determined by South African guidelines (see section 2.2). There are no waiting lists for treatment initiation, approximately 250 adults and 30 children are started on treatment each month, and around 2,500 voluntary counselling and testing sessions are conducted monthly in the clinics or within the mobile and home-based testing services. In addition to those on treatment, more than 20,000 individuals are being monitored prior to requiring therapy. The Hlabisa HIV

Treatment and Care Programme also includes TB screening and treatment, PMTCT, PITC and VCT services, the latter delivered in the fixed clinics, as well as through mobile and home-based units (30). For individuals on ART between 2004 and 2008, retention in care at one year in the programme was 84.0% and mortality in the first year was 10.9% (31). Recent evidence shows a 46% decrease in early mortality for those who initiated ART in 2011/12 compared to the reference period 2008/9 (32).

2.4 The Africa Centre for Health and Population Studies

Hlabisa sub-district hosts the Wellcome Trust-funded Africa Centre for Health and Population Studies, a research institute of the University of KwaZulu-Natal, with a focus on HIV epidemiology and prevention (www.africacentre.com); the Centre partners with the Department of Health in the delivery of HIV treatment and care in the Hlabisa sub-district. A core activity of the Africa Centre is the longitudinal socio-demographic (bi-annual) and HIV (annual) surveillance in a geographically defined area in the south of the sub-district, covering about 40% of the area and of the population in the sub-district – the Demographic Surveillance Area (DSA) (see shaded area of Figure 1).

The TasP trial will take place in the sub-district outside of the Africa Centre surveillance area, so that the on-going HIV surveillance in the Africa Centre area can continue to monitor changes in behaviours and risks over time in a population very similar to the one where the trial will take place. The trial area contains six of the 17 fixed primary health care clinics in the sub-district.

3. Trial objectives

3.1 Overall objectives of the trial (first and second phase)

3.1.1 Main objective

- To compare the effect of ART initiated immediately after HIV diagnosis, irrespective of CD4 count criteria versus South African guidelines, on the reduction in incidence of new HIV infections in the general population in the same setting.

3.1.2 Specific objectives

Among all participants

- To compare the acceptability and feasibility of providing HIV testing to all members of a community between the two trial arms, and more specifically:
    - Acceptability/uptake of initial and repeat HIV counselling and testing (see section 7.3.1.1)
    - Behavioural changes at individual level: sexual behaviours, prevention practices, disclosure (see sections 7.3.1.2 and 7.3.1.3)
    - Community awareness, attitudes and behaviours (see section 7.3.1.5).
    - Societal response (see section 7.3.1.6)
    - Household expenditures, cost-effectiveness and other economic consequences of the trial intervention at individual level (see section 7.3.1.4)

Among HIV-infected participants only

- To compare acceptability and uptake of entry into care and ART between the two arms
- To compare participant retention, mortality and morbidity, TB, virological treatment failure, acquired HIV drug resistance, toxicity and cases of vertically-acquired HIV infections between the two arms (see section 7.3.2)
- To compare HIV testing experience, ART knowledge and perception, self-reported adherence to ART, quality of life, between the two arms (see section 7.3.2)

Within the health system

- To evaluate the challenges faced by the health care system and health care professionals in providing the trial intervention and coping with the increased number of trial participants (see section 7.5)

3.2 Objectives specific to the first phase

3.2.1 Main objective

- To validate and update the parameters of the model used to estimate the trial sample size and HIV incidence, in terms of: uptake of HIV testing, linkage to care upon HIV diagnosis, internal migration and ART initiation.

3.2.2 Specific objectives

Among all participants

- To estimate the acceptability and feasibility of providing HIV testing to all members of a community, and more specifically:
    - Acceptability/uptake of initial and repeat HIV counselling and testing (see section 7.3.1.1)
    - Behavioural changes at individual level: sexual behaviours, prevention practices, disclosure (see sections 7.3.1.2 and 7.3.1.3)
    - Community awareness, attitudes and behaviours (see section 7.3.1.5).
    - Societal response (see section 7.3.1.6)
    - Household expenditures, cost-effectiveness and other economic consequences of the trial intervention at individual level (see section 7.3.1.4)

Among HIV-infected participants

- To estimate acceptability and uptake of entry into care and ART
- To estimate participant retention, mortality and morbidity, TB, virological treatment failure, acquired HIV drug resistance and toxicity (see section 7.3.2)
- To estimate HIV testing experience, ART knowledge and perception, self-reported adherence to ART, quality of life (see section 7.3.2)

Within the health system

- To evaluate the challenges faced by the health care system and health care professionals in providing the trial intervention and coping with the increased number of trial participants (see section 7.5)

Other objectives

- To calculate the incidence of HIV infections in the general population in the clusters selected for the first phase to confirm the assumptions made in the sample size calculations for the main trial
- To better define the trial procedures on the basis of experience in the first phase as the acceptability of HIV testing and entry into care may present unexpected challenges
- To revise the protocol, if changes in national ART guidelines or new scientific evidence on the effect of early ART were to become available.

4. Overall trial plan

4.1 Description of the two trial phases

4.1.1 First phase

The first phase of the trial is planned over a 24-month period (see section 4.2). The aim of this first phase is to validate the hypothesis defined for the overall trial design (number of clusters, number of participants, incidence, HIV prevalence) and to verify the feasibility and acceptability of the intervention within the community.

The first phase will be conducted on a limited number of participants (n=10 000) and a limited number of clusters (2×5, see section 8).

In the initial four clusters, three rounds of home-based HIV testing of six, four and four months will be conducted. HIV-infected participants identified in all clusters will be followed-up between 7-24 months depending on the time of entry in the trial (first or third HIV testing rounds, see Figure 4).

For the additional 6 clusters, 2 rounds of home-based HIV testing of six months each will be conducted and this will coincide with the last 12 months of follow-up in the initial 4 clusters. Follow up of HIV-infected participants in these 6 clusters will be 1-12 months in the first phase.

4.1.2 Second phase

If in the first phase the procedures and approach are shown to be feasible and acceptable, if the aims of the trial are still deemed relevant within the context of international research advances and the research strategy of the Africa Centre and partner institutions, and in agreement with the Steering Committee (SC) and recommendation of the Scientific Advisory Board (SAB) and the Data Safety Monitoring Board (DSMB), the trial will be rolled-out to the remaining clusters (n=12, see section 8) in the second phase.

Four HIV testing rounds of six months each will then be conducted in all 22 clusters. HIV infected people from the phase 1 will continue to be followed in the TasP trial clinics until the trial ends when their care will be transferred to the programme as appropriate.

4.2 Trial timelines

Figure 2 summarises the timeline of the overall trial, first and second phase.

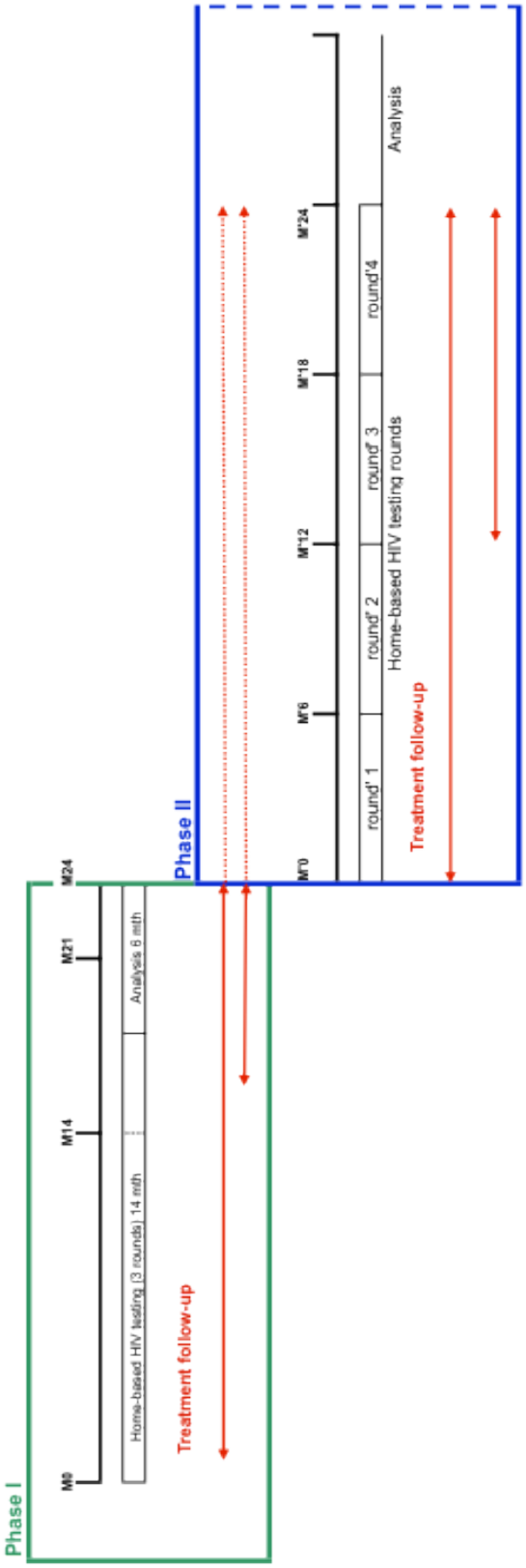


Figure 2
Timeline for the overall TasP trial

4.2.1 First phase (2011-2013)

For the initial 4 clusters

- October 2011 – February 2012: Preparation of the trial, recruitment and training of staff, logistics, ethics application, liaison with Department of Health.
- March – October 2012 inclusive: First round of HIV testing and enrolment in the four (2×2) clusters (this first round will take six months to allow registration of household members and formal introduction of the trial to households, etc.).
- Nov 2012 – August 2013: Two further rounds of HIV testing of four months each

For the additional 6 clusters

- August – December 2012: preparation for the addition of 6 new clusters
- January 2013 - February 2014: Two rounds of HIV testing of six months each

For all 10 clusters

- September 2013 – April 2014: Data analysis and review of results to date to inform decision regarding continuation of the trial. The final decision will be made by the SC according to the recommendations of the SAB and the DSMB.
  - In case of discontinuation: HIV-infected participants enrolled in the trial clinics will be transferred to the Hlabisa ART programme.
  - In case of continuation: HIV-infected participants will be followed-up during the second phase for a further 24 months (see section 6.4)

4.2.2 Second phase (2013-2016)

- November 2013 – March 2014: Preparation of the trial in the 12 new clusters
- April 2014 – March 2016: Enrolment in the 12 (2×6) new clusters and follow-up in the 10 phase 1 clusters during four rounds of HIV testing of six months each
  - April – December 2016: Data analysis and publication of final results according to the recommendations of the SAB and the DSMB

4.3 Description of the trial participants

Trial participation will be offered to all individuals meeting the following criteria:

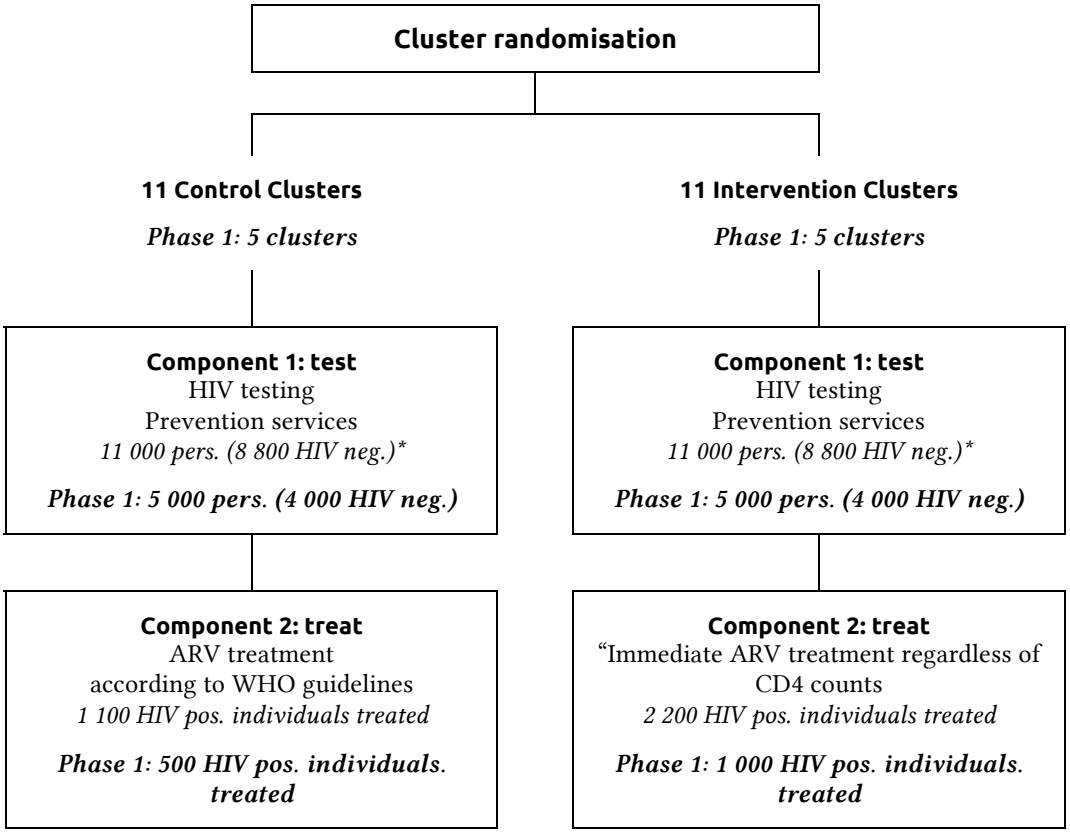
- aged ≥16 years;
- member of a household in the designated cluster (head of household defines the membership status in Zulu culture);
- able and willing to give written informed consent for trial participation and/or HIV counselling and testing.

Note: Individuals considered unable to provide informed consent will include those with severe uncontrolled psychiatric disorders, and those with neurological impairment resulting in an inability to participate in the informed consent process.

5. Trial components

The TasP trial consists in HIV testing of all members of the community at regular intervals (component 1) and comparing two ART initiation strategies for HIV-infected participants (component 2) as summarised in Figure 3 below.

Figure 3
Description of the different components of the TasP trial



** expected number of subjects within the 22 clusters.*

5.1 Component 1: HIV counselling and testing and comprehensive prevention programme

This first trial component will be identical in both intervention and control clusters:

- Provision of HIV counselling and testing to all members of the trial clusters (see section 6.2.2)
- Access to a full set of preventive services for all trial participants, services already available in DoH clinics for HIV-negative participants and made available within the trial clinics for HIV-infected participants; this will include Information, Education and Communication (IEC) and condom distribution, circumcision services, syndromic management of STIs and post-exposure prophylaxis, family planning (see section 6.3)

5.2 Component 2: ART for HIV infected participants

Within the second component, HIV-infected patients identified within the trial will be offered ART according to different eligibility criteria between the intervention and control clusters:

- in the intervention clusters: all HIV-infected adults will be offered ART regardless of their immunological and clinical staging;
- in the control clusters, HIV-infected people will be assessed clinically and immunologically and when eligible for treatment as per South African guidelines will be offered ART.

6. Trial conduct

6.1 Preparing the community

At the beginning of phase 1, a detailed community entry, education and trial promotion strategy that builds on the Africa Centre's extensive community engagement programme will be implemented based on the preparatory fieldwork conducted during late 2010, funded by the ANRS and the Africa Centre.

Key elements of the Africa Centre's existing and ongoing community engagement programme that provide opportunities to promote the trial include: bi-weekly sponsored community 'edu-tainment' road shows; annual community soccer and netball tournaments; annual community 'fun-run'; a widely circulated community magazine in isiZulu *(Umbiko)*; participation in a local community radio and a new programme of 'edu-tainment' music CDs distributed and played by operators of the local mini-bus taxi association.

The funded exploratory work involved a community consultation process using in-depth interviews and consumer research panels with a range of key community informants meeting several times during the pre-pilot phase to determine what additional community education and awareness activities are needed for the first phase. The resulting community entry strategy for the trial itself will be developed jointly by the investigators and the Africa Centre's Community Liaison Office and tested with the community research panels in the preparatory period of the trial (see section 7.4.5).

6.2 Baseline assessment, enrolment of participants, HIV counselling and testing

6.2.1 Approaching households, obtaining individual consent, and administrating population-based questionnaires

The procedures presented below apply to each round of HIV testing. They are the same for the intervention and control clusters, for phase 1 and for phase 2.

All households within each of the trial clusters will have been identified and GPS coordinates noted. A team of trial community testers, all of whom will be DoH-trained VCT counsellors, will approach the household and seek permission to enter from the household head (or most senior household member present if head is absent). After entering, the testing team will explain the trial and the procedures for testing and seek the permission of the household head to offer trial participation and HIV counselling and testing to adult members of the household. Specific information sheets for each component will be provided to all individuals (See Appendix 15.4).

Once the head of household has agreed to allow the team to enter the household, he/she will be asked to complete the *Tasp household registration questionnaire* (THR) on the netbook and the *TasP household information assets questionnaire* (HHI) (see section 7.4.1).

Once permission to proceed has been granted by the head of household, a private space will be identified and all individual adult household members will be invited to give written permission to complete the *TasP home-based individual questionnaire* (IQ), see section 7.4.1), with/without anonymous sampling of blood for HIV surveillance, with/without undergoing confidential HIV counselling and testing (see section 6.2.2 below). Individual household members may participate

in the trial by agreeing to the individual questionnaire with/without HIV testing (separate consent forms, *Home-Based Individual Questionnaire and DBS Consent Form – CZ1 – and Home-Based HIV Testing Consent Form – CZ2*). People who do not want to be tested for HIV in the household can attend any of the DoH clinics, or the trial clinic, for testing and will be informed of this possibility.

The content of IQ is described section 7.4.1.

Participants who give consent to the anonymous collection of blood for HIV-related tests will have blood collected by field workers by finger prick and stored on filter paper as dried blood spots (DBS) (see testing procedures section 6.4.6).

The HIV counselling and testing procedures are described below (see section 6.2.2).

In each round of testing, the team will be able to return on up to two more occasions to offer trial participation and/or HIV testing to members of the household who were not present during the initial visit, after which the untested members of the household will receive a written invitation to attend the trial clinics where HIV counselling and testing will also be available.

For participants who decline both HIV counselling and testing and the questionnaires, we will obtain basic demographic data from the household head. Participants who decline either testing or the questionnaire in the follow-up rounds will be asked to provide key, basic socio-demographic, knowledge of HIV status and HIV testing history data to the testing team (see section 7.4.1).

6.2.2 HIV counselling and testing procedures

Different HIV testing strategies currently operate in the trial area. HIV testing is available in DoH hospital and the 17 fixed primary health care clinics. This includes VCT clinics and PICT (provider initiated counselling and testing), including the routine testing of pregnant women and TB patients in clinics. In addition, some non-government organisations (NGOs) provide testing at fixed sites in Mtubatuba town and KwaMsane and may take testing to community venues and events. Further, the DoH/Africa Centre partnership programme, the Hlabisa HIV Treatment and Care Programme (see section 2.3), provides the largest and most comprehensive range of HIV testing services available, employing DoH-trained counsellors. The testing options available in the Hlabisa HIV Treatment and Care Programme include mobile clinics, offering testing in communities routinely, mobile testing clinics at community events, and home-based VCT offer in households across the whole of the Hlabisa sub-district, an initiative in the Programme started in 2009 which has proved to be highly acceptable with a high uptake rate (see section 1.1.4).

Within the TasP trial we will extend the provision of home-based VCT in households on a more regular basis with six monthly visits and combine the current range of community and clinic testing options, thus achieving a maximum (near universal) HIV testing coverage in the area and increasing options for repeat HIV testing.

During each HIV testing round, individuals providing written informed consent will receive pre-test HIV counselling privately and confidentially, delivered by a DoH trained counsellor.

Rapid HIV testing will be performed. The screening test will be Determine, and the confirmatory test will be First Response. Test results will be provided approximately 20 min after testing.

All participants who test HIV-positive will be referred to the trial clinic for further assessment, including a point-of-care CD4 count. Results from the baseline viral load test will confirm HIV positive status. Where there is discrepancy in results between the VL test and the rapid antibody test, the DBS from the home-based testing stored in the Africa Centre virology laboratory can be accessed for confirmatory antibody testing.

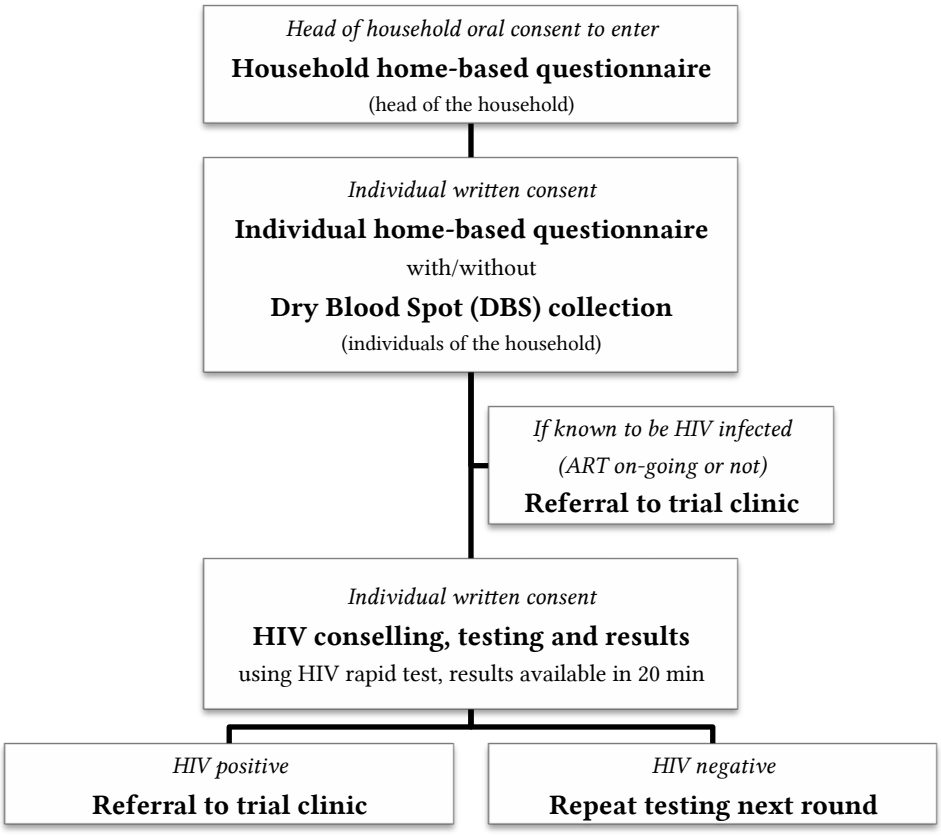
The individual post-test HIV counselling session will take place as per routine DoH procedures, covering the prevention of acquisition of HIV for negative people and the implications of HIV infection for positive people.

The same home-based HIV VCT procedures will be used in successive rounds of community testing to ensure a high uptake of testing and repeat testing overall, particularly as those who decline testing in one round become familiar with the procedures.

A standardised referral procedure will be developed to provide an opportunity to children and minors to be tested according to the South African guidelines at the DoH clinics and other facilities.

Figure 4 summarises the home-based procedures at each round of testing.

Figure 4
Home visit chart.



6.2.3 Referral and linkage to care procedures

During each home-based VCT round, at the end of the counselling and testing session, all participants will be given the same referral/prevention card (regardless of their test result and/or parts of the trial they may have consented to). The referral card will contain information about the TasP trial clinics and the available services (treatment and care, VCT, condoms, referral to circumcision,

etc.). Each participant will be asked to take their referral card with them when they attend clinics in order to identify them as a trial participant. A thumbprint will be taken at the TasP clinic to confirm a participant's correct identity and their correct service eligibility (i.e. treatment, care and prevention or VCT and prevention).

During post-test HIV counselling, HIV-infected participants will all be referred to the trial clinic in their cluster for further assessment as to their treatment eligibility (see section 6.4 below). HIV-infected participants will be informed that, if they have not attended the trial clinic within 3 months of referral, they will be contacted by a member of the study team (tracking team) either by phone or during a home visit for additional counselling and support to facilitate linkage to care.

A trained research psychologist will work with the tracking team to explore cognitive, psychological and normative aspects, which determine clinical linkage among individuals who test positive in the trial, but have not linked to care within 3 months of testing. All participants will be asked a screening question regarding the information received on the trial to test recall and understanding of opportunities to link to care. Thereafter psychological assessments will be completed using short validated screening tools with participants in their homes. This assessment includes psychological measures of depression, anxiety, somatisation (using the PHQ9; PHQ15 and GAD7) and health perceptions (MOS-36); normative aspects including stigma (HIV Stigma Scale - Revised) and family functioning (FAD). A brief cognitive screen (Oxford Cognitive Screen) on executive function will be administered using a tablet. This assessment will take approximately 45 minutes.

6.3 Preventive interventions

All participants, whether from intervention or control clusters, will have access to a full set of preventive interventions described below. HIV-negative participants will access these services, as does the general population, within DoH fixed clinics. All HIV-infected participants will be provided these services during their follow-up visits within the trial clinics.

6.3.1 Information and education, condom promotion and distribution

Specific behaviour change information and education, condom promotion and distribution activities, in line with what is currently provided in the Hlabisa HIV Treatment and Care Programme, will operate alongside those sponsored by national and provincial governments as well as various NGOs. VCT counsellors and clinic staff are trained in essential behaviour change counselling and available to provide this to trial participants both during VCT sessions or clinic visits. Social marketed condoms are currently routinely available through the DoH clinics as well as for purchase in small convenience shops (*spaza* shops) in the community, more formal shops, petrol stations and other outlets. On the basis of our audit and mapping of prevention and HIV testing services additional condom distribution plans for both intervention and control clusters will be implemented.

6.3.2 Male circumcision

The phased implementation of a national programme of male circumcision has started in South Africa and KwaZulu-Natal's roll-out started at test sites in 2010. During 2011, the plan involved the setting up of mobile surgical facilities (in

'camps') where a trained physician performs the procedure for young adult males. The Africa Centre works closely with the DoH in implementing the programme in the sub-district as part of the Hlabisa HIV Treatment and Care Programme. However, since then the mobile camps have not been regular, and the programme has been taken over by NGO's working in the district; in addition circumcision is available from the district hospital, but there is limited capacity. Male circumcision is also available from private medical practitioners in the area and is covered by some employees' medical-aid schemes. Rates of male circumcision among participants in the Africa Centre's HIV surveillance have been low.

6.3.3 Syndromic management of sexually transmitted infections

All HIV-infected participants (male and female) will undergo a standardised STI symptom screen at the time of enrolment in the trial clinic, and at regular intervals once enrolled in HIV care. Symptom screen for women will include: lower abdominal pain, vaginal discharge, dysuria, and genital ulcers. Symptom screen for men will include: urethral discharge/dysuria, genital ulcers, and scrotal swelling/pain. This will be treated syndromically according to South African guidelines. The importance of partner treatment will be stressed and partner notification slips will be issued as per routine practice. All management will be in line with national guidelines and no additional diagnostic services will be included in the trial phase.

6.3.4 Post-exposure prophylaxis after sexual assault

All incidents of sexual assault for trial participants will be reported immediately to the police and management will follow standard guidelines. Post-exposure prophylaxis (PEP) will be offered to HIV-negative participants reporting penetrative anal or vaginal sexual assault who present within 72 hours**.** This consists of ZDV 300 mg bd + 3TC 150 mg bd (Combivir) and LPV/r (Kaletra) 400/100 mg bd for four weeks and will be administered either at Hlabisa hospital or at the existing crisis centre.

6.3.5 Family planning

All female participants will be asked about their use of family planning methods at the time of trial enrolment. Family planning advice will be offered to both HIV-positive and HIV-negative female participants, as part of the post-test counselling within the household. For HIV-infected people, there will be more opportunity for discussion at the trial clinics, whereas HIV-negative people will be referred to the DoH services. Dual methods (hormonal contraception + barrier) will be encouraged for all participants with no immediate pregnancy intentions. Any request to commence contraception will require referral to the fixed DoH primary health care clinic – this will be facilitated with a standardised referral form. HIV-negative participants will ordinarily be offered either oral contraceptives (several options) or injectable contraceptive (medroxyprogesterone acetate 150mg, 12-weekly). HIV-positive participants will be encouraged to use an injectable contraceptive.

6.4 Management and care of HIV-infected participants

6.4.1 Pre-treatment assessment visit

All participants newly diagnosed with HIV infection during any of the home-based VCT rounds will be referred to their trial clinic for immediate further assessment. Trial clinics will be informed about whom to expect.

Trial clinics (one per cluster) will be situated in close proximity to residences (< 45 minutes walking distance for all participants within the cluster).

These trial clinics will be staffed by a counsellor and a nurse. A referent physician will be available weekly at each clinic and on-call if necessary.

At the trial clinics, **all newly documented HIV-infected participants** will be provided standard counselling/ART education and adherence sessions by the ART counsellor and nurse, over one to three visits. They will be asked using separate documents to: 1) provide self-reported information and an anonymous blood specimen for viral load testing (see below) and 2) receive care and/or treatment at the trial clinics as per DoH standards. The HIV-infected participants consenting to treatment will then undergo a clinical evaluation which includes medical history, physical examination, WHO clinical staging (review of current and previous morbidity), basic anthropometry (weight and height), as per DoH procedures using the following CRFs: *Clinic baseline visit - Counsellor (CBC), Clinic Follow-up - Counsellor (CFU), Clinic history and examination-nurse (CHE).*

Patients will be referred to the ART counsellor to respond to the *Social science clinic-based baseline questionnaire* (SCB) and specifically questions regarding HIV testing experience, ART perception, disclosure and economic situation (see Table 3). This baseline interview will take place anytime during the pre-treatment visits.

In the intervention clusters, the clinical evaluation will involve completion of the following:

- Blood tests: CD4 count (point of care*), VL, haematology (full blood count), biochemistry (urea, creatinine, electrolytes, liver function tests, glucose, lipids), hepatitis B surface antigen (HBsAg) and plasma storage,
- Urine tests: dipstick urinalysis, beta hCG to all women of childbearing age.
- Other screening: Sputum will be collected for TB investigation (microscopy and culture), as appropriate following screening on clinical symptom

In the control clusters, the pre-treatment assessment will be decided after obtaining the CD4 count measured at point of care and/or according to the clinical staging (see ART initiation criteria in section 6.4.1 below):

- Patients eligible for ART will undergo baseline investigations performed as above
- Patients not eligible for ART will have a blood sample collected for baseline VL measurement and storage; they will be invited to return to the study clinic in 4-6 months based on the CD4 count

All participants will be seen within two weeks of this W0 pre-assessment visit, to review this pre-therapeutic assessment and, if indicated, initiate treatment at W2.

In both clusters, **patients refusing ART** will be offered the opportunity to remain in care and will be asked to consent to six-monthly clinical assessment: describe (see section 6.4.4.3).

In both clusters, **participants already established on ART** from the Hlabisa HIV Treatment and Care Programme will be encouraged to be included in the trial and to transfer their care to the trial clinics. Participants already established on ART from private/other HIV treatment providers will be encouraged to take part in the trial monitoring procedures. They will be offered the option of 1) transferring follow-up to the trial clinic (the same follow-up procedures as for patients newly established on ART will then apply) or 2) continuing follow-up from their normal provider, without any discriminatory measures applied to them. During the home visit, all HIV-infected participants will be asked to give consent for their clinical records to be obtained from their normal provider should they choose not to attend the trial clinics. Information accessed would include ART status, ART regimen if on ART, CD4 counts and viral loads. This information will be used to estimate the ART treatment coverage in each cluster as this is directly linked to HIV transmissions. The nurse at each trial unit will liaise weekly with the Hlabisa HIV treatment programme clinics to ensure ease of information collection for patients who received clinical care outside of the trial clinics.

* *Note on CD4 point of care:* We will use the Alere PIMA™ device tool (http://pimatest.com/en/home.html) to measure CD4 in the clinics. The system has built-in quality control mechanisms, in addition to which the trial will develop its own quality control procedures (in association with CD4 laboratory, NHLS). Quality control will be performed on a 10% of participants selected by systematic random sampling using the enrolment log of each clinic as a sampling frame. All subsequent samples from the identified individuals requiring haematology assessment will also be assessed for CD4 count at the NHLS laboratory at Hlabisa hospital.

6.4.2 ART initiation criteria

In the intervention clusters, there are no immunological criteria for starting ART; all HIV-infected participants are eligible for ART.

In the control clusters, HIV-infected participants will be eligible for ART in line with the revised March 2013 South African guidelines (see Appendix 15.1).

- CD4 count $\leq$ 350 cells/mm^3 irrespective of clinical symptoms
- WHO clinical stage 3 or 4 irrespective of CD4 count
- MDR or XDR TB
- All pregnant women for the duration of pregnancy and breastfeeding (option B)

6.4.3 ART drugs used within the trial

6.4.3.1 Description of the drugs

All ART drugs that will be used in the trial are those recommended in the National Department of Health Adult HIV management guidelines (see Table 1).

The standard first-line drug regimen for HIV-infected participants will in both arms be the fixed drug combination (FDC) Tenofovir (TDF – 245 mg) + Emtricitabine (FTC – 200 mg) + Efavirenz (EFV – 600 mg) or Atripla® once daily. Participants who transfer their care while on the generic formulation of the FDC Tenofovir (TDF – 245 mg) + Emtricitabine (FTC – 200 mg) + Efavirenz (EFV – 600 mg) which is available in the government HIV treatment programmes will be able to continue on this but for logistic reasons could be switched to Atripla® as

they would then be less dependent on supplies from the government (See Appendix 15.1).

Table 1
Antiretroviral regimens proposed to TasP patients

1st Line		
All new patients needing treatment, including pregnant women	TDF + FTC (or 3TC) +EFV Fixed drug combination (FDC) preferred	Replace EFV with NVP in patients with significant psychiatric co-morbidity or intolerance to EFV and where the neuro-psychiatric toxicity of EFV may impair daily functioning, e.g. shift workers.
Contraindications to EFV	TDF + (FTC or 3TC) + NVP	Use NVP based regimen: In patients with significant psychiatric co morbidity or intolerance to EFV and where the neuro-psychiatric toxicity of EFV may impair daily functioning, e.g. shift workers.
Contraindication to TDF	AZT+ 3TC +EFV or (NVP)	Renal disease or the use of other nephrotoxic drugs e.g. aminoglycosides
Contraindication to TDF and AZT	d4T + 3TC+ EFV (or NVP)	Renal disease and anaemia or the use of other nephrotoxic drugs, aminoglycosides
Contraindication to TDF, AZT and d4T	ABC + 3TC + EFV (or NVP)	Renal disease, anaemia, peripheral neuropathy, the use of other nephrotoxic drugs
Currently on d4T-based regimen	TDF + FTC(or 3TC) + EFV FDC preferred	Mandatory if patients experience toxicity and patients who are at high risk of toxicity (high BMI or pregnant). Switch to TDF if virally suppressed and the patient has normal creatinine clearance, even if well tolerated.
2nd Line		
Management of virological failure		If plasma HIV RNA >1000 copies, Check for adherence, compliance, tolerability and drug- drug interaction and assess psychological issues. Repeat VL test 2 months later. If plasma VL confirmed >1000copies change regime to second line therapy
Failing on a TDF-based 1st line regimen	AZT+3TC+ LPV/r	Patients with anaemia and renal failure switch to ABC
Failing on a d4T-based 1st line regimen	TDF+3TC (or FTC) and LPV/r	
Dyslipidaemia or diarrhoea associated with LPV/r	Switch LPV/r to ATV/r	
Third line		
Failing any 2nd line regimen	Specialist referral	
Should be expert and genotype resistance testing based decision and supervised care Patients failing on second line therapy will be managed by an expert panel. The drugs for third line will be managed centrally. More discussion is required to deal with the modalities	Most likely regimen would be Raltegravir/Darunavir/ /Etravirine adjusted according to genotype Interpretation. Should be by expert and take into account prior exposure and predictable mutations	

6.4.3.2 Supply

Atripla® will be provided by MSD during the study period, All other drugs will be provided by the KwaZulu-Natal Provincial Department of Health according to the standard of care.

6.4.3.3 Drug handling and storage

Trial drugs provided and shipped by MSD will be held centrally at Hlabisa Hospital pharmacy, under the supervision of the trial pharmacist. Supplies will be delivered weekly to the treatment sites within the trial area and kept in secure storage facilities.

At each delivery, the pharmacist will record the trial patient identification code, the name of the drug, the number of the batch, the expiry date and the accountability on the Drug Accountability form.

All trial drugs will be labelled with the patient name as per South African standards, trial number, and dosing requirements.

Patients will be provided with 4-weekly supply of drugs initially. Participants who have undetectable viral loads and no ongoing medical problems will be allowed 8-weekly supply of drugs to decrease frequency of clinic attendance to save them time and transport costs.

Participants will be requested to return all empty bottles and to bring any bottles in use to their follow-up visits. Unused drug must be returned to the trial site if a participant withdraws from the trial. Unused drugs will be disposed of through the existing disposal mechanisms in place at Hlabisa Hospital pharmacy.

6.4.4 Patient follow-up

The follow-up procedures for HIV-infected participants will be the same in both intervention and control clusters.

6.4.4.1 ART initiation visit

ART initiation will take place ideally within two weeks of enrolment at the trial clinic, unless purposely delayed for clinical reasons (e.g. TB treatment).

The results of baseline investigations of all patients eligible for ART initiation and consent for treatment will be reviewed with the nurse. Nurses will initiate ART in uncomplicated cases. As per the Hlabisa HIV Treatment and Care Programme, there will be specific guidelines regarding clinician referral prior to ART initiation (e.g. for patients with persistent TB symptoms but negative sputum smear, and patients with abnormal renal or liver function). Appendix 15.5 presents a flowchart of the follow-up provided to HIV-infected participants in the intervention and control clusters.

For patients already on ART and transferred from private/other HIV treatment providers, their ART initiation date will be the date of their first visit to a TasP clinic (for the trial purposes, it will not reflect their duration on ART).

6.4.4.2 Treatment duration

Once the decision to initiate ART has been made, patients will receive ART and be followed-up within the trial for a maximum duration of four years depending on time of enrolment in trial (see Table 2).

Table 2
Follow-up calendar for HIV-infected participants eligible for ART

	W0	W2	W4	W6	W10	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23	M24
Consent	x																										
Medical history	x																										
Nurse																											
Physical examination	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight, height	x					x			x			x			x			x			x			x			x
WHO clinical staging	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Morbidity/hospi	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
TB/STI screening (if appropriate)	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CD4 point of care	x					x			x						x						x						x
ART initiation		x							x						x						x						x
Adherence monitoring			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory																											
HIV VL	x					x			x						x						x						x
Genotyping	As clinically indicated, in cases of confirmed virological failure																										
CD4 counts (quality control)	x								x						x						x						x
Haematology	x								x						x						x						x
Biochemistry (U&Es, LFTs)	x					x			x						x						x						x
HBsAg	x																										
Beta hCG	x					x			x						x						x						x
Urinalysis	x					x			x						x						x						x
Plasma storage (-80°C)	x					x			x						x						x						x
Blood volume (ml)																											
Clinic-based survey																											
HIV testing experience	x																										
ART perception, decision	x								x						x						x						x
Disclosure and couple	x								x						x						x						x
Social and community support	x								x						x						x						x
Stigma and discrimination	x								x						x						x						x
Health expenditure	x								x						x						x						x
Economic situation	x								x						x						x						x
Sexual behaviour									x						x						x						x
ART knowledge									x						x						x						x
Self-reported ART adherence									x						x						x						x
HIV quality of life									x						x						x						x
Satisfaction with care									x						x						x						x

TB: Tuberculosis; STI: Sexually Transmitted Infections; ART: Antoretroviral Treatment; VL: Viral Load; U&Es: Urea and Electrolytes test; LFT: Liver function tests.

	M24	M25	M26	M27	M28	M29	M30	M31	M32	M33	M34	M35	M36	M37	M38	M39	M40	M41	M42	M43	M44	M45	M46	M47	M48
Consent																									
Medical history																									
Nurse																									
Physical examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight, height	x			x			x			x			x			x			x			x			x
WHO clinical staging	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Morbidity/hospi	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
TB/STI screening (if appropriate)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CD4 point of care	x			x			x						x						x						x
ART initiation	x						x						x						x						x
Adherence monitoring	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory																									
HIV VL	x			x			x						x						x						x
Genotyping	As clinically indicated, in cases of confirmed virological failure																								
CD4 counts (quality control)	x						x						x						x						x
Haematology	x						x						x						x						x
Biochemistry (U&Es, LFTs)	x			x			x						x						x						x
HBsAg																									
Beta hCG	x			x			x						x						x						x
Urinalysis	x			x			x						x						x						x
Plasma storage (-80°C)	x			x			x						x						x						x
Blood volume (ml)																									
Clinic-based survey																									
HIV testing experience																									
ART perception, decision	x						x						x						x						x
Disclosure and couple	x						x						x						x						x
Social and community support	x						x						x						x						x
Stigma and discrimination	x						x						x						x						x
Health expenditure	x						x						x						x						x
Economic situation	x						x						x						x						x
Sexual behaviour	x						x						x						x						x
ART knowledge	x						x						x						x						x
Self-reported ART adherence	x						x						x						x						x
HIV quality of life	x						x						x						x						x
Satisfaction with care	x						x						x						x						x

TB: Tuberculosis; STI: Sexually Transmitted Infections; ART: Antoretroviral Treatment; VL: Viral Load; U&Es: Urea and Electrolytes test; LFT: Liver function tests.

Any patient deciding to permanently discontinue ART will be offered the opportunity to transfer to the DoH fixed clinics while remaining under active follow-up in the trial: participants will be tracked during the household HIV testing rounds, their patient records may be accessed (see section 6.4.1).

During the first phase, all HIV-infected participants will be followed-up between 1 and 24 months. At the end of the first phase, HIV-infected patients will either be transferred to the Hlabisa ART programme if the trial stops, or followed-up until the end of the second phase.

6.4.4.3 ART follow-up visits

- **Participants receiving ART**

Participants initiating ART will be reviewed by the trial nurse monthly when they collect their medication until they have two consecutive undetectable viral loads measured three months apart following which follow up will become 8-weekly in those with no on-going medical issues.

Clinical evaluation (4-weekly or 8 weekly)

The nurse will document weight and proceed with a review of current morbidity and illnesses/hospitalizations since last visit (CHE form).

Interview/Questionnaire (six-monthly)

HIV-infected participants, whether on treatment or not, will be administered the social science clinic-based survey and interviewed at M6, M12, and 6-monthly until M48 (counting from entry into care), regarding specific topics according to visits (see Table 3). The clinic-based survey will be divided in two parts:

- one part administered by the ART counsellor who will ask non-sensitive questions such as disclosure or health expenditures: the *Social science clinic-based counsellor-administered questionnaire* (SCC);
- one part administered by an independent interviewer who will ask sensitive questions (which are subject to social pressure and thus to social desirability bias) such as sexual relations or adherence: the *Social science clinic-based independent interviewer-administered questionnaire* (SCI).

Here below in Table 3 is presented the distribution of topics to be asked either by the counsellor or interviewer.

Table 3
Topics of Social science clinic-based survey, by questionnaire

Topic	W0	M6	M12	M18	M24	M30	M36	M42	M48
HIV testing experience	C								
Economic situation	C	C	C	C	C	C	C	C	C
Health expenditures	C	C	C	C	C	C	C	C	C
ART perception and decision	C	C	C	C	C	C	C	C	C
Disclosure and couple	C	I	I	I	I	I	I	I	I
Social and community support	C	I	I	I	I	I	I	I	I
ART knowledge		I	I	I	I	I	I	I	I
Sexual behaviour		I	I	I	I	I	I	I	I
Self-reported adherence to ART*		I	I	I	I	I	I	I	I
HIV Quality of Life		I	I	I	I	I	I	I	I
Stigma and discrimination		I	I	I	I	I	I	I	I
Satisfaction with care		I	I	I	I	I	I	I	I

C: counsellor-administered questionnaire
I: independent interviewer-administered questionnaire;
** only for ART-treated patients.*

Adherence monitoring

Both an independent interviewer and the ART counsellor (who is not responsible for the treatment delivery) will monitor adherence at each visit for all participants receiving ART. This will include three categories of adherence measurement tools:

- Subjective (monthly): self-report (as per standard South African treatment guidelines, see section 7.3.2.5)
- Objective, technical (monthly): pill count
- Objective, biological (quarterly): viral load + resistance test if viral failure

Sub-optimal adherence will prompt an individual session with the HIV counsellor and nurse. Persistent sub-optimal adherence (over three consecutive visits) will prompt referral to the trial clinician. Specific problems may warrant referral to members of the Hlabisa HIV Treatment and Care Programme multidisciplinary team (pharmacist, social worker, psychologist, dietician, and home-based carers).

Laboratory assessments (M3, M6, M12, 6-monthyl up to M48)

Participants initiating a Tenofovir-based ART regimen such as Atripla will require monthly urea, electrolytes and creatinine for the first 3 months, at 6 months and then 6 monthly.

Participants initiating a Zidovudine-based ART regimen will require monthly FBC for the first three months, at 6 months and then 6 monthly.

Other screening (as required):

Sputum will be collected for TB investigation (GeneXpert, microscopy and culture), as appropriate following screening on clinical symptom

- **Participants not receiving ART**

Participants not receiving ART (not yet eligible for treatment or refusing treatment) will be referred to the trial nurse for pre-ART care and positive prevention services (see section 6.3). Their six-monthly clinical assessment will include:

- Clinical evaluation with physical examination, WHO clinical staging (review of current morbidity and illnesses/hospitalizations since last visit), STI screening, TB screening, pregnancy test if appropriate, weight.
- Biological assessment: CD4 counts (point of care) 4-6 monthly to check treatment eligibility in the control clusters.
- *Interview/Questionnaire:* HIV-infected participants will be administered the *clinic-based questionnaires* (SCC and SCI) and interviewed regarding specific topics according to visits (see Table 3).
- Based on their immunological status, treatment initiation will be proposed according to the procedures (pre-treatment assessment, treatment initiation and follow-up) described in sections 6.4.1, 6.4.2, 6.4.3 and 6.4.4 above.

Table 4
Follow-up calendar of HIV-infected participants not eligible for ART

	W0	M6	M12	M18	M24	M30	M36	M42	M48
Consent	×								
Medical history	×								
Nurse									
Physical examination	×	×	×	×	×	×	×	×	×
Weight, height	×	×	×	×	×	×	×	×	×
WHO clinical staging	×	×	×	×	×	×	×	×	×
Morbidity/hospi	×	×	×	×	×	×	×	×	×
TB/STI screening if appropriate	×	×	×	×	×	×	×	×	×
CD4 point of care	×	×	×	×	×	×	×	×	×
Laboratory									
Beta hCG	×	×	×	×	×	×	×	×	×
Clinic-based survey									
HIV testing experience	×								
ART perception	×	×	×	×	×	×	×	×	×
Disclosure and couple	×	×	×	×	×	×	×	×	×
Social and community support	×	×	×	×	×	×	×	×	×
Stigma and discrimination	×	×	×	×	×	×	×	×	×
Health expenditure	×	×	×	×	×	×	×	×	×
Economic situation	×	×	×	×	×	×	×	×	×
Sexual behaviour		×	×	×	×	×	×	×	×
ART knowledge		×	×	×	×	×	×	×	×
HIV quality of life		×	×	×	×	×	×	×	×
Satisfaction with care		×	×	×	×	×	×	×	×

W0 = date of entry into care
TB: Tuberculosis; STI: Sexually Transmitted Infections; ART: Antiretroviral Treatment.

- **Participants on ART who prefer to remain within the Hlabisa HIV treatment and care programme**

Participants on ART who, after visiting the trial clinic, would prefer to remain within the Hlabisa HIV treatment and care programme will be asked permission for their records to be accessed by the trial nurse as per trial protocol (trial nurses will attend the nearest fixed clinic once a week). During home visits, all participants would be asked to give consent for their HIV records to be accessed by the trial team. Information required will be ART regimen, CD4 count and viral load. Linkage to existing records will be done using South African identification number and date of birth.

Adherence support

The importance of long-term adherence will be emphasised in the pre-treatment period during the treatment literacy classes, as per standard DoH procedures. In addition, at each trial site a peer support group will operate for the duration of the trial and all participants will be encouraged to actively participate.

Further, the trial clinics are positioned at sites no more than 45 minutes walking away, which for most people will be considerably closer than the DoH clinics. HIV-infected participants will also face a considerably shorter waiting time, in relatively pleasant surroundings.

6.4.5 Trial treatment modifications

Trial treatment modifications will be done according to national guidelines and developed in specific trial guidelines.

6.4.5.1 Occurrence of new pregnancies

Pregnancy testing (urinary hCG) will be offered at monthly follow-up to all women of childbearing age receiving trial drugs. In line with updated national ART guidelines, Atripla® will be used for women of childbearing age and during pregnancy irrespective of trimester of pregnancy (29).

6.4.5.2 Toxicity and treatment failure

In case of toxicity or intolerance, single drug substitutions will be allowed, as per South African guidelines (29, 33). The toxicities monitored will be renal dysfunction (TDF), liver function (NVP) and teratogenicity among pregnant women (EFV).

In case of treatment failure, switch to second-line therapy will be recommended (see appendix 15.1). VL and CD4 cell count will be performed 3 and 6 months after initiation and then 6-monthly for all participants on ART. The decision to switch to second-line ART will be taken on the basis of two consecutive HIV RNA measurements > 1 000 copies/ml at least two months apart (as per current South African national guidelines) (29, 33). Information from genotyping will also be made available in real-time to the trial clinician to guide the decision whether to switch regimens. The standard second-line regimen will be ZDV + 3TC + LPV/r.

Participants positive for HBsAg will continue TDF in their regimen should they need to switch to second-line therapy.

Trial participants fulfilling criteria for immunological and/or clinical failure in the absence of criteria for virological failure will be reviewed by the trial clinician before any switch in drug regimen. Second-line regimen will be prescribed following a

confirmed virological failure while the patient is on therapy, in accordance with South African guidelines.

6.4.5.3 Care of patients at the end of the trial

Trial participants receiving ART at the end of the trial will be transferred into the Hlabisa HIV Treatment and Care Programme and will remain on the same drugs. The drugs will then be provided by the KwaZulu-Natal Department of Health, whether first-line or second-line drug regimens (see Appendix 15.3).

6.4.5.4 Concomitant therapies

- Isoniazid preventive therapy (isoniazid 300 mg orally od) will be provided to HIV-infected participants in the intervention and control clusters as per national and provincial policies at the time of the trial (implementation in progress).
    - Co-trimoxazole (960 mg od) will be provided to HIV-infected participants in the intervention and control clusters if WHO stage II, III, or IV, or CD4 cell count < 200 cells/mm^3.
    - Multivitamins (1 tablet od) supplementation will be provided to HIV-infected participants on ART in the intervention and control clusters as per South African guidelines.

6.4.6 Sample handling and storage

Blood samples will be collected by trial field staff at the time of enrolment and by the nurse during subsequent visits to the trial clinics for HIV-infected trial participants according to the schedule presented table 1. The trial will utilise both the National Health Laboratory Service (NHLS) laboratory at Hlabisa Hospital and the Africa Centre laboratory at the University of KwaZulu-Natal, Nelson R. Mandela School of Medicine in Durban. Storage of samples will take place only at the Africa Centre laboratory. No samples will be transported out of South Africa without seeking appropriate permissions and approvals from the Ethics Committee, the University and South African regulators. Detailed procedures for sample collection, transport, processing, and storage will be included in a separate laboratory procedures manual/protocol.

The DBS samples collected during the HIV testing rounds will be transported daily via the sample processing unit at the Africa Centre to the Africa Centre laboratory in Durban. Two (2) of the DBS will be used on arrival at the laboratory for HIV testing. The remaining DBS will be stored at -80°C in the Africa Centre Virology Laboratory in Durban.

Blood will also be collected by venepuncture:

- at the initial clinic visit in all HIV-infected participants in the intervention clusters and in HIV-infected participants meeting ART initiation criteria in the control clusters
- at subsequent clinic visits for all HIV-infected participants on ART (M3, M6, M12, and 6-monthly up to M48) according to the schedule presented in Table 2.

A total of 30 ml will be drawn each time:

- 10 ml of blood will be sent to the NHLS laboratory for routine haematology, biochemistry, and HBV testing (these samples will not be stored)
- 20 ml of blood (2×10 ml tubes) will be sent to the Africa Centre laboratory for plasma viral load testing and storage at -80°C.

7. Trial outcomes and tools

7.1 Definition of trial outcomes

Table 5 summarises the definition of each trial outcome. If not explicitly mentioned, these outcomes will be documented in both phases of the trial, within the 10 clusters for the first phase and within 22 clusters during the overall trial.

Table 5
Definition of trial outcomes

Outcome	Definition, indicators	Comparison	Tool	See
General population level				
HIV incidence	◉ Results of DBS, molecular epidemiology findings (clusters), primary resistance ◉ Incidence estimates assessed by socio-demographic characteristics	IC vs.CC *Second phase only*	IQ	7.2
Acceptability of initial HIV counselling and testing	◉ HIV testing history at baseline ◉ Attitudes towards HIV testing at baseline and changes over time ◉ Different estimates of coverage/uptake of HIV testing per method of calculationSocial determinants of HIV testing uptake at individual and community levels	IC vs.CC HIV+ vs. HIV-	IQ IDI	7.3.1.1
Prevention practices	◉ Circumcision uptake over time ◉ Contraceptive use and pregnancies over time	IC vs.CC HIV+ vs. HIV-	IQ	7.3.1.2
Sexual behaviours	◉ Sexual partnerships patterns over time, disinhibition ◉ Safe sex and condom use over time ◉ Conjugal relationships (disclosure, unions, communication)	IC vs.CC HIV+ vs. HIV-	IQ, SCS	7.3.1.2
Quality of life	◉ Quality of life at baseline and over time	IC vs.CC HIV+ vs. HIV-	IQ, SCS, CAP, IDI	7.3.1.3
Household health care expenditures Treatment/care cost and cost-effectiveness	◉ Cost analysis ◉ Economic impact of HIV infection on the household welfare (health care use and health care expenditures) ◉ Budget impact	IC vs.CC HIV+ vs. HIV-	THR, HHI, IQ, SCS, CRF	7.3.1.4
Community awareness	◉ Stigma toward PLWHA, perception of stigma ◉ Perception about ART preventing HIV infection	IC vs.CC HIV+ vs. HIV--	IQ, SCS, IDI	7.3.1.5

Outcome	Definition, indicators	Comparison	Tool	See
HIV-infected participants				
Acceptability / uptake entry into care	◉ Expectations and perceptions of early treatment over time ◉ Knowledge of HIV care and treatment ◉ Time to initiation of treatment ◉ Modalities of entry into care (health structures used) ◉ Socio-cultural and economic determinants of entry into care	IC vs.CC	IQ, HHI, CRF, SCS, CAR	7.3.2.1
Therapeutic success	◉ Patterns of retention and referral over time and their determinants	IC vs.CC	SCS, CRA	7.3.2.2
Programme retention	◉ Patterns of retention and referral over time and their determinants	IC vs.CC	SCS, CRA	7.3.2.3
Morbidity, mortality and treatment	◉ Mortality and severe morbidity (leading to hospitalization) ◉ Tuberculosis (incidence) ◉ Other morbidity events (infectious or not) by CD4 strata ◉ Immunological and virological response ◉ Socio-economic determinants of response to treatment ◉ First-line treatment, durability, switches to second-line treatment, adverse events leading to drug discontinuation ◉ Hepatitis B co-infection	IC vs.CC	CRF, SCS, IQ	7.3.2.4
Adherence to ART	◉ Estimates, patterns and measurement of adherence over time ◉ Determinants of adherence by CD4 strata	IC vs.CC	CRF, SCS, IDI, CAP	7.3.2.5
Acquired HIV drug resistance	◉ Prevalence and incidence of acquired and transmitted drug resistance	IC vs.CC	CRF	0
Virological failure	◉ Persistent VL > 1000 copies/ml	IC vs.CC	CRF	6.4.5.2
Toxicity	◉ Monitoring of renal dysfunction (TDF), liver function (NVP), teratogenicity (EFV)	IC vs.CC	CRF	6.4.5.2
Vertically-acquired HIV infection	◉ Uptake of PMTCT intervention(s) and relation with care program ◉ Pregnancy outcomes with Efavirenz first-line ART and transmission ◉ Overall HIV paediatric testing/treatment patterns in sample	IC vs.CC *Second phase only*	CRF	7.3.2.6

IC: Intervention cluster; CC: Control cluster;
HIV+: HIV-infected participants (treated or not); HIV-: HIV-negative participants;
THR: TasP Household Registration questionnaire; IQ: TasP Individual Questionnaire;
HHI: TasP Household Information Assets questionnaire; SCS: Social science Clinic-based Survey (SCB, SCC and SCI)
CRF: Case Report Form (CBC, CFU, CHE);
CAR: Clinic Activity Report; IDI: in-depth interviews; CAP: Consumer Advisory Panel.

Table 6 presents the outcomes that will be measured within the planned sub-studies if funded.

Table 6
Outcomes documented within sub-studies

Outcome	Definition, indicators	Comparison	Tool	See
Health care system				
Experience of care	◉ Training and experience in HIV care, working conditions, practices and knowledge about ART management	IC vs.CC *Second phase only*	SCS, SS CAR	7.5.1
Characterisation of health facilities and activity	◉ Type of health services, clientele, human resources, working times, technical equipment, HIV-care organization ◉ Unit costs of the resources used	IC vs.CC	CAR, SS	7.4.3
Budget impact	◉ Impact of TasP (level of coverage, rate of ART switches, drug prices) on health care system	IC vs.CC	CAR, THR, IQ, HHI, SCS	7.5.2

IC: Intervention cluster; CC: Control cluster;
HIV+: HIV-infected participants (treated or not); HIV-: HIV-negative participants;
THR: TasP Household Registration questionnaire; IQ: TasP Individual Questionnaire;
HHI: TasP Household Information Assets questionnaire; SCS: Social science Clinic-based Survey (SCB, SCC and SCI)
CAR: Clinic Activity Report; SS: Specific Survey.

7.2 Primary outcome

HIV incidence will be measured after multiple HIV testing periods of 24 months in 12 clusters, 36 months in 6 clusters and 48 months in 4 clusters depending on the person years of observation in individuals initially identified to be HIV negative.

7.2.1 HIV status measurement, using DBS with longitudinal follow-up

HIV testing will be longitudinally linked at the level of the participant and be conducted in six-monthly intervals. HIV testing will follow the standard South Africa DBS protocols used in the Africa Centre population-based HIV surveillance in past years (34). For the first phase of the trial, the duration of the three testing rounds will be six, then four and four months for the first 4 clusters and 6-monthly for the additional 6 clusters. For the second phase of the trial, four rounds of 6-monthly HIV testing will be conducted in all 10 phase 1 clusters and the additional 12 clusters in phase 2 over a period of 24 months.

Serologic status will be determined by antibody testing with a broad-based HIV-1/HIV-2 ELISA (Vironostika® HIV-1 Microelisa System (Biomérieux, Durham, NC, USA) followed by a confirmatory ELISA if the first test is positive (Wellcozyme HIV 1+2 GACELISA; Murex Diagnostics Benelux B.V., Breukelen, The Netherlands). In cases of discordant results a third ELISA test will be carried out.

7.2.2 A locally validated test for recent infection: capture BED enzyme-linked immunoassay (cBED assay)

For HIV-positive DBS a cBED assay will be performed during the first phase only to establish whether the HIV infection is recent (less than 6 months) or non-recent and confirm incidence estimates.

The addition of a test of recent infection to the standard longitudinal HIV testing serves three purposes, it will:

- Allow an immediate assessment of HIV incidence in the trial population at baseline (to confirm the assumptions made re sample size; without the need for a second longitudinal assessment).
- Improve the precision of the overall longitudinal measurement.
- Allow inclusion of individuals who refuse repeated testing but consent to testing once in the sample for incidence estimation and thus increase the power of the trial.

The cBED assay has been locally calibrated (35) and is thus an appropriate measure of HIV incidence at baseline for a community-randomized trial. Moreover, some of the calibration problems encountered in applications of the BED assay in other settings (36), become irrelevant in repeated application of the BED assay to estimate HIV incidence *differences* over time, since it is reasonable to assume that calibration parameters remain constant over time intervals of a few years.

While it would thus theoretically be possible to rely solely on BED assay testing in cross-sections of the population, which are not longitudinally linked at the individual level, such a measurement strategy does not seem advisable. The BED assay has not yet achieved acceptance as a routine approach to measure HIV incidence. Relying solely on the BED assay could thus reduce the perceived strength of evidence emanating from the TasP trial. However, we will use the cBED assay to identify people with likely recent seroconversion in the first round.

7.3 Secondary outcomes

7.3.1 Both within the general population level, stratified by HIV status, and among HIV-infected participants

7.3.1.1 Acceptability and uptake of HIV testing

Acceptability and uptake of HIV testing, current knowledge of HIV status, recent HIV testing history will be calculated for each successive rounds of home-based HIV testing and will be based on data collected during the home visit.

Acceptability of HIV testing will be estimated among different population subgroups, and will be defined among others as:

- the proportion of participants who are tested for HIV among all those eligible (individuals identified though the household registration)
- the proportion of participants who are tested for HIV among those not previously tested
- the proportion of participants who are tested HIV-negative at first round and who return to be tested once or more during the subsequent testing rounds. In addition, the uptake of HIV testing estimations will be refined using the data

from trial clinics and the DoH clinics on persons who attend for VCT. Participants from the trial sites who attend either service with their referral cards, given out during the rounds of home-based testing. Their data can be added into the total to provide estimates of testing coverage and the acceptability of different testing modalities. These outcomes will be calculated for successive rounds of testing. Essential socio-demographic data on non-responders (i.e. those declining HIV testing and the questionnaires and not subsequently attending either trial or DoH clinics for VCT) will be collected in each round and can in turn be linked in order to estimate an overall uptake rate over individual and over successive rounds of home-based HIV VCT. It will also be possible to estimate the appropriateness of the time intervals between testing rounds to maximise uptake.

Other proxy acceptability indicators can be calculated including uptake of HIV treatment and care among those testing HIV-positive either in the home-based HIV VCT or the local clinics (trial or DoH). We will also have individual level data on participants' HIV-testing histories, disclosure of HIV status, perceptions and expectations of treatment and collected at initial enrolment into treatment and care. It will be possible to calculate these estimates for each individual round of testing and cumulatively over the trial period.

7.3.1.2 Behavioural changes at individual level and sexual partnerships

Measurement of sexual partnerships, relationship status, prevention behaviours (e.g. condom use and HIV testing outside the trial), circumcision status, changes in contraceptive usage, attitudes towards PLWHA, perception and knowledge of HIV treatment, will be collected from all enumerated participants during the successive rounds of home-based testing. This will facilitate longitudinal as well as repeat cross-sectional analyses regardless of participants' self-reported HIV status.

7.3.1.3 Quality of life

Quality of life will be explored:

- At cluster-level, among all participants responding to the *IQ questionnaires* during the first and last rounds of home-based HIV testing during the first phase. The EQ-5D scale will be used for this purpose since this instrument is a short generic health instrument which can be administered to both HIV-infected people and HIV-negative people or people of unknown HIV status.
- Among all HIV-infected participants attending the study clinics. These measurements are planned for at W0 (i.e. date of entry into care for treatment ineligible patients and any of the pre-treatment visits for ART-eligible participants), M6, M12, and 6-monthly up to M48 (see Table 2, Table 3 and Table 4). The quality of life module will be designed using standardised validated instruments appropriate to the context and culture of the participant population:
    - the *Patient Reported Outcomes Quality Of Life specific to HIV* (PROQOL-HIV): this instrument comprises 43 items (39 items for health-related quality of life and 4 individual items) and takes into account a comprehensive set of dimensions related to the quality of life in PLWHA such as sleep, treatment's perception and treatment management, perceived HIV-symptoms and impact of treatment's side effects, which are not (or not adequately) taken into account in other HIV instruments like the WHOQOL-HIV (37). Its psychometric

properties have been evaluated and validated in different context including Sub-Saharan Africa and the instrument has been shown to be sensitive to differences in culture, gender and ethnicity (38). As the PROQOL-HIV has not been validated as an isiZulu language instrument, a short linguistic validation study could be implemented (to be described at a later stage)

- the *HIV/AIDS stigma instrument for PLWHA* (HASI-P): this tool assesses stigma perceived in PLWHA, which is one of the dimensions of the quality of life. This instrument has been built to measure perceived stigma by PLWHA in Southern African countries and its psychometric properties have been validated in IsiZulu language (39). This face-to-face questionnaire includes 33 items regarding the occurrence of different events, which may have happen because of the HIV status (e.g. ask to not touch child, blamed for HIV status, called bad name) as well as thoughts or feelings.

7.3.1.4 Cost-effectiveness performance

A cost-effectiveness analysis (CEA) will be carried out based on data from the TasP trial and will be completed with a mathematical (Markov) model to estimate the effectiveness and costs of the strategies compared over time, i.e. comparing treatment initiation as soon as HIV infection is diagnosed versus delayed treatment initiation according to WHO recommendations.

The main outcomes of this CEA will be the number of life years gained and also the number of Quality Adjusted Life Years (QALYs) saved.

A generic health instrument is required to determine different healthcare states which can be classified according to preferences. We will use the EQ-5D scale, which has been widely used in the literature to conduct cost-utility evaluation, both in Northern and in Southern countries, including South Africa (40, 41). This instrument has been found to discriminate between different health states amongst PLWHA and has been validated in isiZulu formats (42, 43).

Both direct costs, as well as indirect costs will be evaluated both at the cluster level and among HIV-infected participants. The questions for the CEA will be integrated into the *IQ* at the cluster level within the *CRF* and *the clinic-based questionnaires* to be administered to HIV-infected participants. The following costs will be collected throughout the trial period at different time periods:

- At the cluster level:
  - Direct costs: travel costs and out-of-pockets expenditures for health;
  - Indirect costs: income loss due to the illness (human capital approach, based on the estimation of patients' and family income loss due to illness and due to health care utilization);
- Among HIV-infected participants:
  - Direct costs documented using the CRF (ART prescribed, laboratory tests, physician visits, hospitalizations, and concomitant treatments) and CAR (human resources dedicated to HIV-care, consultation time, costs of laboratory tests…);
  - Direct costs within the clinic-based questionnaires: travel costs, out-of-pockets healthcare expenditures;

- Indirect costs: income loss due to the illness documented at baseline (date of entry into care), at treatment initiation, and during follow-up for HIV-infected people (see Table 2, Table 3 and Table 4).

7.3.1.5 Community awareness, attitudes and behaviours

Community awareness, attitudes and behaviours will be extensively studied in the first phase. These are measured at the individual level in the *IQ questionnaires* completed during each successive round of home-based testing. Other global indicators will be derived from participation rates in successive rounds of home-based testing. The extent to which the same methodology or a more complex one will be used in the second phase will be decided at the end of the first phase.

7.3.1.6 Societal response

Societal response is a composite outcome, which will be assessed during the second phase of the trial only, using a variety of methods and indicators:

- changes in attitudes regarding testing, treatment and persons living with HIV measured during home surveys;
- changes in individuals community, economic and social participation (employment, living in couple, parenthood,) and experience of people living with HIV (stigma and discrimination) surveyed at trial clinics using the social science clinic-based questionnaires and explored within in-depth interviews of HIV+ individuals on treatment;
- perception and analysis of the social impact of the programme in panels of people in different subgroups (young adults, male and female adults separately, HIV+ individuals, key informants of social leaders and traditional healers)

With these various outcomes we will be able to compile an extensive array of measures that can be combined and compared between clusters and between individuals (HIV-infected and non-infected). This will in turn be supplemented with qualitative data, which will provide a nuance image of the overall social impact of the programme and the trial.

7.3.2 Only among HIV-infected participants

7.3.2.1 Acceptability and uptake of entry in care and treatment

Using the patient identifiers and mechanisms already described we will be able to monitor acceptability and uptake of treatment at several levels.

At the individual level we will be able to estimate the time from receipt of HIV test result to enrolment into treatment at the trial clinics or DoH fixed clinics (if any participant chooses that option). We will be able to monitor the transfer of care of patients currently being monitored (as yet ineligible for ART) in the fixed clinics to the trial clinics. The employment of a tracker will ensure that people eligible for treatment in the trial clinics who do not attend, and those that subsequently default from care, are followed-up, are appropriately assisted to access the trial clinics, if necessary, and that they are not otherwise lost to follow-up.

In addition to measurement of these key public health outcomes, with the data collected at treatment enrolment it will be possible to characterise in detail the population entering into treatment and care and to estimate social factors that facilitate entry (e.g.

household composition, social support, disclosure to family, treatment knowledge). All of these intermediate measures will be useful in determining the need and content of any special interventions to support treatment uptake in the main trial.

7.3.2.2 Therapeutic success/evaluation of ART

This will be estimated as the proportion of HIV-infected participants who have undetectable VL after six months of ART.

7.3.2.3 Programme retention

Retention in care will be assessed at 12 months, 24 months and 36 months post-enrolment. Retention will be defined as those still under active follow-up in the trial. Loss to follow-up on ART will be defined as ≥ 3 consecutive missed appointments. For those not eligible for ART, loss to follow-up in control clusters will be defined as > 9 months from last clinic visit and/or CD4 cell count.

7.3.2.4 Mortality, severe morbidity, and tuberculosis

Secondary endpoints to be compared between the intervention and control clusters include all-cause mortality, HIV-related mortality, WHO stage IV disease, serious non-AIDS events, and tuberculosis. Serious non-AIDS events include cardiovascular disease (stroke, myocardial infarction), end-stage renal disease, decompensated liver disease, and non-AIDS-defining cancers. Tuberculosis includes both pulmonary and extra-pulmonary disease, either with or without microbiological confirmation.

7.3.2.5 Adherence

Adherence will be measured every 4 to 8 weeks depending on frequency of clinic attendance for patients on ART using a scale that has already been translated and validated by Africa Centre researchers with patients from the Hlabisa Treatment and Care Programme where previous analysis has focused on consistency of reported non-adherence (44). This tool, using visual analogue scale, pill identification test and pill count, will be included in the CFU questionnaires.

However, as non-adherence was rarely reported and as the questions used performed poorly in identifying patients with treatment failure (44), we will test an additional scale constructed to limit both recall and social desirability bias and which has been tested in different settings (45-47). This tool includes several questions related to dose taking during the previous 4 days and the respect of the dosing time schedule during the previous 4 weeks. Adherence scores which are computed using a validated algorithm allowing to classify patients into highly adherent, moderately adherent and lowly adherent have been found to be significantly associated with viral load (46). Another item focusing on the occurrence of treatment interruptions lasting more than 2 consecutive days during the previous 4 weeks was found to be a predictor of resistance development (48) and has already been tested in another context (45). This second measure of ART adherence will be surveyed every 6 months (i.e. at M6, M12, and 6-monthly up to M48) and included in the *Social science clinic-based interviewer-administered questionnaire* (SCI).

7.3.2.6 Paediatric HIV infection

The sub-district has a well-functioning PMTCT programme, which includes HIV DNA testing (PCR on a DBS) of infants at six weeks of age, repeated one month after

cessation of all breastfeeding. A PMTCT database has been developed in the sub-district, charting the progress of pregnant women from the time of antenatal booking through to infant HIV testing after cessation of all breastfeeding. It has been shown in this programme that ART introduction in mothers and infants may already have had more impact on early life mortality than PMTCT itself (49).

In the trial intervention clusters all HIV-infected women will be initiated on ART irrespective of the CD4 count or the clinical stage. In the control clusters, women who are not yet eligible for HAART (i.e CD4>350 cells/μL) will be managed according to the best available PMTCT guidelines approved by the South African national authorities (Currently WHO option B) (29). This involves the prescription of FDC triple therapy (TDF+FTC+EFV) to pregnant women and breastfeeding mothers with CD4>350 until one week after the complete cessation of breastfeeding. This is adapted in certain situations such as the presence of active psychiatric illness or renal disease. Women receiving TDF/FTC/EFV for prophylaxis rather than for their own health will undergo, WHO clinical staging and hepatitis B testing prior to discontinuation of ART. If a woman treated with TDF/FTC/EFV has stage 3 or 4 disease or evidence of hepatitis B infection (hepatitis B surface antigen positive) then the regimen will not be stopped after the cessation of breastfeeding but will continue lifelong. CD4 count will be done 6 months after the cessation of breastfeeding or if the last CD4 count was done more than 12 months ago.

Women in both the intervention and control clusters will be asked about pregnancy at each of their routine visits; if pregnant, data will be collected as part of the trial including date of delivery, mode of delivery, stillbirth, premature termination, infant outcome, and infant DNA status at 6 weeks and after cessation of all breastfeeding if known, as antenatal care, delivery and post-natal care are managed in the DoH clinics.

7.3.2.7 HIV drug resistance

HIV-1 genotypic resistance testing will be performed for:

- HIV infected individual initiating ARV and identified with virological failure during the trial. The virological failure is defined as a viral load > 1 000 copies/ml on two separate occasions two months apart. The HIV-1 genotypic resistance will be performed on paired samples from the same participant: one from time of virological failure and second from pre-treatment if available
- HIV infected individual already on ARV at trial entry and identified with virological failure at enrolment
- all participants who seroconvert within the trial

The HIV-1 genotypic resistance test will be done at the Africa Centre laboratory utilising stored plasma samples of HIV infected individual receiving ART and stored DBS. Procedures will follow an existing and internationally validated protocol established for an on-going clinical study of ART failure in the HIV Treatment & Care Programme. Results will be returned to the trial clinician within 14 days of sample collection. Genotyping for all participants who seroconvert within the trial - these results will not be available to clinicians in real-time.

The pre-treatment samples will be used to assess the surveillance of transmitted drug resistance during the trial whereas virological failure genotypes will be used to estimate the level of developed resistance mutations. Sequences will be produced using the ANRS guidelines for genotyping and analysed using drug resistance algorithms, such as the Stanford HIVdb, ANRS and Rega algorithms.

Further, given the short time of the trial and potency of the ARV drugs to be used in the trial, in a sub-study (n~10) we will also consider genotyping at the DNA level of participants with undetectable VL while on ART to assess development of resistance at low viral replication levels and sequencing minority populations using either direct PCR or pyrosequencing methods in order to study the link between minority populations and clinical outcome.

7.3.2.8 Molecular epidemiology

We will analyse all sequences using a phylodynamics framework. Phylodynamics can be used in order to estimate the date of origin of epidemiologically important events such as the introduction of a new viral strain in a geographical area and identification of transmission networks between intervention and control clusters.

7.4 Data collection tools

A number of detailed standard operating procedures (SOPs) will be developed for the counsellors involved in the home-based testing and surveillance, the trial clinic nurses and counsellors, the physicians, the pharmacy and the laboratory technicians. A combination of quantitative and qualitative trial instruments will be used to assess key intermediate process, behavioural and outcome indicators in the trial.

7.4.1 Household and individual home-based questionnaires

Throughout the trial (first and second phase), in each round of home-based HIV testing, we will collect basic information using home-based questionnaires at household and individual level.

In the first round, the *TasP household registration questionnaire* (THR) will be administered to the head of household to document household-level social and demographic characteristics: number and age of residents. Housing characteristics (water, electricity), household income, food security among others will be documented using the *TasP household information assets questionnaire* (HHI). These household questionnaires will be repeated to allow for the updating of information about household members at each round in order to document changes in household.

During the first phase of the trial, the *TasP home-based individual questionnaires* (IQ1 to IQ3) will be composed of a core questions repeated at each round and a set additional questions specific to certain rounds: individual-level social and demographic characteristics, HIV testing behaviour, sexual behaviour, partnership and sexual network patterns, attitudes and beliefs about HIV infection, HIV testing and treatment, stigma and disclosure, healthcare use and healthcare expenditures and changes within the households, and quality of life (see Table 7).

In phase 2 of the trial, identical *home-based individual questionnaires* designated IQ will be administered during the six-monthly rounds of HIV testing. The phase 2 IQ will address all components listed in Table 7.

Table 7
Data collection during the HIV testing rounds, among the general population: Household and individual questionnaires (first phase of the trial)

	IQ1	IQ2	IQ3
Home-based Household questionnaire			
Household head verbal consent	×	×	×
Household composition and socio-economic characteristics	×		
Changes in household composition (including in-out migrations/mortality/newly eligible)		×	×
Home-based Individual questionnaire			
Individual consent for questionnaire	×	×	×
Knowledge/beliefs about HIV infection	×		×
Knowledge/expectations about treatment	×	×	×
HIV testing history	×		
HIV testing attitudes/beliefs	×		×
Uptake of testing opportunities	×	×	×
Self-reported knowledge of HIV status	×	×	×
Disclosure of HIV status	×		×
Sexual partnerships	×		×
Condom use	×		×
Contraceptive use	×		×
Circumcision status	×		×
Risk behaviours (alcohol etc.)		×	×
Quality of life	×		×
Stigma towards PLWHA		×	
Health care use		×	×
Health care expenditure		×	
Home-based HIV testing			
Individual consent for DBS and/or HIV testing	×	×	×
DBS	×	×	×
Home HIV counselling and testing (rapid test)	×	×	×

7.4.2 Social science Clinic-based survey

The clinic-based survey exploring HIV-infected participants' behaviours and socio-economic status will be composed of different sets of questions administered repeatedly every six months or specifically at baseline (i.e. date of entry into care for non-eligible patients and date of any of the pre-treatment visits for ART-eligible patients), as presented in Table 3. The topics explored will be: testing experience (baseline only), ART knowledge, ART perception and decision, disclosure, sexual behaviour, self-reported ART adherence, HIV Quality of Life, stigma and discrimination, social and community support, economic and health expenditures, satisfaction with care.

The clinic-based survey will be divided in three questionnaires:

- the *Social science Clinic-based Baseline questionnaire* (SCB), administered by the ART counsellor at baseline;

- the *Social science Clinic-based Counsellor-administered questionnaire* (SCC) on non-sensitive questions such as disclosure or health expenditures, administered each six months of follow-up and
- the *Social science Clinic-based independent Interviewer-administered questionnaire* (SCI) with sensitive questions (which are subject to social pressure and thus to social desirability bias) such as sexual relations or adherence, administered each six months of follow-up.

7.4.3 Case Report Forms (CRF)

The case report forms will be completed by the counsellors and the research nurses in the trial clinics. There will be baseline (CBC) and follow up (CFU) CRFs to be completed by the counsellors and a combined history and clinical examination (CHE) CRF to be completed by the research nurses. The same CRFs will be completed for all participants irrespective of their ART status at enrolment into the trial (See Table 5).

7.4.4 Clinic Activity Reports (CAR)

Throughout the trial, each trial clinic will keep detailed monthly activity records. In addition in phase 2 we will attempt to audit patient waiting times, staffing levels, stock outage, the adequacy of trial logistics and support using tools developed for the task.

7.4.5 Qualitative data

In the first phase only, two qualitative studies are planned to address acceptability of repeat testing, adherence and quality of life among those starting treatment in the trial clinics.

In the first of these we will convene a **consumer advisory panel** (CAP) in each of the four clusters. This panel will work with the social science team and the trial's community liaison officer to provide an on-going monitoring of the community experiences of the trial, perceptions and understanding of the intervention and early advice on any possible problems. The members of each panel will also serve as key informants and expert advisors to help the trial team ensure that community entry, awareness and education plans are fully developed for the second phase of the trial. The four community consumer panels will be conveyed according to a purposive sampling framework. Africa Centre researchers are currently using this methodology to develop and deliver youth HIV prevention interventions. In this instance we will assemble and engage repeatedly with the four purposively selected groups on a bi-monthly basis to discuss specific issues, which we believe the panel members, shared in common. Our community consumer panels will comprise four purposively selected groups from among the different communities (two members from each community). The four panels will be comprised of women, men, elderly, health care workers, and traditional authorities. Each panel will meet on six separate occasions with the same facilitator. All sessions will be video-recorded with participants' permission. Panel meetings will adopt a combination of different approaches including conventional focus group discussions and participatory action methods including joint problem solving and assumption of expert advisor roles.

The second small qualitative study will use repeat **in-depth interviews** (IDI, n=15) to explore the adherence and quality of life in HIV-positive people initiating treatment in the trial clinics. This is a unique opportunity to examine adherence and quality of life qualitatively, and in the context of people who would not normally be receiving treatment. It also offers an important opportunity to explore understandings of the

importance of adherence in the context of both personal health benefits and HIV prevention.

7.5 Sub-studies

7.5.1 Survey of health care professionals

The implementation of universal testing and treat immediately intervention will represent major challenges for the health care system and especially for human resources which are one of the key factors for the success of the intervention. Sub-Saharan Africa countries currently encounter lack of qualified health care professionals, unequal geographical distribution of health resources, generalized low wages, difficult working conditions and lack of carrier development (50, 51). Such factors have been shown to have an impact on human performance and may jeopardize quality of care, as well as HIV treatment delivery (52).

To identify potential obstacles to the implementation of TasP in HIV care, treatment and prevention services and to identify changes needed to improve the adherence to TasP principles by service delivery personnel, a quantitative survey will be conducted among health care providers in charge of PLWHAs and working in the facilities included in the TasP trial, both the trial clinics and the DoH fixed clinics. Data will be collected using a quantitative survey instrument previously used in a research programme about HIV care among medical professionals in Cameroon (53). Data collected will include information on socio-demographic characteristics, training and experience in HIV care, working conditions, practices and knowledge about HIV and ART management, opinions about the TasP intervention. This survey will be carried out once separate from the routine care and in the second phase of the trial.

In addition, data relating to the characteristics of the health care facilities where TasP will take place, such as types of health services, size of HIV clientele, number of ART-treated patients, human resources in charge of HIV care, working time devoted to the care of PLWHAs and staff compensation to estimate the cost of human resources involved in patient care, shall be obtained through access to institutional reports, computer systems and interviews of each health centre's managers and staff. This second survey will be carried out at baseline and at 12-month, both in the second phase of the trial.

7.5.2 Budget impact analysis

A budget impact analysis (BIA) will be planned in the first and second phase of the trial to examine the potential financial impact, at macro level, that is on national, regional or local health budgets, of the introduction of the TasP strategy into the healthcare system. This approach will be a complement of the CEA but does not include additional data collection. The impact on the total costs will be estimated. A variety of sensitivity analyses will be carried out varying for example the level of coverage, the rate of switching to second-line regimens, or drug prices.

8. Methodological and statistical considerations

8.1 Cluster selection

The randomisation units within the TasP trial will be clusters within Hlabisa sub-district outside of the DSA (see Figure 1). Randomisation will occur at the start of the first phase.

The area consists of 150 local areas (neighbourhoods). These were aggregated into 34 clusters of between one and six contiguous neighbourhoods, each cluster comprising an average of 1 000 individuals >15 years of age. Clusters were designed to encompass social networks based on earlier studies in the DSA (54), to keep the potential for cross-arm contamination to a minimum. To further reduce the potential for contamination, we ensured that all resulting clusters were of significant geographical size (>15km^2 in area). This meant that the number of individuals in peri-urban clusters were larger than their rural counterparts.

Adjacent communities representing relatively distinct social and sexual networks[1] were grouped together to form the units of randomization (median population $\geq$ 15 = 1 000; median area = 19 km^2). From a statistical efficiency perspective (least sample size) more clusters of fewer people should be used. However, having very small units of randomization would result in a large potential for contamination. With this trade-off between statistical efficiency and contamination potential in mind we combined adjacent neighbourhoods together to form relatively large randomization units (with similar numbers of participants) with a distinct social identity. This considerably reduces the risk of contamination whilst still retaining a relatively large number of clusters for the trial (56).

To further evaluate the potential impact of contamination of the results on the outcome of the trial we have run extensive geographical simulations of possible randomization scenarios. The results of these analyses demonstrate that chance groupings of neighbouring communities randomized to the same arm of the trial result in 'super-clusters' with a median of aprooximately 4 000 participants $\geq$ 15 years of age and median size of 48 km^2. Empirical data from a sexual behaviour survey conducted in 2005 showed that 55% of men interviewed reported that their most recent partner in the past year lived in the same immediate *izigodi* (a Zulu term for an administrative area headed by a local chief), which have a median area of 16.9 km^2. Extrapolating from these results, we are expect that only a very small proportion of trial participants will have sexual partners outside these 'super-clusters' (median size=48 km^2). The exceptions to this rule will be people residing near the borders of these 'super-clusters' and the chance occurrence of singleton communities in the randomization.

We considered trying and further reducing the small amount of inter-arm contamination by the designation of a series of 'buffer' communities around each community used in the trial. However, this was rejected for two reasons: a) It would have the undesirable effect of reducing the size of the 'super-clusters' and hence increase the chance of having partners outside the area to which the participant was randomized and b) It would increase the risk of an HIV-negative participant in an intervention community of having an HIV-positive untreated partner in the

[1] The 312 neighbourhoods in the sub-district were demarcated by visiting each of the 26 000 homesteads in the sub-district and asking a key respondent to name the local area (neighbourhood) where they lived. From this data, a GIS methodology was used to digitize local areas around clusters of responses to the local areas question (55).

neighbouring buffer communities (because the level of ART coverage in buffer communities would be even lower than control communities where ART coverage will increase through increased access to VCT services delivered as part of the trial).

8.2 Modelling exercise and sample size calculation

8.2.1 Principles of the model

We used STDSIM to provide estimates of the potential impact of the TasP trial. STDSIM is a well-established stochastic microsimulation model of the spread and control of HIV (57-71). The model that simulates the life course of individuals in a dynamic network of sexual contacts and consists of four modules: demography, sexual behaviour, transmission and natural history, and interventions. The demography module covers the processes of birth, death, and migration. Processes for initiation and dissolution of sexual relationships, mixing according to age preference, sexual contacts within relationships, and sexual contacts between female sex workers and their male clients are defined in the sexual behaviour module. In the transmission and natural history module, transmission probabilities per sexual contact are specified for HIV and 5 other STDs. The interventions module specifies the timing and effectiveness of control measures in curbing transmission (e.g. condom use) or enhancing survival (e.g. antiretroviral therapy). STDSIM has been extensively used to evaluate behavioural interventions (60-62, 72), syndromic treatment for STIs (63, 69), male circumcision (70), explain different HIV epidemics in sub-Saharan Africa (64), and, more recently, the impact of ART on HIV epidemics (57-59, 73). For the impact estimates of the TasP trial we used the previously published quantification for rural KwaZulu-Natal, South Africa. The model was built using data from the Africa Centre and accurately captures demographic, behavioural, and epidemiological characteristics of the local epidemic (58, 59, 73).

8.2.2 Model input parameters

Table 8 gives an overview of the main parameters and assumptions related to the trial impact estimates. We simulated an intervention of bi-annual screening of the population aged 15 and over, and compared the impact of immediate ART for all HIV infected individuals (treatment-arm) with ART only for those with CD4 cell counts of ≤350 cells/μL. We ran the model separately for all clusters in order to capture the phased roll-out design of the trial. We assumed the intervention to be rolled-out in a total of 22 clusters: four clusters start in 2012, six in 2013, and a further 12 in 2014. We examined the impact on incidence rates, cumulative incidence, and ART coverage up to end-2016. The parameter settings used are those that gave a 30% reduction in cumulative incidence.

Table 8
Parameter settings and characteristics of HIV epidemic as modelled by the STDSIM model.

Parameters and baseline epidemic characteristics	Assumptions
Reduction in infectiousness due to ART	90%
Proportion having partners in clusters in opposite arm of the trial	10%
HIV testing uptake (both arms)	
HIV test offer among those registered	90%
Test acceptance among those offered	80%
Linkage to care upon diagnosis among those accepting the test	70%
HIV prevalence in end-2011 (population aged 15+)	24%
HIV incidence in 2011 (population aged 15+)	2.4/100 PY
Proportion of all HIV infected people on ART in end-2011	39% (64% of those eligible at ≤350 cells/μL)

Note: Model was quantified to represent the HIV epidemic in rural KwaZulu-Natal, South Africa, using demographic, behavioural, and epidemiological data from the Africa Centre. Model and quantification described in detail elsewhere (58, 59, 73).

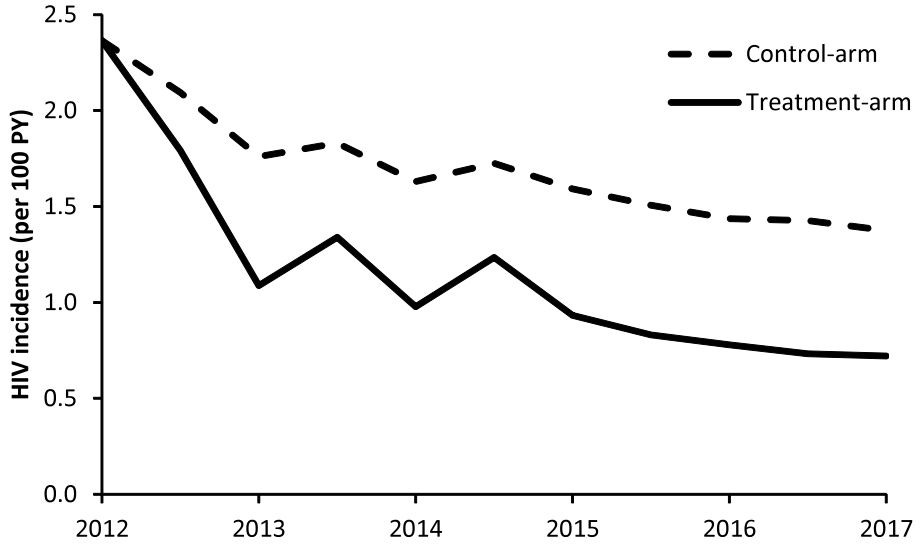
Our model predictions give an estimated reduction of cumulative incidence in end-2016 of 31.7%, or 28.8% by end-2015 (Table 9). Incidence rates in the control arm would decline from 2.4/100 PY in 2012 to 1.4/100 PY at the end of 2016. In the intervention arm, incidence would decline from 2.4/100 PY to 0.7/100 PY over the same period (see Figure 5). Mid-2015 we will be in a strong position of conduct an interim analysis to show whether a significant reduction in incidence could be detected either at the end of 2015 or 2016. The details of this analysis are described in detail below.

Table 9
Projected 5-year impact of cluster-randomized trial of treatment as prevention on HIV incidence and ART coverage in rural KwaZulu-Natal, South Africa.

	Early-2012	Mid-2014	End-2015	End-2016
Incidence rate (per 100 PY)				
Control-arm	2.4	1.7	1.4	1.4
Treatment-arm	2.4	1.3	0.8	0.7
Average incidence over 5 year period (per 100 PY)				
Control-arm	n/a	n/a	n/a	1.7
Treatment-arm	n/a	n/a	n/a	1.2
Cumulative incidence reduction				
Treatment-arm versus control-arm	n/a	22.9%	28.8%	31.7%
Proportion of HIV infected people on treatment				
Control-arm	39%	59.4%	64.5%	66.5%
Treatment-arm	39%	81.6%	89.7%	90.8%

Note: Population is screened bi-annually. All HIV infected people in the treatment-arm are offered immediate ART, and HIV infected people in the control arm are offered ART when their CD4 cell count is below 350 cells/μL.

Figure 5
Projected 5-year impact of cluster-randomized trial of treatment as prevention on HIV incidence rates in rural KwaZulu-Natal, South Africa.



Note: Population is screened bi-annually. All HIV infected people in the treatment-arm are offered immediate ART, and HIV infected people in the control arm are offered ART when their CD4 cell count is below 350 cells/μL. Spikes in incidence are explained by the enrolment of additional clusters (6 in 2013, 12 in 2014).

8.2.3 Sample size calculation based on model assumptions

The initial design proposed a cluster-randomised trial with 2x17 clusters, covering a total population of 34,000 adults aged 16 years and above followed over two years. However, a phased approach of trial implementation was adopted as feasibility and acceptability were deemed critical for the overall evaluation of the intervention. In this design at the end of 2015, four clusters would be followed up for four years, six clusters for three years and a further 12 clusters for two years. This would give a total of 22 clusters, 58 cluster-years of follow up for a total trial size of 22,000.

■ **Primary Outcome**

Our sample size calculations are based on an overall 34% reduction in cumulative HIV incidence in HIV-negative participants over 58 cluster-years of observation (see Table 10). To have sufficient numbers to be able to demonstrate this difference, our sample size calculations indicate that 22 clusters (11 in each arm), with 1,000 participants >15 years of age in each cluster (N=22,000; 17,600 HIV-negative), are required to achieve this objective. Underlying statistical parameters are as follows: a 80% power to detect this difference, an alpha-type-one error of 5% (two-tailed) and an allowance of 20% of study participants lost to follow up. We assume also a coefficient of variation of 0.25 to account for within-group variation between clusters.

Table 10
Estimated power to show a 34% reduction in cumulative incidence using the Satterthwaite approximate F test for two-sample comparison of proportions with clustering for 22 clusters (2012-2015).

Reduction in cumulative HIV incidence	34% end 2015 (1.49 vs 2.25%/year)
CV	0.25
Power	80%
Number of Clusters	22
Cluster Size	1 000
Total number of HIV negative adults	17 600
Total number of cluster-years	58
	4 for 4 yrs
	6 for 3 yrs
	12 for 2 yrs

In the control arm we expect an average HIV incidence of 2.25 per 100 person-years over the course of the trial (this is 17% lower than the incidence currently observed in the Africa Centre DSA and recognises that incidence will likely decline in the overall population as a result of public sector roll-out of ART according to South African guidelines).

In the intervention arm we expect an average HIV incidence that is 34% lower than the control arm i.e. 1.485 per 100 person-years.

To take into account the different follow up times in the different groups of clusters opened at different times, we based our calculations simply on the proportion sero-converting in the intervention versus control clusters over the course of the trial. This approach will yield appropriately conservative sample size estimates.

In each cluster we expect to register 800 HIV-negative individuals of whom we expect to be able to successfully follow up 640. The average follow-up time for each individual is derived by subtracting half a year from the follow-up time in the cluster in which they reside. So for example, in the two control clusters that are followed up from 2012 to 2015, the total person-years of follow up = 640*2*3.5 years =4,480 which at an annual incidence of 2.25 per 100 person-years would equate to 100.8 sero-conversions observed by 2015.

Overall, the total person-years of follow up in each arm of the trial will be an estimated 15,040 (and 30, 080 person-years of observation in the whole trial). Thus, at an annual incidence of 2.25%, 4.8% of those observed to be HIV-negative at baseline would have been observed to seroconvert in the 11 control clusters by the end of 2015 that is 338 new HIV infected. The corresponding figure for the 11 intervention clusters would be 3.1725% for around 223 new HIV infected. Therefore, the number of HIV infected patients in the 11 intervention clusters will be 2098 (338+1760) and 1983 in the 11 control clusters (see Table 11). (Note that this method, using average follow up time provides very similar total person-years as in the approach accounting for different follow up times in different clusters.)

Table 11
Participants at risk of sero-conversion and expected number of incident cases

	Expected annual HIV incidence	Total	Nb of HIV+ at T0	Nb of HIV+ followed	Nb HIV- at T0	Nb HIV- followed*	Total HIV- person-years	Nb new HIV+ by end 2015
Cont	2.25%	11,000	2,200	1760	8,800	7,040	15,040	338
Interv	1.485%	11,000	2,200	1760	8,800	7,040	15,040	223

* assuming 20% of loss to follow-up

■ **Secondary outcomes**

Within the overall trial, two kinds of secondary objectives are distinguished: those measured on the total population (acceptability and uptake of HIV testing, behavioural changes…) and those measured in HIV-infected patients only (morbidity and mortality, virological response and resistance). We describe below some of our expectations regarding the latter.

Mortality rates in HIV-infected patients

Assuming a 9 per 100 person-years rate of early mortality in the control clusters based on published data from the Hlabisa HIV treatment and care programme (32) for the post-2011 CD4 350 eligibility threshold, and assuming that the median duration of follow-up while being infected is two years for prevalent cases and one year for incident cases, HIV infected patients will contribute 3858 person-years in the 11 control clusters and 3743 person-years in the 11 intervention clusters. Following these assumptions, we will be able to show a reduction of at least 33% (incidence of 6 per 100 py) in the intervention clusters.

If we were to use only data from phase 1 on the 5+5 clusters, then we would be able to detect a reduction of 50% in the rate of early mortality (from 9 to 4.5 per 100 person-years of follow up) only.

Proportions in HIV-infected patients (adherence, virological success, resistance)

Assuming about 182 HIV-infected patients per cluster (around 4000 infected patients in total) we will be able to show, with a statistical power of 80%, at least a 17% difference for characteristics with a prevalence of 60% or 22% for a prevalence of 80% or 25% for a prevalence of 90% (that is for example, an adherence of 90% in control vs. 65% in intervention clusters).

If we were to use only data from phase 1 on 5+5 clusters, then we would be able to detect a difference in the proportions by cluster arm in a variable that has a 90% prevalence of 37% (compared to the 25% noted above for the 22 clusters).

Calculations were performed according to Hayes & Bennett formulas for rates and proportions assuming 20% of loss to follow-up, 5% type I error.

8.3 Randomization

Randomisation was performed by the trial statisticians (F. Tanser, R. Thiebaut) at the start of the trial for all 34 clusters. Random numbers were generated for all 34 communities in the trial area using MapInfo 10.0. Communities were randomly allocated in equal measure to control and intervention communities (17:17). To minimise the degree of between-cluster variation, communities were stratified on the

basis of predicted HIV prevalence. Randomisation was carried out within each stratum to derive an equal number of control and intervention communities per stratum.

8.4 Plan of analysis

8.4.1 Criteria for continuation/discontinuation at the end of the first phase

Given our proposed phased approach, interim analyses will be conducted at three possible time-points over the course of the trial. As well as analysing levels of uptake of HIV testing and coverage of treatment, we will analyse differences in cumulative HIV incidence between intervention and control communities at the end of 2013 (≈≈19% of total person-time of observation accrued) and 2014 (≈≈53% of total person-time of observation accrued). Our modelling results demonstrate that any initial reduction in HIV incidence is likely to be relatively modest given the expected non-linear decline in incidence overtime (74). However, the trial will be discontinued if the interim analyses provide clear evidence of sexual disinhibition or reduced treatment adherence in the intervention clusters relative to the control clusters, that is, that the hazard ratio of acquiring new infection (intervention versus control) is >1.0 ($p<0.05$). In 2014 we will conduct a predictive power analysis to quantify the likelihood of observing a significant reduction in incidence if any observed reduction is sustained to the end of 2015. The predictive power probabilities will be calculated using the available information and several prior distributions. Futility will be concluded if the predictive power probabilities are < 0.2 or efficacy if > 0.8.

8.4.1.1 Feasibility

Clear indication that given the parameters measured during the first phase (HIV prevalence in the clusters and assessment of incidence at baseline on the basis of cBED, initial HIV testing uptake, repeated HIV testing uptake, ART treatment uptake, migration and the extent of sexual partnerships with people outside the trial setting) the TasP trial will lack the statistical power to detect significant HIV incidence differences between the intervention and control communities. Such observations will lead to the conclusion that the trial is not feasible.

The criteria used to decide on continuation of the trial after the first phase are those that substantially affected the impact of the intervention in mathematical modelling simulations: prevalence of undiagnosed HIV infection before the trial, CD4 level of HIV-infected participants who are undiagnosed or diagnosed but not yet on ART before the trial, ART initiation criteria in the control arm, internal migration, test acceptance and the linkage to care. The thresholds are defined according to the results of the mathematical model (see section 8.2).

8.4.1.2 Acceptability

Clear indication from the clinic-based survey (section 7.4.2) and the qualitative in-depth interviews conducted during the first phase that the TasP approach is not acceptable in our setting. Acceptability will be assessed using a combination of quantitative and qualitative analyses of community attitudes and beliefs about HIV, HIV VCT, stigma and disclosure, participation in TasP, and the acceptability of ART for the benefit of other community members.

The DSMB will, in addition to the criteria indicated in the protocol, be able to consider additional parameters measured during the first phase such as tuberculosis incidence.

A complete "pause" between the TasP first and the full trial phase is not feasible logistically, because it would imply discontinuation of structures built during the first phase in the intervention and control communities which would need to be utilized during the full trial phase. However, detailed data analyses and interpretation will take place in half-yearly intervals throughout the first phase, ensuring that TasP trial procedures are adopted in real-time to fully take into account the lessons learned during the first phase.

8.4.2 Statistical analysis

An intention-to-treat analysis, assuming sexual partnerships occur within clusters, based on the randomisation clusters, will be used for the primary trial outcome (incidence of HIV-1 infection). Incidence rates per 100 person-years will be calculated for the whole follow-up period and compared between the intervention and control arm. Cluster randomized trials require more a complex analysis than that for individual randomised controlled trials (75). Observations on participants in the same cluster tend to be correlated; therefore it is imperative that the intra-cluster variation must be accounted for during the analysis of the trial. If this correlation is ignored in the analysis and the same techniques are employed as for individual randomised controlled trials, the associated variance of the estimate would be underestimated and lead to unduly narrow confidence intervals. To ensure valid estimates, adjusted incidence rate ratios in the intervention group relative to the control group will be based on a multi-level Poisson regression taking into account the intra-cluster correlation and the repeated measurements when needed.

In detail: we will perform analyses using cluster-level approaches as robustness analyses for checking consistency of the results. However, we will focus on Poisson regression (including random effects) for the main outcome (HIV incidence) and logistic regression with generalized estimated equation (GEE) approach for binary outcomes, thus allowing for both levels (individual and cluster levels) with easy adjustment for confounding factors (76). As the method does not perform well for a low number of clusters, we plan to use the correction (of the sandwich estimator and statistics distribution i.e. t-distribution) proposed by Mancl & Derouen (77) which is particularly appropriate when the cluster size does not vary.

Because of the possibility that the randomisation may lead to some imbalance in the distribution of risk factors across the trial arms, an adjustment for baseline characteristics known to be associated with HIV transmission risk in this population will be undertaken. These include HIV prevalence of the cluster, age, sex, marital status, education level attained and migration status.

In addition, the extensive data related to population movements and partnership patterns which will be collected over the course of the trial will be used in a parallel set of secondary analyses to identify risk factors that influenced the risk of transmission. If the intervention does not have a significant impact, these important analyses will help to identify which factors were likely to have led to the trial result.

Data analysis and preparation of papers will be led by various members of the TasP team as commensurate with their expertise. The TasP team is composed of researchers from the Africa Centre, from INSERM U897/ISPED – Bordeaux, from INSERM U108 – Paris, from INSERM U912 – Marseille, from CEPED UMR 196, from the Hôpital Cantonal in Geneva, from CEPAC and Massachusetts General Hospital – Boston and from EA 3620 – Paris.

Rules will be established to define data analysis, communication and publication plans. New concepts sheets for analyses not yet identified will be developed over the course of the trial. These documents will be developed by the SC.

8.4.3 Safety

During the trial, each HIV-infected participant receiving ART will be followed carefully within the TasP clinics, by the TasP clinic nurse and the physician "on call", in order to detect the occurrence of any adverse event. The physician will be the trial coordinator (south), specialist in HIV medicine. He will rotate around the trial clinics, with scheduled visits at each trial clinic per week, but will be available to see urgent cases, including those with adverse events, if required. In addition the TasP trial will appoint a trial nurse manager who will be a trained 'NIMART' nurse[2]: (nurse-initiated management of ART). The trial nurse manager will also rotate around the trial clinics and be available to give advice and see patients with adverse events.

This follow-up will include interviewing each patient and conducting a clinical examination to identify any change in the patient's condition or any event that has occurred since the last protocol visit. The medical management of a patient experiencing an adverse event is under the responsibility of the physician/investigator. All adverse events will be reviewed by the HIV physician and must be reported and followed until resolution.

8.5 Adverse events: definitions and reporting

An adverse event (AE) is defined as any unfavourable, expected or unexpected clinical or biological sign or symptom occurring during the trial, whether or not considered related to the trial drug or to participation in the trial.

All AE observed or reported by the patients will be recorded at each trial visit (whether scheduled or unscheduled) in the CRF, regardless of their severity and the causal relationship to the trial drug. They will not be limited to AE related to one or more drugs but will also include any signs, symptoms or defined illnesses that occur during the trial.

In the case of an AE, the investigator's responsibility is to assure proper clinical management and follow-up until resolution or stabilization. If the AE becomes worse, it should be notified and followed as stated in section 9.2 below.

All AE will be graded for severity according to the "ANRS scale to grade the severity of adverse events in adults" version 1.0 dated November 4th, 2008 (English translation of the French version 6 dated September 9th, 2003). The investigator must indicate whether, in his/her opinion, this AE could have been expected or not.

8.6 Serious adverse events: definition and reporting

8.6.1 Definition

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

[2] NIM-ART is a new initiative in SA to respond to the scale-up of ARV treatment in the country with a severe shortage of health personnel. NIMART equips nurses with the skills to diagnose, initiate and manage patients on ARVs, and is being rolled out in all provinces in SA.

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- results in a congenital abnormality/birth defect

Within the frame of the trial the SAE also include:

- grade 4 clinical and biological events
- acute renal failure or Fanconi's syndrome

All events meeting the definition of SAE have to be reported. The SAE notification form must be completed by the investigator in charge of the patient follow-up, with due care being paid to the grading and causality.

8.6.2 Assessment of causality

All adverse events are to be assessed for the relationship to the study drug. Until proven otherwise, it should be assumed that the event is related to the study drug.

Causality will be assessed based on the following definitions:

- **Not related**: The event is clearly related to other causes, such as the clinical event of the patient or a concomitant treatment without any pharmacological interaction with the experimental drug.
- **Possibly related**: Clinical or biological event with a compatible chronological, aetiological and semi logical relation.
- **Relationship impossible to determine**: A potential causal relation between the experimental drugs and the event may exist, it may neither be affirmed nor excluded at the time of the declaration through a lack of clinical elements.

8.6.3 SAE reporting

The SAE should be reported if they occur:

- from the date of the informed consent signature for ART (even if no drugs were administered)
- during the entire duration of the trial
- up to one month after the end of the trial if the event is suspected to be related to the trial
- **and** any time after the completion of the trial if the event is suspected to be related to ART

8.6.3.1 Initial notification

The trial co-ordinator/HIV physician will notify each SAE to the trial investigator at the Africa Centre as soon as he is aware of the event. The trial co-ordinator/HIV physician will complete the trial specific "Initial Serious Adverse Event Notification" form. The form will include: study ID of participant, date of SAE and detailed description of the SAE.

The trial investigator at the Africa Centre will sends the notification to the ANRS pharmacovigilance unit within two working days of being notified of the event.

ANRS pharmacovigilance unit
Fax: +33 1 53 94 60 02
Mail: pharmacovigilance@anrs.fr

8.6.3.2 Complementary notification

The investigators or their designee are responsible for the clinical, therapeutic and biological follow-up of each SAE until resolution or stabilization.

The investigators have to report each SAE evolution (resolution, aggravation, death, final status at the end of the trial) using a "Complementary SAE Notification Form". Complementary information has to be reported in the following cases:

- systematically within 8 days in case of death and life-threatening event to clarify any relevant complementary information
- to report new information on the SAE diagnosis, its evolution, or the causal relationship to the study drug
- to answer any complementary information requested by ANRS pharmacovigilance unit

Complementary information reporting should follow the same procedure as describe above for the initial notification.

8.6.3.3 Reporting to Ethics Committee / DSMB / KZN Department of Health / Steering Committee

All SAE will be reported to the UKZN Biomedical Research Ethics Committee, the trial DSMB, the trial Steering Committee and the KwaZulu-Natal Department of Health.

8.7 Pregnancy reporting

Pregnancy is not considered as an AE or SAE. However the investigator must report all pregnancies occurring in HIV-infected women on ART during the trial on the "*Pregnancy notification form*" as soon as these are confirmed. Women of child bearing age will be asked about the possibility of being pregnant at each trial clinic visit; women who consider they may be pregnant will be offered an immediate pregnancy test

As soon, as a pregnancy becomes known, the nurse in charge of the patient should immediately report to the physician to adapt ART as needed.

Any pregnancy occurring during the trial and its outcome should be immediately reported to ANRS, using the trial "pregnancy notification form". The participant has to agree with collecting data on her pregnancy.

The investigator has to notify each pregnancy as soon as the investigator is aware to coordinating centre (same system as for SAE above, we can just say see section 9.2).

The ANRS pharmacovigilance unit reports all pregnancies in the International Antiretroviral Pregnancy Registry.

The medical surveillance of the women and their children will be reinforced, specifically regarding serious pathology occurring during pregnancy and any congenital abnormalities in the infant at delivery. A SAE initial report form should be filled if any anomaly is detected.

Any Voluntary Interruption of Pregnancy, Therapeutic interruption or miscarriage needed a hospitalisation is considered as a SAE to notify as mentioned in section 9.2 above.

All pregnancy outcomes should be reported using the "Pregnancy outcome notification form" using the same procedure described above.

8.8 Annual safety report

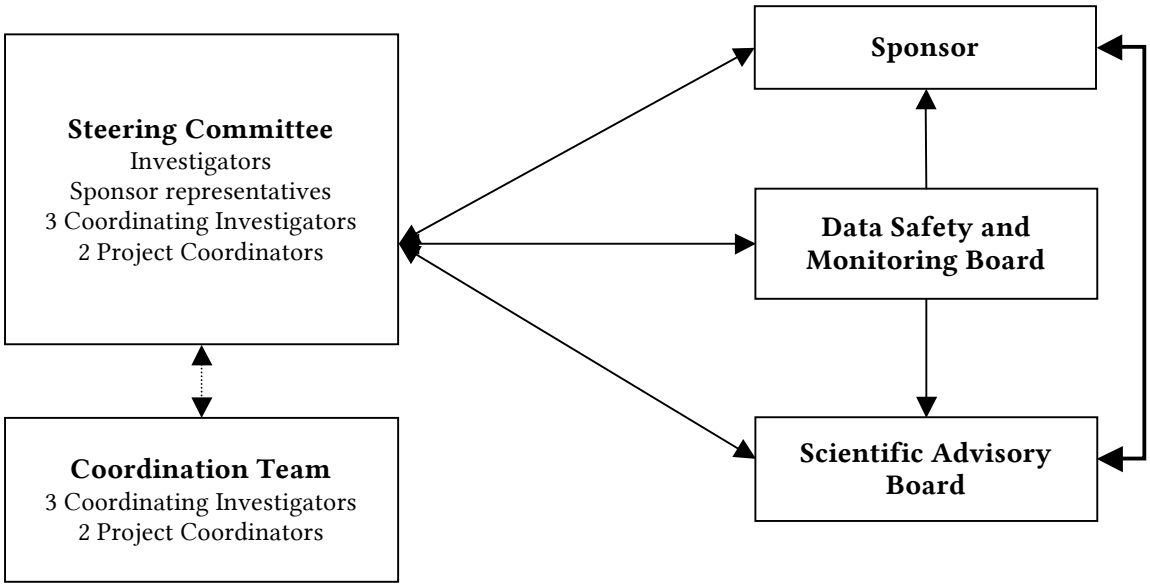
The ANRS pharmacovigilance unit coordinates the production of an Annual Safety Report in order to assess the benefit/risk balance throughout the duration of the trial.

This report is written in collaboration with the coordinating investigators and the clinical project manager. It is submitted to the research coordination team. It is sent to the trial coordinating team and may be used for communication with the University of KwaZulu-Natal Biomedical Research Ethics Committee and KwaZulu-Natal Department of Health.

9. Trial oversight

Figure 6 below summarises the trial oversight organisation.

Figure 6
Trial oversight



9.1 Steering Committee (SC) and Coordination Team (CT)

The **Steering Committee (SC)** will be responsible for the conduct of the trial and its overall organization. The SC is the trial decision body, for all scientific and administrative aspects. The SC will be co-chaired by the Coordinating Investigators. It will comprise the team investigators in South Africa, France and Switzerland and representatives of the Sponsor as listed on page 3 (The ANRS 12249 TasP Trial Team). The SC will meet as regularly as needed on conference calls and face-to-face meetings.

The SC ensures the correct implementation of the study and compliance with the protocol, and verifies its ethical compliance. It decides about any relevant changes to the protocol, necessary for continuation of the study.

The SC is responsible for the scientific promotion and communication of the trial data. Any sub-studies using the trial data should be discussed and approved by the SC.

The SC written report is sent to the investigators and to the Sponsor.

The Coordination Team (CT) is composed of the three Coordinating Investigators, the two Project Coordinators (one in South Africa and one in France), and any relevant participants to discuss specific issues. The CT undertakes the day-today management of the trial. The CT will meet by teleconference, which will usually be held at monthly

intervals although may be needed more frequently in the initial phases, frequency to be decided by the Project Coordinators.

The CT reports regularly to the SC for updates on trial progress and potential issues and, sends a *quarterly* progress reports (the content will be defined jointly at the beginning of the trial) to the Sponsor and to the Steering Committee.

The CT together with the SC coordinates and prepares the progress and scientific reports, communications and presentations to the SAB, DSMB, Ethical Committees and national regulatory bodies.

9.2 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) is the group that monitors the main safety and efficacy outcome measures and the overall conduct of the trial, with the aim of protecting the safety and the interests of the trial participants. The DSMB is appointed by the Sponsor before the implementation of the study and follows the current ANRS procedures "Independent Committee for ANRS sponsored clinical trials in developing countries".

The DSMB is an independent consultative committee in charge of alerting the scientific committee, the Coordinating Investigators and the Sponsor of any modification in the trial risk benefit ratio.

The DSMB is composed of six independent experts covering the main disciplines of the trial (biostatistics, HIV adult medicine, prevention, and bioethics). All members must be free from any direct involvement with the trial; any competing interests, both real and potential, must be declared.

The DSMB meets on a regular basis (frequency is decided by the board) throughout the trial and at least once a year. In the event of a serious or unexpected problem, an extraordinary meeting may be requested by the SC, the SAB Chair or the Sponsor to discuss on questions relative to the scientific and ethical integrity of the study. The first session of the DSMB will be held prior to the implementation of the trial to agree with the trial investigators the stopping rules needed to monitor the safety issue.

The DSMB, appointed for the needs of the study, will have access to all intermediate data and results decoded by cluster, as well as to any information justifying any change affecting the course of the study. It will monitor the trial regularly with a focus on issues relating to quality of trial conduct, such as rates of recruitment, adherence to trial interventions, visit schedules, losses to follow-up, respect of ethical principles and safety data.

DSMB meetings will be organized in two parts: an open session with the trial investigators and sponsor representatives followed by closed sessions with DSMB members and the trial statistician if relevant.

DSMB written reports signed by the chair will be sent to the Coordinating Investigators, the chair of the trial SAB, the chair of the Steering Committee and the sponsor.

9.3 Scientific Advisory Board (SAB)

The Scientific Advisory Board (SAB) is the group that oversees the overall conduct of the trial. Its mission is to make sure and to report, particularly to the Sponsor, whether the study is carried out properly scientifically, ethically and logistically.

The SAB is appointed by the Sponsor before the implementation of the study.

A first meeting will be convened prior to the beginning of the trial and the following meetings will be scheduled at least once a year till the end of the trial. In the event of a serious or unexpected problem, an extraordinary meeting may be requested by the SC, the SAB Chair or the Sponsor. Meetings of the SAB will be organized whenever possible in South Africa.

The SAB formulates written recommendations to the SC and to the Sponsor. The SC is expected to give its written feed back to the SAB and the Sponsor.

10. Ethic and regulatory aspects

10.1 Ethics and competent authorities

This trial will be conducted in compliance with the protocol and with the following:

- the ethical principles outlined in the most recent version of Declaration of Helsinki
- the guideline for Good Clinical Practice (ICH E6 May 1996)
- the ANRS Ethics charter for research in developing countries (May 2002, amended October 2008)
- in accordance with the approval from the University of KwaZulu-Natal Biomedical Research Ethics Committee
- the Research Committee of the KwaZulu-Natal Department of Health
- and approval of the local population through the Africa Centre Community Advisory Board.

The trial protocol was submitted for approval to the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (see Appendix 15.7) and for health authorities' authorisation to the KwaZulu-Natal Department of Health in South Africa.

This final version of this protocol was approved and signed by the three Coordinating Investigators and the Sponsor (cf. signatures on page 1).

10.1.1 Africa Centre Community Advisory Board (CAB)

The Africa Centre's Community Advisory Board (CAB) is an autonomous body consisting of approximately 30 members chosen by the community, whose main role is to link the Africa Centre with the community. The CAB membership comprises representatives from the traditional authorities, local councillors, community members and representative from the local offices of key provincial government departments including Health, Education and Social Development. Through the CAB, community input will be provided into trial design (cohort selection criteria), questionnaire content, participant follow-up plans, informed consent procedures, risk reduction interventions, community education and outreach, recruitment, retention planning and dissemination of trial findings. All research initiatives at the Africa Centre are presented to the CAB for discussion before seeking ethics approval from the University of KwaZulu-Natal's Ethics Committee.

10.1.2 Biomedical Research Ethics Committee of the University of KwaZulu-Natal

The Biomedical Research Ethics Committee is mandated to fulfil its function by the Senate of the University of KwaZulu-Natal. The essential function of the Committee is to review the protocols of all human subjects health research projects proposed to be undertaken by students and members of staff of the University. The purpose of this review is the protection of the dignity, rights, safety and well-being of all human participants of research. Special attention is given to research that may include vulnerable participants. The Committee is available to review, advise on, and approve or reject research protocols involving human participants submitted to it by researchers. Research to be reviewed will be in accordance with the stipulations of the National Health Act of the Republic of South Africa.

The membership of the Committee comprises of a Chairperson, two Deputy Chairs, at least two laypersons with no affiliations with the institution (preferably from the community), at least one member with knowledge of and current experience in research areas that are regularly considered by the Committee, at least two members with knowledge of and current experience in professional care, counselling or treatment (e.g. general practitioner, psychologist, etc.), at least one member who is legally trained. Decisions are made at meetings at which at least a quorum of 50 % plus one is present.

10.1.3 KwaZulu-Natal Department of Health (DoH)

The mission of the KwaZulu-Natal Provincial DoH is to develop a sustainable, co-ordinated, integrated and comprehensive health system at all levels, based on the primary health care approach through the district health system. In total there are 11 health districts in the province, with Africa Centre situated in the Umkhanyakude District. The District has five district hospitals. The hospital doctors are general practitioners, many with special interests. Despite not having specialist posts, the hospitals all perform surgery including caesarean sections, and offer excellent opportunities for surgical and anaesthetic experience. Supported by the hospitals are 52 residential clinics staffed with primary health care nurses. Most of these clinics are visited twice monthly by medical and paramedical staff. Since 2004 the Africa Centre has partnered with the DoH in the Hlabisa sub-District in the roll-out of antiretroviral treatment, with the financial support from PEPFAR. The Africa Centre's support has focused on the Hlabisa hospital and its 17 peripheral clinics. The Africa Centre provides assistance with infrastructure, training and transfer of skill; including management skills. The focus of the Africa Centre's HIV Treatment and Care Programme has always been one of building sustainability. The DoH has provided a letter of support to the TasP project (see Appendix 15.3).

10.2 Community, participant and patient information and consent

Community engagement and provision of adequate patient/participant information are keys in the success of the trial. The KwaZulu-Natal DoH has developed and approved an extensive array of community and patient information materials relating to all aspects of HIV – prevention, treatment and care. These are already widely available in the clinics and will be made available in the trial clinics as well. The social science team, with the community liaison office, is developing other information and community education materials for use in the trial as part of the initial preparatory work started in 2010. Examples of the materials being prepared include a community information leaflet (see Appendix 15.4), and the referral cards given to all participants during the home-based testing rounds. The four community advisory panels described above and Africa Centre Community Liaison Office will also contribute to the development of community, participant or patient information materials to ensure their appropriateness. Development and provision of any printed materials will follow normal approval processes in respect to their scientific content, input from trial Steering Committee, trial ethics and the provincial DoH as appropriate.

We will use the routine community road shows that are part of the Hlabisa Treatment and Care Programme's activities to ensure that there is a continuous feedback loop between the investigators and the communities. Over the years these road shows have been demonstrated to be a highly effective communication tools to promote HIV testing and treatment, and to educate the communities about the range of services and options

provided by the programme. The content of any materials to be disseminated through the road shows will be approved by the trial investigators.

Consent for the collection of data and the retention of residual samples will be collected from individuals following the procedures of the Africa Centre and approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee. Consent forms are presented in appendix 15.4. In each instance when consent is sought an individual will be fully briefed by the counsellor or clinical staff member and asked to provide a signature, the signature will then be countersigned by the staff member with the inclusion of a date time. For participants unable to write their own name, they will be asked to 'make their mark' (customarily an 'X'). In the event that a participant needs to do this the counsellor will need to have a second witness, normally another household member or Africa Centre counsellor, to verify the mark. This will only apply during the home-based testing rounds and when a person is not in possession of a South African national identity document. For participants that attend trial clinics for treatment and care, who are unable to write and do not possess a South African national identity document the process of making a mark/providing a thumb-print will be witnessed by two clinic staff members, unless the person attends with a 'treatment supporter' or family member, to avoid the potential for inadvertent disclosure of HIV status.

10.3 Data confidentiality

Current Africa Centre procedures require all staff to sign confidentiality and Acceptable Use Policy agreements, stating they have read and understood them and that they agree to abide by them. There are also formal policies in place regarding e.g. password usage and email security.

Each trial subject will be identified by a unique trial number and this alone will be used throughout the trial to identify the participant.

Personal identification details (Name, Id. No, clinic numbers, address, etc.) will only be made available to a) those whose job within the operational activities of the trial makes having such information absolutely essential, and b) to senior members of the trial administration (coordinating investigators, ANRS trial monitors, DSMB statistician) at the discretion of the trial coordinating investigators.

Completed questionnaires will be stored in a secure environment (in locked cabinets within the secure, access-controlled, Data Centre) and access will be granted only on a 'need to know' basis. These completed questionnaires and other study-related documents will be digitally archived according to the SOP developed in the AC for this purpose following strict quality control procedures.

Staff will be required (and trained) to always email personal information in password-protected attachments, not in the body of email, nor in unprotected attachments. Similarly, transmission of personal information via text (SMS) or fax messages, even for valid operational purposes, will be forbidden.

Data used for analysis, as opposed to day-to-day operational activities, will never contain personal identifying information, and will only be issued under a formal Data Use Agreement which must be signed by the data user, the Africa Centre Director, and the trial coordinating investigators. It imposes conditions on data use including that data will be stored securely, will not be passed to others, used only for the agreed purposes, and that it will be destroyed after completion of the agreed analyses, as per Africa Centre standard procedures.

10.4 Protocol amendments

Any substantial change to the protocol will be described in an amendment, which will be ratified by the trial SC, and forwarded to the sponsor for agreement and to the pharmaceutical company partners in the trial (where appropriate) for information and comments. These amendments will then be forwarded to the Biomedical Research Ethics Committee of the University of KwaZulu-Natal for approval. Any amendment should be signed by the Sponsor, the Coordinating Investigators and the Biomedical Research Ethics Committee of the University of KwaZulu-Natal before its implementation.

10.5 Investigators responsibilities

The Coordinating Investigators agree to conduct this trial in full accordance with the provisions of this protocol and will comply with all requirements regarding the obligations of clinical investigators as outlined in the ICH – E6 good clinical practice (GCP) guidelines. They agree to maintain all trial documentation until the trial sponsor consents to disposal of files in writing. They are fully aware of the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the trial are informed about the obligations incurred by their contribution to the trial.

10.6 Insurance

The ANRS, as the Sponsor, will take a civil liability insurance policy, for the trial to cover all HIV infected patients receiving ARV treatment. A copy of the insurance certificate is given in Appendix 15.6.

11. Data management and monitoring

11.1 Data collection and storage of forms

Questionnaires, electronic or paper-based CRFs will be used for data collection on site. The questionnaires and CRFs will be designed, completed, stored and relayed according to GCP principles and using local accredited GCP trainers. The completed questionnaires, CRFs and supporting documentation will be kept securely, in locked cabinets at the Africa Centre location, as trial source documents for potential review and/or audit during or after the trial. No source documents will be destroyed without specific permission in writing from the project coordinators. Only the coordinating investigators, the project coordinators and the authorised trial personnel will have access to the completed questionnaires, CRFs and supporting documents. Data capture and storage will be undertaken using computer systems compliant to GCP. To ensure correct operation according to SOP all system users will be trained and evaluated on a regular basis in line with Africa Centre policy. In-country and external monitoring will be organized to ensure that all the trial procedures are respected on site and to verify the data validity and reliability.

11.2 Data management

The Africa Centre Information Technology (IT) network is a technologically advanced Microsoft-based setup, professionally designed and maintained according to Microsoft 'best practices', by a large South African IT services company in collaboration with the Africa Centre IT Manager and his staff. Servers (mostly virtualised) are all located at the Africa Centre in a secure computer room and the network is protected by uninterrupted power supply (UPS) firewalls, up-to-date virus and malwares scanning software. Users are all given their own logins and sign confidentiality and 'Acceptable Use Policy' agreements. A comprehensive system of backups and archiving is in place, with some held off-site (transported and stored by a professional security company). A disaster recovery plan is in place and reviewed regularly.

The data collection, entry and management for the trial will be modelled closely on the current practices and procedures for existing Africa Centre surveys and trials for which a large suite of SOPs and policy documents exist (see www.africacentre.com) and which have been developed over more than 10 years of field operations. Many of the staff involved have considerable experience of managing clinical trials and the surrounding business processes as well as our surveillance systems and various demographic and health surveys. Currently the Data Centre prints and processes about 1.2 million pages per annum.

Every questionnaire will be individually bar-coded, with its details recorded in a database, and scanned at each stage of its life from printing and issue to fieldworkers through to final archiving, hence achieving an end-to-end 'chain of ownership' and clear visibility of where every form is at any moment. All completed forms will, on return from the field, first be checked visually by our Quality Control Department before being passed to staff in our secure Data Centre for data entry, and subsequent digital scanning and archiving. All entered data will be carefully checked for consistency and accuracy and, if necessary, correction.

All data will be stored in a MS-SQL Server database located on one of our own database servers, managed by professional Database Administrators. Access to read, enter, modify or delete data will be granted via the standard authentication and access-control

features of MS-SQL Server and MS-Windows. Laboratory results will be transmitted, using already-established procedures, directly into the database, via a secure (https) connection from the Africa Centre Laboratory's Laboratory Information System. Data issued for analysis by scientists will all be anonymised and covered by formal, signed Data Use Agreements, which cover acceptable use, security, destruction after use etc.

Overall, the Africa Centre offers a very high quality, tried and tested professional data collection and management service, conforming to good clinical practice and trial specifications. Compliance with the ANRS rules and regulations will be verified before trial start.

11.3 Exchange of data

The trial data are stored at the Africa Centre. All members of the SC can have access to specific trial data as per their research interests, as appropriate and following agreed procedures. Requests for data for specific analyses must be accompanied by a data analysis plan, as well as, if required, ethics certification by recognised ethics committees abroad. All requests for analysis will need to be discussed and approved by the SC.

Any exchange of trial data will be through secure connections, password-protected (see trial SOPs for further details).

11.4 Quality assurance, monitoring, audits and inspections

All trial procedures will be standardised and compiled in a manual of operations. A training session will be scheduled before the trial starts for all trial staff.

In accordance with Good Clinical Practice (GCP) to ensure the quality of the trial, each investigator accepts monitoring visits, audits and inspections.

11.4.1 Monitoring

A **Trial Initiation Visit** will take place before the first patient enrolment in the trial. During this visit, the monitor/monitoring team (from UKZN clinical trials centre or from ANRS) will review the trial material: documents compiled in an Investigator file, trial products and will verify that the investigational team understands the protocol and GCP requirements.

During the trial, a representative of the Africa Centre/monitoring team will make regular **Monitoring Visits** to the clinical service, hospital pharmacy and laboratories involved in the trial to (i) ensure that the study is conducted according to the protocol and GCP and (ii) to help the investigational team in solving problems. During these monitoring visits, the monitor will have access to the source document for patient validation data reported in CRF (at any time, the investigator or his representative can be contacted for any matter relating to the protocol, its practical application or the measures to take facing certain events).

Once all participants have been enrolled, and all study procedures have been completed, and all clinical data has been duly recorded in the CRFs and reported to the Sponsor, a **Close-out Visit** must be done by the monitor, to ensure that the Investigator File and other trial documents are archived properly; in addition, the monitor must collect all unused trial material, documents and products.

The monitor will submit a written report to the sponsor or its representative after each trial-site visit or trial-related communication.

11.4.2 Audits and inspections

The trial may be audited by the Sponsor or with his express authorization by other agencies.

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, is to be able to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

12. Archiving

The investigators on site will digitally archive the patient information sheet, informed consent forms, protocol and amendment(s), CRF model, correspondences, patients' CRF and sources data/documents and will keep this information for 15 years at the Africa Centre, in accordance with GCP for clinical trials.

13. Results publications

The investigator team will meet to define the core publications from the first phase, responsibility for overseeing additional papers and plans for analysis (including the core papers) will be overseen by a publication committee.

The main trial results on the effectiveness of 'treatment as prevention' must receive prior approval from the coordinating investigators and SC in respect of the agreement contracted between ANRS and the pharmaceutical company, which provided drugs.

The publication of the main trial results should include the name of the sponsor, all the investigators who included or followed-up participants in the trial, the composition of the SC and the possible participation of pharmaceutical company, which provided drugs. Each publication in a scientific journal or subjected to a scientific conference or for the media should include:

- that the sponsor is Inserm-ANRS: "*French National Institute of Health and Medical Research - French National Agency for Aids and Viral Hepatitis Research (Inserm-ANRS) is the sponsor of the TasP trial.*";
- the source of funding if co-financing and/or if different from the sponsoring ("*French National Institute of Health and Medical Research - French National Agency for Aids and Viral Hepatitis Research (Inserm-ANRS) and the Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) funded TasP phase 1"* and "*The French National Institute of Health and Medical Research - French National Agency for Aids and Viral Hepatitis Research (Inserm-ANRS) and the International Initiative for Impact Evaluation (3ie) funded TasP phase 2"*
- the pharmaceutical company which provided drugs ("*Trial conducted with the support of MERCK & Co. Inc and Gilead Sciences.*").

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15. Appendices

15.1 Appendix 1. National Department of Health Antiretroviral Treatment guidelines (March 2013)

health

Department:
Health
REPUBLIC OF SOUTH AFRICA

THE SOUTH AFRICAN ANTIRETROVIRAL TREATMENT GUIDELINES

2013

Date of Implementation 1 April 2013

24 March 2013

Acronym glossary

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ART	Antiretroviral Treatment
ARV	Antiretroviral
AZT	Zidovudine
CD4	Cluster of Differentiation 4
d4T	Stavudine
DNA PCR	DNA Polymerase Chain Reaction
EFV	Efavirenz
FBC	Full Blood Count
FTC	Emtricitabine
Hb	Haemoglobin
HepBSAg	Hepatitis B Surface Antigen
HIV	Human Immunodeficiency Virus
IPT	Isoniazid Preventive Therapy
LPV/r	Lopinavir/ritonavir
MCH	Maternal and Child Health
MDR/XDR-TB	Multi-Drug Resistant / Extensively Drug Resistant Tuberculosis
NVP	Nevirapine
PHC	Primary Health Care
SRH	Sexual and Reproductive Health
TB	Tuberculosis
TDF	Tenofovir
WHO	World Health Organization

The South African Antiretroviral Treatment Guidelines 2013

1. Goals of the programme

a. Save lives and improve the quality of life of people living with HIV
b. Achieve best health outcomes in the most cost-efficient manner
c. Implement nurse-initiated treatment
d. Decentralise service delivery to PHC facilities
e. Integrate services for HIV, TB, MCH, SRH and wellness
f. Diagnose HIV earlier
g. Prevent HIV disease progression
h. Avert AIDS-related deaths
i. Retain patients on lifelong therapy
j. Prevent new infections among children, adolescents, and adults
k. Mitigate the impact of HIV and AIDS

2. Objectives

a. Ensure timely initiation of ARVs for treatment and prevention according to the Presidential mandates
b. Contribute to strengthening of the public and private health sectors' capacity to deliver high quality integrated health and wellness services
c. Implement cascade management and continuum of care
d. Minimize unnecessary drug toxicities
e. Improve clinical outcomes, promote adherence and improved retention of patients in care
f. Optimize the benefits of treatment as prevention by increasing coverage and annual HCT
g. Introduce fixed dose combination of highly effective ARV and improve adherence to treatment, care and support

3. Specific Objectives

1 To prioritise initiation of combination antiretroviral treatment for:
  1.1 Patients with CD4 counts <350 cells/mm^3 or with severe HIV disease (WHO 3 or 4) irrespective of CD4
  1.2 Patients co-infected with drug sensitive or resistant TB who should be initiated with ART irrespective of CD4 count
  1.3 Pregnant women with CD4 $\leq$ 350cells/mm^3 for lifelong ART and CD4 >350cells/mm^3 for prophylaxis
  1.4 Introduce fixed dose combination (FDC) ART for patients initiated with ART for the first time
  1.5 Introduce FDC ART for HIV positive pregnant women irrespective of CD4 count during pregnancy and during the breastfeeding period
  1.6 Phased introduction of FDC to patients with other co-morbidities (diabetes, hypertension and respiratory diseases, including TB)
  1.7 Phased introduction of FDC to patients who require switching due to drugs toxicity or switching from Stavudine (d4T) based regime
  1.8 Phased introduction of FDC to patients who are stable of ART and VL suppressed
2 To test all HIV exposed children under-five years and treat all those found to be infected with HIV.
3 To standardise first and second line therapy for children, adolescents, and adults in the public and private sector.

4 To move patients currently on Stavudine-containing regimens to Tenofovir-based FDCs, once creatinine clearance has been checked. Stavudine (d4T) to be used only under specific circumstances.
5 To strengthen capacity of nurses to initiate ARVs for treatment of pregnant women who are HIV positive for their own health and to prevent mother to child transmission.
6 To strengthen PHC facilities to initiate, manage, monitor and refer patients.

4. Adults and Adolescents

4.1 Standardised national eligibility criteria for starting ART regimens for adults and adolescents

Eligible to start Lifelong ART
▪ CD4 count ≤350 cells/mm3 irrespective of WHO clinical stage **OR** ▪ Irrespective of CD4 count ○ All types of TB (In patients with TB drug resistant or sensitive, including extra pulmonary TB) ▪ WHO stage 3 or 4 irrespective of CD4 count
Require fast track (i.e. ART initiation within 7 days of being eligible)
▪ HIV positive women who are pregnant or breast feeding **OR** ▪ Patients with low CD4 <200 **OR** ▪ Patients with Stage 4, irrespective of CD4 count **OR** ▪ Patients with TB/HIV co morbidity with CD4 count < 50 **(**Patients with Cryptococcus meningitis or TB meningitis (defer ART for 4-6 weeks)
Patients with CD4 above 350, Not yet eligible for ART
▪ Transfer to a wellness programme for regular follow-up and repeat CD4 testing 6-monthly. ▪ Advise on how to avoid HIV transmission to sexual partners and children ▪ Initiate INH prophylaxis if asymptomatic for TB ▪ Provide counselling on nutrition and contraception and do annual pap smear

4.2 Standardised national ART regimens for adults and adolescents

1st Line		
All new patients needing treatment, including pregnant women	TDF + FTC (or 3TC) +EFV FDC preferred	Replace EFV with NVP in patients with significant psychiatric co-morbidity or intolerance to EFV and where the neuro-psychiatric toxicity of EFV may impair daily functioning, e.g. shift workers.
Adolescents	ABC + 3TC + EFV	At age 18 years an adolescent if eligible must be switched to the FDC
Contraindications to EFV	TDF + (FTC or 3TC) + NVP	Use NVP based regimen: In patients with significant psychiatric co morbidity or intolerance to EFV and where the neuro-psychiatric toxicity of EFV may impair daily functioning, e.g. shift workers.
Contraindication to TDF	AZT+ 3TC +EFV or (NVP)	Renal disease or the use of other nephrotoxic drugs e.g. aminoglycosides
Contraindication to TDF and AZT	d4T + 3TC+ EFV (or NVP)	Renal disease and anaemia or the use of other nephrotoxic drugs, aminoglycosides
Contraindication to TDF, AZT and d4T	ABC + 3TC + EFV (or NVP)	Renal disease, anaemia, peripheral neuropathy, the use of other nephrotoxic drugs
Currently on d4T-based regimen	TDF + FTC(or 3TC) + EFV FDC preferred	Mandatory if patients experience toxicity and patients who are at high risk of toxicity (high BMI or pregnant). Switch to TDF if virally suppressed and the patient has normal creatinine clearance, even if well tolerated.
2nd Line		
Management of virological failure		If plasma HIV RNA >1000 copies. Check for adherence, compliance, tolerability and drug- drug interaction and assess psychological issues. Repeat VL test 2 months later. If plasma VL confirmed >1000copies change regime to second line therapy
Failing on a TDF-based 1st line regimen	AZT+3TC+ LPV/r	Patients with anaemia and renal failure switch to ABC
Failing on a d4T-based 1st line regimen	TDF+3TC (or FTC) and LPV/r	
Dyslipidaemia or intractable diarrhoea associated with LPV/r	Switch LPV/r to ATV/r	
Third line		
Failing any 2nd line regimen	Specialist referral	
Should be expert and genotype resistance testing based decision and supervised care Patients failing on second line therapy will be managed by an expert panel. The drugs for third line will be managed centrally. More discussion is required to deal with the modalities	Most likely regimen would be Raltegravir/Darunavir/ /Etravirine adjusted according to genotype Interpretation. Should be by expert and take into account prior exposure and predictable mutations	

4.3 Standardized National Monitoring for Adults and Adolescents with HIV

At initial Diagnosis of HIV	Purpose
Confirm HIV result with rapid antibody test	Ensure that national testing algorithm has been followed
Do CD4 count if HIV positive and WHO clinical staging	To assess eligibility for ART To assess eligibility for fast-tracking
Screen for pregnancy or ask if planning to conceive	To identify women who need ART for life or ARV prophylaxis for PMTCT (see section 6)
Screen for TB symptoms using the WHO questionnaire	To identify TB/HIV co-infected
Do the CD4 count on the same day	To identify eligibility for ART or ARVs for prophylaxis if pregnant
Do HB or FBC if requires AZT Creatinine if requires TDF For patients initiated on Nevirapine based regime do ALT	To detect anaemia or neutropenia, To detect renal insufficiency To exclude liver disease

On ART	Purpose
CD4 at 1 year on ART	To monitor immune response to ART
VL at month 6, 1 year on ART and then every 12 months	To identify treatment failures and problems with adherence
ALT only if on NVP and develops rash or symptoms of hepatitis	To identify NVP toxicity
FBC at month 3 and 6 if on AZT	To identify AZT toxicity
Creatinine at month 3 and 6, 1 year then every 12 months if on TDF	To identify TDF toxicity
Fasting cholesterol and triglycerides at month 3 if on LPV/r	To identify LPV/r toxicity

At Routine Follow-Up Visits for those not yet eligible for ART	Purpose
Repeat CD4 count at 6 months	To see if they have become eligible for ART
WHO clinical staging at every visit	To see if they have become eligible for ART
Screen for TB symptoms to identify TB suspects Offer IPT if no TB symptoms	To identify TB/HIV co-infection To prevent TB activation
Offer prevention for HIV positives	To prevent HIV transmission and re-infection To prevent STIs

4.4 Indications for urgent up-referral prior to initiation or when on therapy

- eGFR less than 60 ml/min
- Hb less than 8 g/dl
- BMI less than 18.5 kg/m2
- In a patient with TB or other opportunistic infection , poor response to TB or OI treatment

5. Infants and Children

5.1 Standardised national eligibility criteria for starting ART regimens for Infants and Children

Eligible to Start ART
▪ All children less than 5 years of age, irrespective of CD4 • Children 5 years to 15 years with WHO clinical stage 3 or 4 or CD4 ≤350 cells/µl
Require Fast-Track (i.e. start ART within 7 days of being eligible)
▪ Children less than 1 year of age ▪ WHO clinical Stage 4 ▪ MDR or XDR-TB ▪ CD4 Count < 200 cells/µl Or < 15%

5.2 Standardised national ART regimens for Infants and Children

First Line Regimen	
All infants and children under 3 years (or < 10kg)	ABC + 3TC + LPV/r
Children ≥ 3 years (and ≥ 10kg)∞	ABC + 3TC + EFV
Currently on d4T-based regimen	Change d4T to ABC if viral load is undetectable If viral load >1000 copies/ml manage as treatment failure If viral load between 50 – 1000 copies/ml – consult with expert for advice
Second Line Regimen	
Failed first line Protease Inhibitor (PI)-based regimen	
Failed first line PI-based regimen	**Recommended second line regimen**
ABC + 3TC + LPV/r	**Consult with expert for advice***
d4T + 3TC + LPV/r	
Unboosted PI-based regimen	
Failed First line NNRTI based regimen (discuss with expert before changing)	
Failed first line NNRTI-based regimen	**Recommended second line regimen**
ABC +3TC + EFV (or NVP)	AZT + 3TC + LPV/r
d4T +3TC + EFV (or NVP)	AZT + ABC + LPV/r
Third line regimens	
Failing any 2nd line regimen	Refer for specialist opinion – Regimen based on genotype resistance testing, expert opinion and supervised care Access to third line ART will be managed centrally by the National Department of Health

∞ Children ≥ 3 years and exposed to NVP for 6 weeks or longer (PMTCT) should be initiated on ABC + 3TC + LPV/r

*Recommended Second Line regimen under expert advice NB: Some paediatric second line ART agents are not licensed by the MCC and are not available for routine use at the time of publication of this guideline	
ABC + 3TC + LPV/r	No previous daily NVP for PMTCT AZT + 3TC+ EFV* + LPV/r * Use NVP if <3 years or <10kg Previous daily NVP for PMTCT Treat with third line regimen
d4T + 3TC + LPV/r	No previous daily NVP for PMTCT AZT + ABC + EFV* + LPV/r * Use NVP if <3 years or <10kg Previous daily NVP for PMTCT Treat with third line regimen
Previously on a regimen with unboosted PI (e.g. ritonavir alone), or with rifampicin while on LPV/r	Must be managed by an expert on basis of genotype resistance testing to confirm PI susceptibility.

5.3 Standardized national monitoring for Infants and Children with HIV

At initial Diagnosis of HIV	Purpose
Verify HIV status	Ensure that national testing algorithm has been followed
Document Weight, Height, Head Circumference (<2yrs) and Development	To monitor Growth and Development + identify eligibility for ART
Screen for TB symptoms	To identify TB/HIV co-infected
WHO Clinical Staging	To determine if patient is eligible for ART
Do the CD4 count	Children < 5 years – Baseline, DO NOT wait for CD4 count to start ART
	Children ≥ 5 years – To determine eligibility for ART and start cotrimoxazole prophylaxis as per national guidelines
Hb or FBC if available	To detect anaemia or neutropenia

At Routine Follow-Up Visits (patients not yet on ART)	Purpose
Document Weight, Height, Head Circumference (<2 years) and Development	To monitor Growth and Development and to see if patient has become eligible for ART
Check that a CD4 count has been done in the last 6 months	To determine if patient has become eligible for ART
WHO Clinical Staging	To determine if patient has become eligible for ART
Screen for TB symptoms	To identify TB/HIV co-infection

At Initiation of ART (Baseline)	Purpose
Hb or FBC	If less than 8g/dl start ART and refer for specialist opinion
CD4 count (if not performed in last 6 months)	Baseline assessment
HIV Viral Load (VL)	Baseline assessment
Cholesterol + Triglyceride if on PI-based regimen	Baseline assessment
Creatinine + urine dipstix if on TDF regimen	If abnormal refer for specialist opinion
ALT (if jaundiced or on TB treatment)	To assess for liver dysfunction

On ART	Purpose
Height, Weight, Head Circumference (<2yrs) and Development	To monitor Growth and Developmental stage
Clinical assessment	To monitor response to ART and exclude adverse effects
CD4 at 12 months into ART, and then every 12 months	To monitor response to ART, stop cotrimoxazole prophylaxis as per national guidelines
VL at 6 months and 12 months into ART, THEN 6 monthly in children <5 years AND 12 monthly in children 5 - 15 years	To monitor viral suppression response to ART To identify treatment failure and to identify problems with adherence
Hb or FBC at month 1, 2, 3 into ART and then annually if on AZT	To identify AZT-related anaemia
Cholesterol + Triglyceride at 12 months into ART and then every 12 months if on PI-based regimen	To monitor for PI-related metabolic side-effects
Clinical drug-related adverse events	To identify drug-related adverse events If develops jaundice or rash on EFV or NVP do Liver function test and refer to specialist

6. HIV-positive pregnant and breastfeeding Women and HIV-exposed Infants

6.1 Standardised national ART and ARV regimens for women who are HIV positive and pregnant, breastfeeding and their HIV-exposed Infants

Maternal Regimens		
Woman	**Regimen**	**Comment**
1st antenatal visit		
All women at first antenatal visit (any gestational age)	FDC initiated immediately	If there is a contraindication to the FDC: Start AZT immediately and review within a week. (Refer to PMTCT algorithm 1)
Currently on lifelong ART	Continue the ART regimen If the woman is on a compatible regimen (EFV, 3TC, TDF) change to FDC	Check a VL when pregnancy diagnosed
2nd antenatal visit (1 week later)		
Creatinine ≤ 85µmol/l Any CD4 cell count	Continue FDC	
Creatinine > 85µmol/l **Contraindication to TDF** (renal disease) CD4 ≤350cells/mm^3	AZT + 3TC + EFV	If haemoglobin <7g/dl AZT is contraindicated. Use d4T instead of AZT. (Refer to PMTCT Algorithm 3) Refer for investigation for cause of renal disease
Creatinine > 85µmol/l **Contraindication to TDF** (renal disease) CD4 >350cells/mm^3	AZT in pregnancy sdNVP + sd TDF + FTC and AZT 3hrly in labour	(Refer to PMTCT Algorithm 3)
Contraindication to EFV (active psychiatric illness) CD4 ≤350cells/mm^3	TDF + FTC + NVP	Substitute LPV/RTV for NVP in women with CD4 counts >250cells/mm^3
Contraindication to EFV (active psychiatric illness) CD4 >350cells/mm^3	AZT in pregnancy sdNVP + sd TDF + FTC and AZT 3hrly in labour	
Labour		
Unbooked and presents in labour and tests HIV positive	sdNVP + sd TDF + FTC and AZT 3hrly in labour Start FDC after delivery if woman will breastfeed	Assess maternal ART eligibility before discharge
Post Natal		
All woman breastfeeding and diagnosed as HIV positive during pregnancy	Continue FDC	If there is a contraindication to the FDC: Start AZT immediately and review within a week.
All woman breastfeeding and diagnosed as HIV positive during breast feeding	FDC initiated immediately	If there is a contraindication to the FDC: Start AZT immediately and review within a week. (See PMTCT algorithm 4)

Infant Regimens		
Infant	**Regimen**	**Comment**
Mother on lifelong ART or antenatal prophylaxis received (including TDF + 3TC/FTC + EFV or AZT)	NVP at birth and then daily for 6 weeks	If mother is breastfeeding and not virally suppressed e.g. late booking or established poor adherence, continue NVP for infant throughout breastfeeding until one week post cessation of breastfeeding
Mother did not get any ART before or during delivery and tests HIV positive post delivery	NVP as soon as possible and daily for 6 weeks	Assess ART eligibility as soon as possible for both mother and baby (as per infant testing algorithm)
Unknown maternal status because orphaned or abandoned	Give NVP immediately* Test infant with rapid HIV test. If positive continue NVP for 6 weeks. If negative discontinue NVP	Follow up at 6 weeks with HIV PCR
Mother on AZT regimen (due to any contraindication to the FDC regimen and had a CD4 >350cells/mm^3)	NVP at birth and then daily for 6 weeks	Test infant with 6 week HIV PCR test. If negative and breastfeeding continue NVP till one week after complete cessation of breastfeeding

***** If rapid HIV test can be done within 2 hours, then wait for HIV result before commencing NVP

ARV Adult Dosing Guide		
Drug	**Dosage**	**Comments**
TDF (Tenofovir)	300mg daily	Tenofovir is contraindicated if serum creatinine>85µmol/L during pregnancy (or creatinine clearance of <50ml/min in non-pregnant adults)
d4T (Stavudine)	30mg 12hrly po	All adult patients now receive 30mg regardless of weight
3TC (Lamivudine)	300mg daily	
FTC (Emtracitabine)	200mg daily	
NVP (Nevirapine)	200mg daily po X 2 weeks then 200mg 12 hourly po For PMTCT purposes single dose (sdNVP) is used as a 200mg tablet given once	Should be used with caution with TB treatment Avoid NVP if CD4 count >250cells/mm^3
EFV (Efavirenz)	600mg nocte	Avoid if active psychiatric illness
lopinavir 200mg /ritonavir 50mg	2 tabs 12 hourly (Lop400mg/Rit100mg)	Preferably taken with food. Boosting required with TB treatment refer to TB guidelines in 7.1 of these guidelines for dose
AZT (Zidovudine)	300mg 12 hourly po	Avoid if severe anaemia (Hb<8g/dl)

NVP Infant Dosing Guide			
	Birth Weight	**Dose**	**Quantity**
NVP syrup (10mg/ml)	<2.0kg	2mg/kg (first 2 weeks) then 4mg/kg (next 4 weeks)	0.2ml/kg 0.4ml/kg
	Birth to 6 weeks 2.0-2.5kg birth weight	10mg/d	1ml
	Birth to 6 weeks ≥ 2.5kg birth weight	15mg/d	1.5ml

7. Special Considerations

7.1 TB Patients

Suspect TB if 2 or more of the following symptoms are present:

1. Cough any duration
2. Sputum production which may occasionally be blood stained
3. Fever
4. Drenching night sweats
5. Unexplained weight loss
6. Loss of appetite, malaise, tiredness
7. Shortness of breath, chest pains
8. New palpable lymphadenopathy

The patient that presents with TB before commencing ART:

HIV positive TB patients qualify for lifelong ART regardless of CD4 cell count.

Complete 2 to a maximum of 8 weeks of TB therapy before commencing ART (**and as soon as possible if CD4 count is less than 50 cells cells/mm3**)

In general, ART should be initiated as soon as the patient is tolerating their TB therapy; this is usually within 2-4 weeks.

EFV-based regimens are generally preferred in patients with active TB; however, other regimens are also effective. Dose adjustment of PI may be required. Patients on Lopinavir/Ritonavir should have their dose doubled slowly over two weeks (to 800/200 mg twice a day).

Patient developed tuberculosis while on ART:

ART should be continued throughout TB treatment.

Patients on Lopinavir/Ritonavir should have their dose doubled slowly over two weeks (to 800/200 mg twice a day); all other regimens can be continued unmodified. Monitor and investigate appropriately for hepatotoxicity symptoms.

Continue these changes to Lopinavir/Ritonavir until two weeks after completion of TB treatment.

Antiretroviral Treatment for Adults with Concomitant TB	
TB develops while on ART	**TB diagnosed before starting ART**
Continue ARV therapy throughout TB treatment. **First-line regimen**. Patient can remain on the regimen they are taking.	**CD4 count >350/mm^3:** Delay ART for two months (until intensive phase of TB therapy is complete). **CD4 count 100 – 350/mm^3**

Second-line regimen: The lopinavir/ ritonavir dose should be doubled (from 2 tablets 12 hourly to 4 tablets 12 hourly) while the patient is on rifampicin-based TB treatment. Monitor ALT monthly. Reduce lopinavir/ ritonavir to standard dose 2 weeks after TB treatment is completed.	Introduce ART between 2-8 weeks **CD4 count of <100/mm^{3}or other serious HIV illness:** Introduce ART regimen as soon as the patient is stabilized on TB therapy (within 2 weeks after starting TB therapy). First line ART regimen: 1. Tenofovir 300mg daily 2. Lamivudine 300mg daily 3. Efavirenz 600mg at night

7.2 INH Prophylaxis

a. All people living with HIV should be screened for active TB and eligibility for ART.
b. Those who are eligible should be started on ART.
c. TB preventive therapy is an effective intervention for HIV infected individuals.
d. All people living with HIV, in whom active TB has been reasonably excluded, should be started on IPT (as soon as practically possible after initiation of ART in those who are eligible for ART).
e. In patients with no TB signs or symptoms, TB prophylaxis with Isoniazid Preventive Therapy (IPT) should be started, unless alcohol abuse, adherence or side-effects are a concern, 5mg/kg to a maximum dose of 300mg daily, with pyridoxine 25mg/day. **A TST (Mantoux) test is required.**
f. Pregnancy is not a contraindication to INH prophylaxis.
g. If no TST is done IPT should be continued for 6 months as per existing guidelines but all effort should be made to perform TST as soon as possible after starting IPT.

Summary Recommendations		
	Pre-ART(CD4>350)	**On ART**
TST not done*	IPT for 6 months	IPT for 6 months
TST negative	IPT for 6 months	IPT for 12 months
TST positive	IPT for at least 36 months	IPT for at least 36 months

8 PMTCT Treatment Algorithms

Figure 1 PMTCT Algorithm 1 New HIV Positive Diagnosis During Pregnancy

Algorithm 1 is for all women who are newly diagnosed as HIV positive anytime during pregnancy AND women who enter ANC with known HIV positive status and not yet on ART.

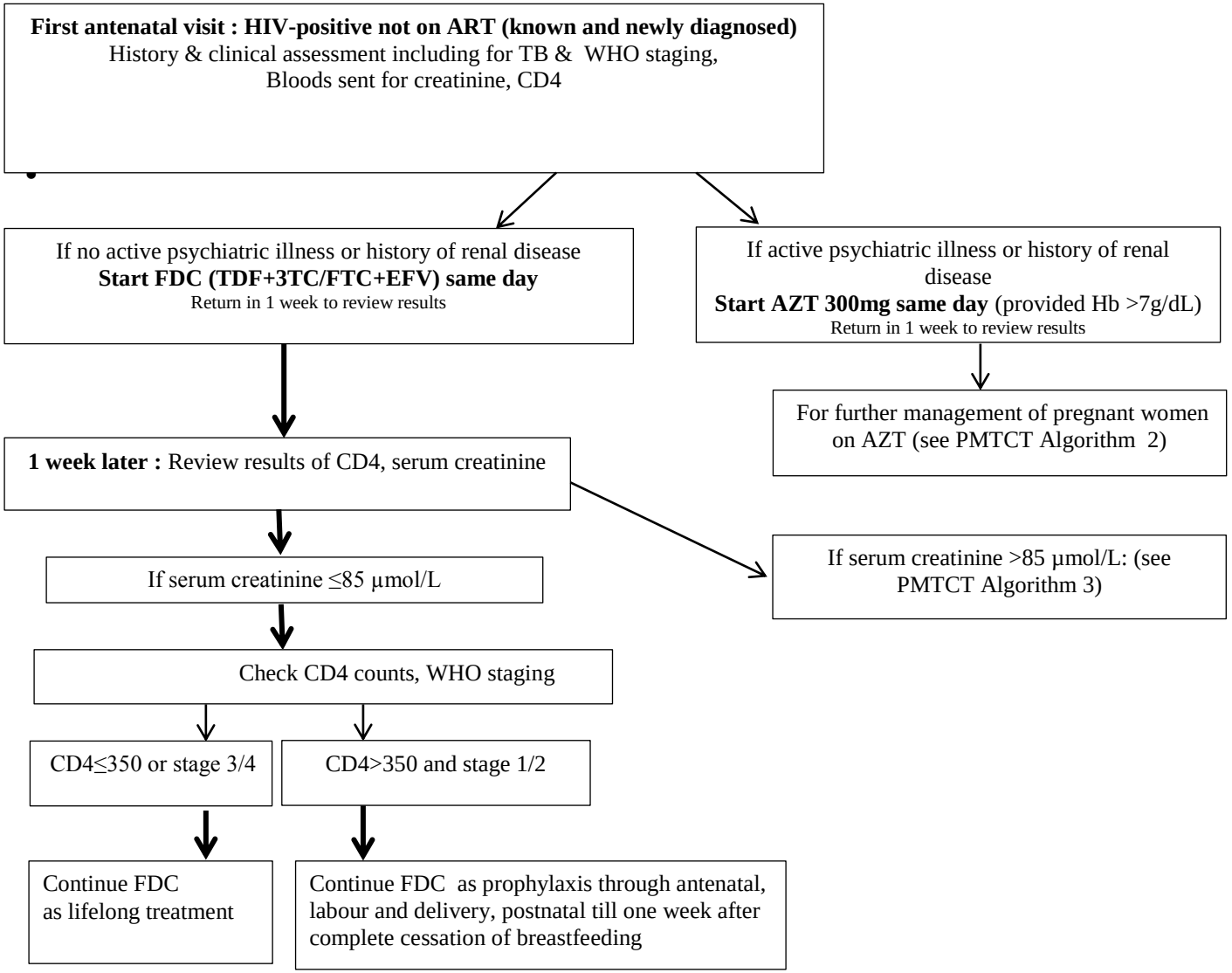


Figure 2 : PMTCT Algorithm 2 : Initiation of Antiretroviral Therapy During Pregnancy in Women with Active Psychiatric Illness

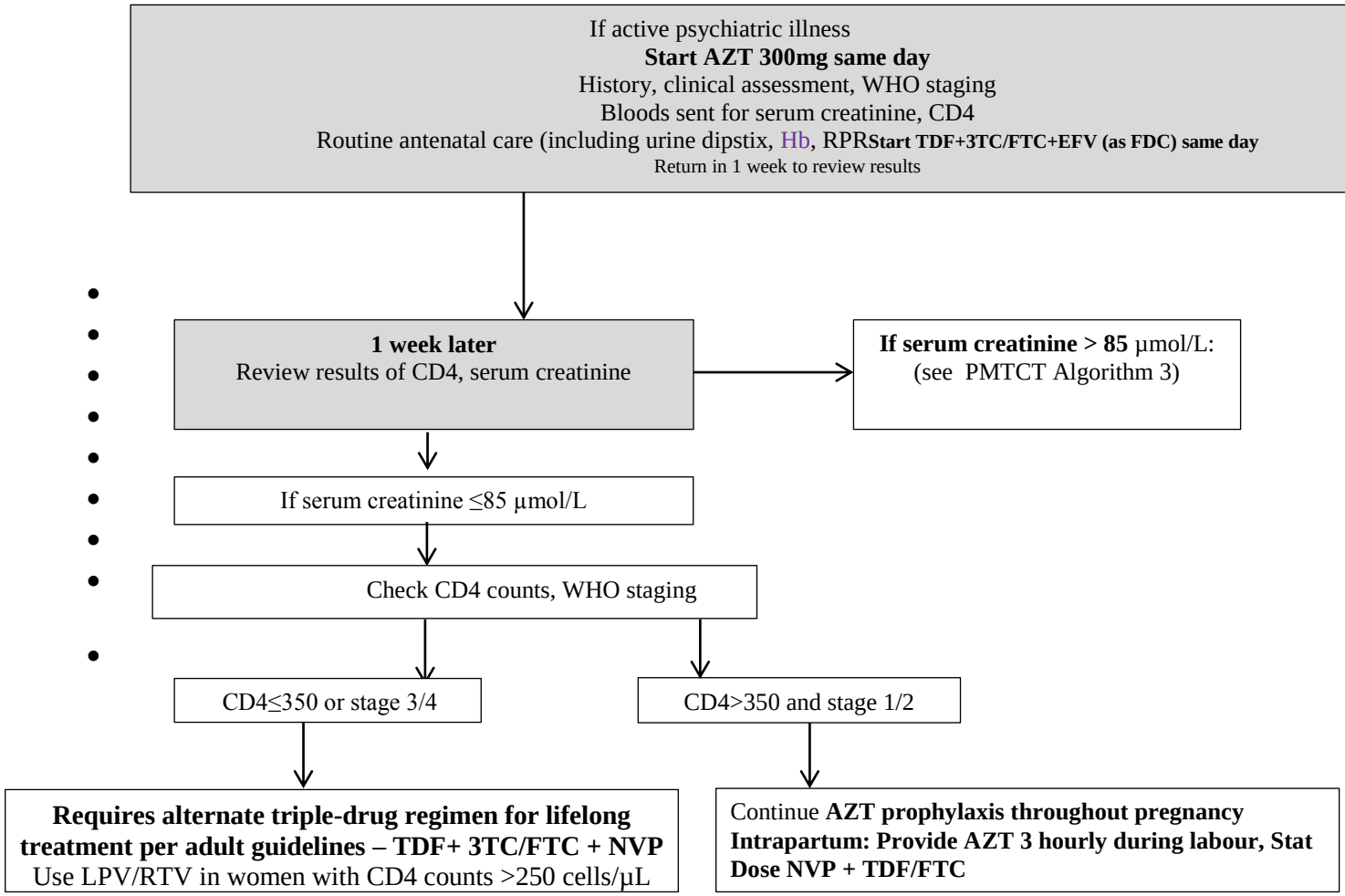


Figure 3 : PMTCT Algorithm 3: Initiation of Antiretroviral Therapy During Pregnancy in Women with Serum Creatinine >85 µmol/L

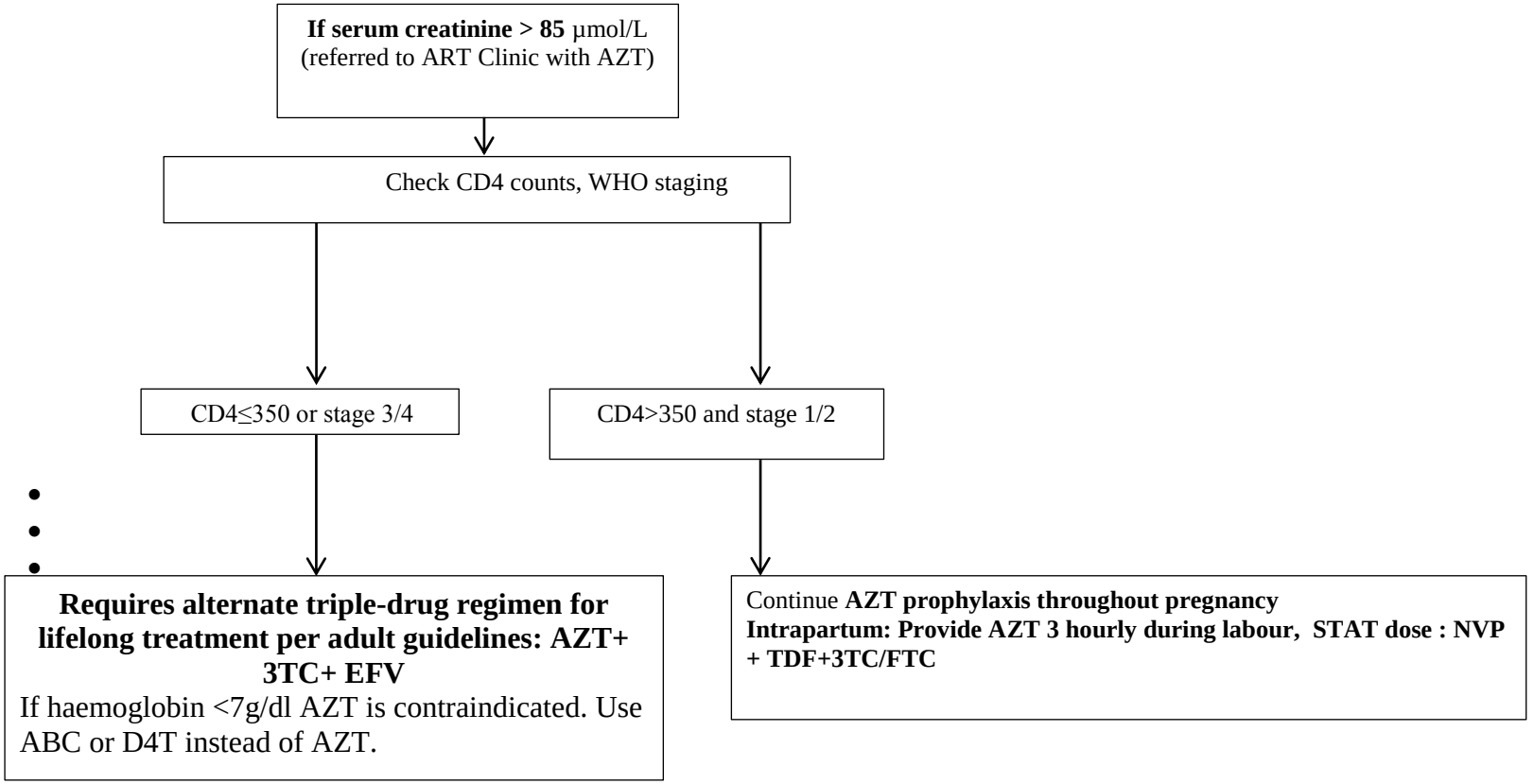
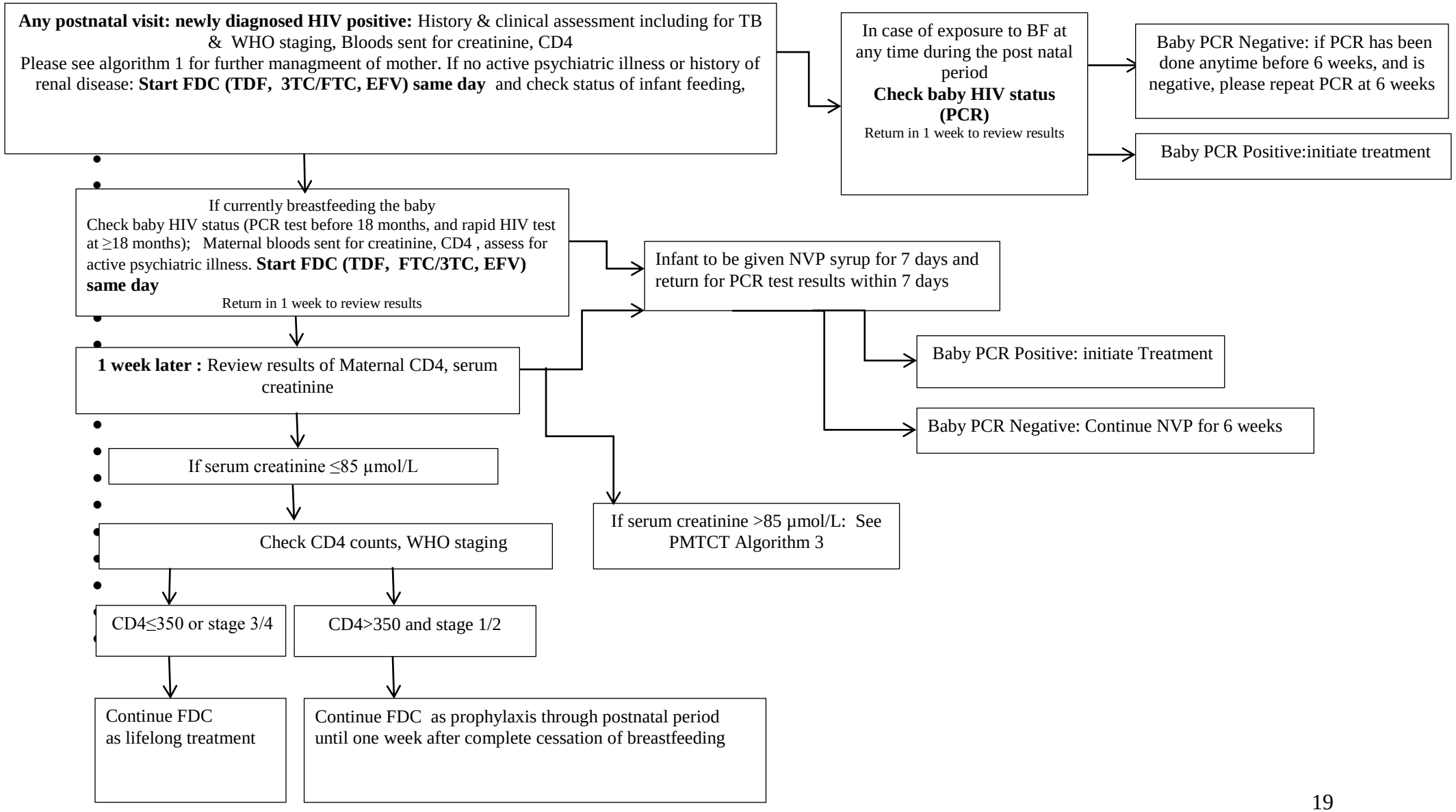


Figure 4 : PMTCT Algorithm 4 : For Women Newly Diagnosed HIV Positive During Postnatal Period



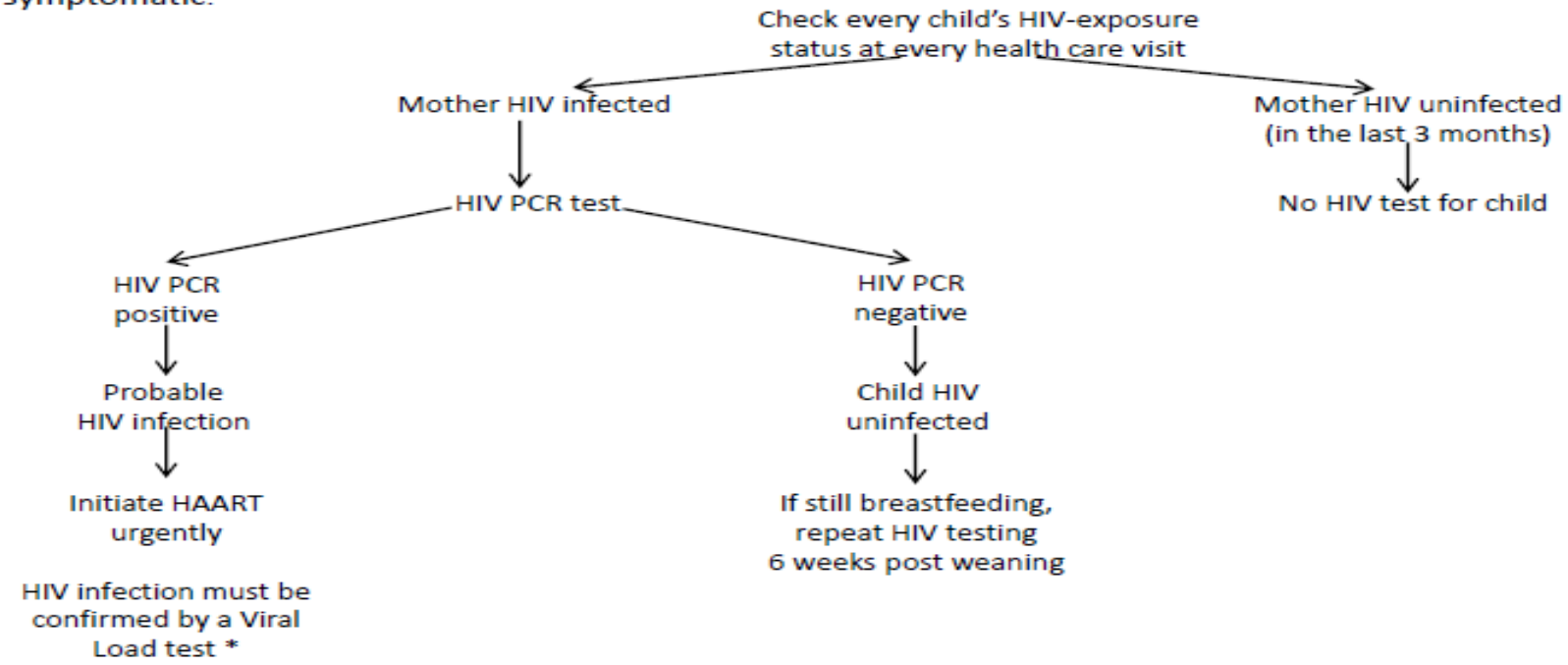
9 Testing Algorithm for Infants

Testing algorithm 1 for infants < 18 months of age

Diagnosis of HIV infection in infants and children

1. Children <18 months old

- All HIV-exposed infants require PCR testing at 6 weeks of age, 6 weeks post weaning and at any age if the child is symptomatic.



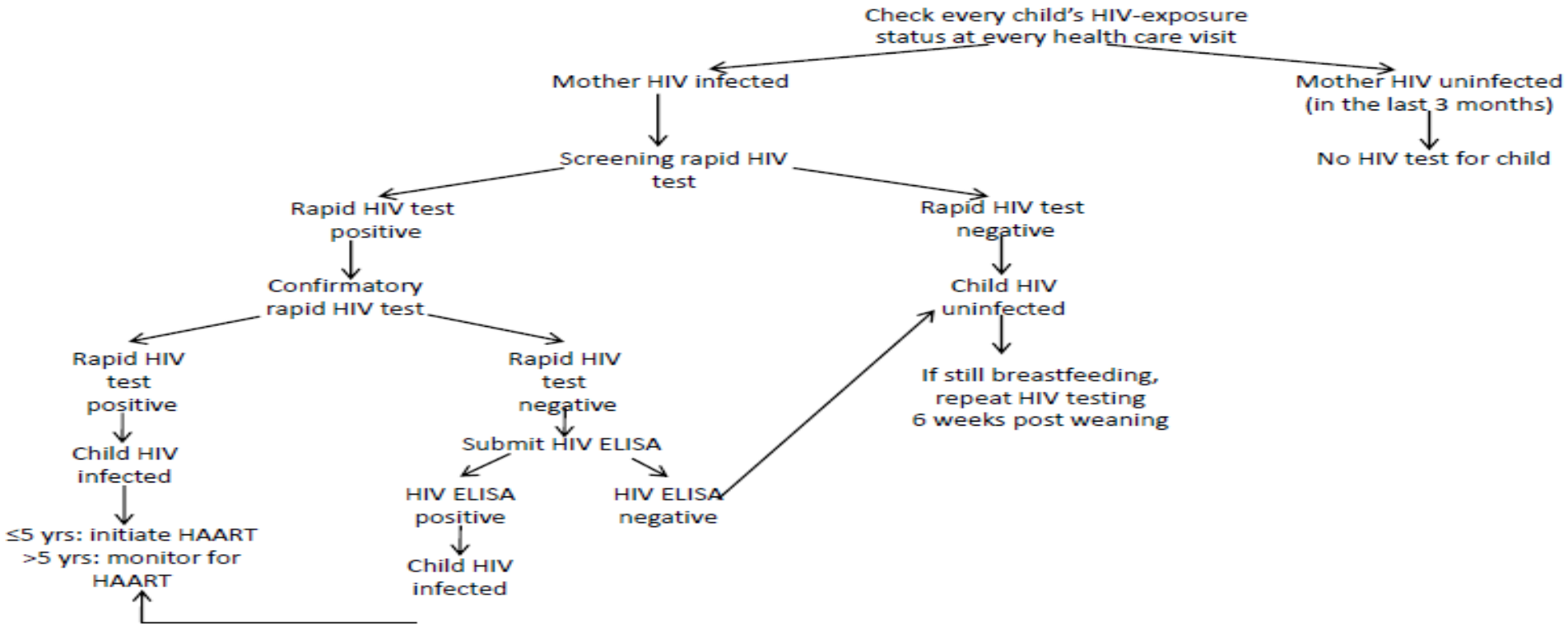
- A detectable Viral Load confirms HIV infection. HAART initiation should not be delayed by waiting for the Viral Load result.

If the HIV infection status of an infant initiated on HAART is in doubt, discuss further HIV testing required with your nearest HIV PCR laboratory

Testing algorithm 2 for infants ≥ 18 months of age

2. Children ≥18 months old

- All HIV-exposed children require a rapid test at 18 months of age, except HIV-infected children on HAART



15.2 Appendix 2. Reviewing the available evidence for the choice of trial medications

Minimal requirements and conditions

HIV-infected participants who will be included in TasP will be randomized in a control group (fitting with South African Department of Health guidelines – see below) or an intervention group (every HIV positive person whatever CD4 cell count will be offered antiretroviral therapy [ART] as soon as possible after HIV diagnosis).

The most recent version of the South African guidelines (2013) suggests initiating ART when the CD4 cell count falls below the 350 cells / mm^3 threshold.

It is advisable that all patients enrolled in TasP, regardless of the randomisation allocation group, have a similar ART regimen. This drug regimen should fulfil the following criteria:

- Appropriate at all CD4 cells strata
- Minimal side effects in otherwise "healthy" patients
- Potent
- High genetic barrier
- Sustainable for many years
- Low pill burden
- Minimal or low laboratory requirements
- Safe
- Affordable
- Covering a large range of the so called "special populations" according to WHO criteria (TB co-infection, hepatitis B co-infection, pregnant women)

Cost and compatibility with national formulary is also critical; however, there are now clear indications from UNITAID (with the creation of the patent pool), WHO (Revised Essential Medicine List [EML]) among others that once the best suitable treatment will be agreed upon, stakeholders will have the possibility to make it available. Newly approved products or late stage development compounds can also be considered given the long-term perspective of a research program such as TasP.

Taking into account all these considerations, a short list of three different first line ART regimens has been identified by the TasP protocol team. Their respective advantages and disadvantages are summarized below:

- **Atripla®-like regimens (EFV 600 mg / TDF 300 mg / FTC 300 mg once daily)**
- **Triple nucleoside regimens TDF 300 mg / AZT 600 mg / 3TC 300 mg**
- **Raltegravir 800 mg / TDF 300 mg / 3TC 300 mg**

Short list of selected regimens for TasP: determinants for choice

Atripla®-like regimens

Atripla® is a complete regimen in a single FDC tablet that contains: efavirenz (EFV) 600 mg, emtricitabine (FTC) 200 mg and tenofovir disoproxil fumarate (TDF) 300 mg

and was approved by the US FDA in July 2006. Current treatment guidelines recommend this triple combination for initial therapy because of its excellent potency, tolerability and favourable safety profile. Atripla® provides ART in a single tablet that can be taken once daily.

An EFV-based regimen was proven virologically superior in the ACTG 5142 trial when compared with a lopinavir (ritonavir-boosted) based regimen in naïve patients (78). A randomized clinical trial has also demonstrated the superiority of a FTC/TDF + EFV combination to a ZDV/3TC + EFV combination for achieving and maintaining HIV RNA below 400 copies up until 96 weeks (79).

The current dosage of the Atripla® FDC has been challenged and a large randomized trial funded by the Clinton Foundation is on-going to assess whether a lower dose of 400 mg of EFV could be as potent as a 600 mg-containing pill, as earlier dose ranging studies suggest.

Limitations: biological monitoring with an Atripla®-like combination is minimal, including hepatic tests at treatment start; most treatment-limiting side effects are clinical (neuro-psychological disturbance), usually resolving over a few weeks after treatment initiation. Some points however merit clarification:

- **TDF and renal function**

TDF is likely to require creatinine clearance monitoring before treatment start and every six months. So far, TDF is not indicated in patients with low creatinine clearance – but clinical experience in such patients is not published. The Center for Infectious Diseases Research in Zambia (CIDRZ) has extensive experience in using TDF-based ART regimens, suggesting that creatinine clearance improvement also occur in TDF-exposed patients with baseline impaired renal function (B. Chi, personal communication, 2009).

- **EFV and pregnancy**

Since 2005, EFV is classified in FDA category D (positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk, e.g. if the drug is needed in a life- threatening situation). Evidence comes from three different sources:

- Animal reproductive studies: EFV caused major central nervous system congenital anomalies in non-human primates at drug exposure levels similar to those achieved in humans (Information, Bristol Myers Squibb, August 2004).
- Retrospective report in humans: case reports (less than 10) of severe neural tube defects in new-born have been reported when females were exposed to EFV in the first trimester of pregnancy.
- Prospective studies: the Antiretroviral Pregnancy Registry[3] did not identify so far a signal for EFV in women reported exposed to EFV in the first trimester of pregnancy (international Interim Report for 1 January 1989 – 31 January 2008). Among 407 live births with first-trimester exposure to EFV, 13 cases of defects have been reported, however, only one case of myelomeningocele and one case of anophthalmia including severe oblique facial clefts and amniotic banding were among these cases. Bera *et al* have monitored 195 women who conceived while treated by an EFV-based ART in South Africa and did not identify any increase in the prevalence of birth defects (80).

[3] APR: http://www.apregistry.com/index.htm

The predictive value of animal studies for humans is questionable and most teratogenic drugs in animal are indeed not teratogenic in humans. Also, retrospective reports does not allow for calculation of the relative risk exposure.

The most recent South African ART treatment guidelines recommend Efavirenz for women of child-bearing age and is also recommended for pregnant women irrespective of the trimester.

- **Low genetic barrier to resistance mutations**

EFV is from the NNRTI class and its genetic barrier to resistance mutation is low. Lima et al have shown that protease inhibitor-based ART were associated with a lower emergence of resistance when compared to standard NNRTI-based regimens (81). It is therefore essential that drug supply is not interrupted and adherence ensured.

- **Availability**

Generic forms of fixed dose combinations of TDF/FTC/EFZ are now readily available in the public sector in South Africa. This regimen is thus the preferred regimen for a universal first-line ART in TasP trial. Two other options are mentioned below for patients not tolerating the first line or for discussion.

Triple nucleoside regimens

Triple nucleoside regimens are no longer recommended in first-line regimens in US DHHS guidelines for their lower virological efficacy; the need for HLAB57*01 test in certain populations (although possibly less a problem in sub Saharan Africa where HLAB57*01 is less than 2%) adds to the complexity of using these types of regimens.

Triple nucleoside regimens such as AZT+3TC+ABC will be difficult to advocate: potency is an issue, adverse events may also be problematic at large scale, and the need for HLAB5701* for abacavir adds further complications for a large universal use. Recent findings that abacavir may promote cardiovascular diseases in high-risk patients may suggest that abacavir be unsuitable for a large population-wide access.

TDF+AZT+3TC however could be an option; this combination was tested in Africa in a very large randomized trial including more than 3000 patients (82). No safety signal was detected. Virological efficacy is unpublished yet.

Raltegravir 800 mg/TDF 300 mg/3TC 300 mg

A raltegravir-based ART could be an interesting option, short-term tolerance excellent and virological safety proven. It has the advantage, as compared of keeping protease inhibitors for second-line regimens. Low genetic barrier might be a problem and studies have shown a reduced efficacy in a maintenance regimen (83). A high variability in inter-patient and intra-patient drug plasma levels may complicate the once daily dosing but needs further evaluation or use in FDCs. However, raltegravir is not licensed by MCC in South Africa and we thus cannot use it. Once daily dosing of raltegravir would not be possible as the trial evaluating once daily dosing was halted early due to lower rate of viral suppression in the once daily arm.

15.3 Appendix 3. Support letter from Department of Health

health

Department:
Health
PROVINCE OF KWAZULU-NATAL

OFFICE OF THE HEAD OF DEPARTMENT
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Tel.:033 395 2589, Fax: 033 345 0792
Email:Beatrice.kayonga@kznhealth.gov.za
www.kznhealth.gov.za

Reference: TasP
Enquiries: DR SM ZUNGU
Telephone: (033) 395 3176

Professor Marie-Louise Newell
Director
Africa Centre for Health & Population Studies

Dear Professor Newell

Re: Treatment as Prevention Project (TasP)

Thank you for keeping the Department informed of the development of this new project that will be carried out by the team of Africa Centre researchers and French colleagues. This is a very exciting initiative and I am writing to confirm the Department's support for this trial.

As discussed during the TasP workshop in December 2010 at the Africa Centre, the Department of Health agrees that through its partnership arrangements with the Africa Centre in the Hlabisa HIV treatment and care programme, the study investigators will assume responsibility for provision of HIV treatment and care in all of the pilot study sites for persons newly identified as being HIV-infected. This will include providing home-based VCT, HIV treatment initiation and clinical follow-up, social and adherence support for patients for the duration of the study. The Department of Health/Africa Centre partnership programme will continue to provide care to those already accessing services through the Hlabisa treatment and care programme's services at local primary healthcare clinics.

We understand the study investigators will take responsibility for the sourcing and providing of suitable HIV drugs that comply with the South African guidelines for delivery to study participants at no cost to the Department for the duration of the study. We understand that it has been possible to source Atripla as the preferred option, for people in both the intervention (treatment for all HIV infected people) and control (people eligible for treatment) clusters. Atripla is registered for use for HIV treatment in South Africa. We also understand that the investigators will obtain appropriate approvals before initiating their research, that an application has been made to the BREC at UKZN and that the full protocol will be submitted to the KZN Department once UKZN ethics has been obtained. The Department undertakes to ensure the ongoing provision of HIV treatment for all study participants as appropriate once the study has been completed, irrespective of any variation from the treatment guidelines at the time.

We understand that as a first phase the trial will occur in only 4 clusters, which will provide the opportunity to learn about the acceptability of the testing approach and the uptake of treatment in people who would not yet be eligible for treatment as per current SA guidelines. This will involve a maximum of 1000 HIV infected people, half of whom will be in the control clusters and approx. 250 will be eligible for treatment; in the intervention clusters an estimated total of 500 will be offered treatment, of whom half would not otherwise be eligible.

Re: Treatment as Prevention Project (TasP)

The Department is happy to support this important initiative and the continued development of its partnership with the researchers and staff of the Africa Centre and the Hlabisa HIV treatment and care programme.

Yours Sincerely

DR SM ZUNGU
HEAD OF DEPARTMENT
DEPARTMENT OF HEALTH: KWAZULU-NATAL
DATE: 19.07.2011

15.4 Appendix 4. Information and consent forms

COMMUNITY INFORMATION SHEET

English Version

TITLE OF THE RESEARCH STUDY:

Ukuphila kwami, ukuphila kwethu - Antiretroviral Treatment as Prevention (TasP) – A cluster-randomized trial in Hlabisa sub-district, KwaZulu-Natal
ANRS 12249
Protocol V2.0 – 09/01/2014

Sponsor: ANRS - National AIDS Research Agency, Paris, France
Coordinating Centre: Africa Centre for Health and Population Studies, University of KwaZulu-Natal
Somkhele, South Africa

This research study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (2 February 2012 and 6 July 2012) and the South African Medicines Control Council of the Department of Health (28 June 2012).

INTRODUCTION:

This leaflet explains an important research study that is being conducted by the Africa Centre in your area. It gives you information about the study, why it is important, what it involves, how you and the local community may benefit and how you can participate and support the study.

Please note that:

- Participation in this research is entirely voluntary;
- People can decide for themselves whether or not to take part, and can decide to withdraw from the study at any time.
- There are no consequences for participants or members of their family or household if they decide not to participate or to withdraw

WHAT ARE WE TRYING TO LEARN IN THIS NEW STUDY?

We want to learn whether it is possible to reduce the number of people who become infected with HIV by increasing the number of people on ARV treatment, by offering people who know that they are HIV-positive ARV treatment as soon as they learn their HIV-positive status, rather than waiting until their CD4 count is reduced or they become sick.

WHAT DO WE KNOW ALREADY? AND HOW WILL THIS NEW APPROACH WORK?

ARV treatment works by allowing our body's own ability to fight HIV to remain strong so it is able to reduce the level of HIV in the body. To be effective and to ensure the best possible results, ARV treatment needs to be taken life-long, that means for the rest of one's life. After taking ARVs regularly for some time people become stronger, and the level of HIV in their bodies becomes very low. HIV doesn't disappear completely – people aren't cured – but as long as they continue to take ARVs regularly then the level of HIV should remain low. When the HIV level is very low, we think that a person is much less likely to pass on HIV to a partner. A recent study of couples where one partner was infected with HIV and the other was not, showed that when the level of HIV in the blood of the infected partner was undetectable (i.e. very low) there was little chance of their HIV-negative partner becoming infected.

Our question then is:
If this is what happens in a couple, what would happen if all the people in the community who have HIV learned their status and all those who are HIV-positive started treatment immediately while they are still well and living life normally? Would this mean that we could reduce the level of HIV in the blood in enough people in the community to reduce the number of new infections that happen?

This is the key question that the *Ukuphila kwami, ukuphila kwethu s*tudy aims to answer.

WHAT ARE WE PROPOSING TO DO?

To answer this question, the *Ukuphila kwami, ukuphila kwethu* research study will be what is called a **cluster-randomised trial.** In this kind of research study, we divide the community into two groups. We make sure things are exactly the same in both groups of communities, but do one specific thing differently in one group of communities to see what happens. Then we compare things between the two groups of communities over time. If things become better, or if they become worse, in one of the two groups, then we can be sure it is because of what we have done, **our intervention**.

To start, we will create two different groups of communities that are similar to each other in important ways. We will make sure that in each group of communities people receive exactly the same treatment and care package as they do in the Department of Health clinics, however the *Ukuphila kwami, ukuphila kwethu* team will take responsibility for doing this and we will deliver care at special clinics set up especially for this study. One group of communities will be selected randomly, by chance, to be the places where we offer ARV treatment earlier, as soon as someone knows that he/she is HIV infected. In the other group of communities, we will be providing ARV treatment at a CD4 level (i.e. 350), when people are still healthy and have few symptoms of HIV infection. These criteria are the same as those of the Department of Health Clinics.

However, before we can offer treatment to any more people, we will need to invite everyone that is willing to come forward and take the important step of learning their HIV status through a process of HIV counseling and testing (HCT) that will be provided by trained counsellors working for *Ukuphila kwami, ukuphila kwethu*. Teams of professional HIV counsellors will be visiting people in their homes. We will seek the permission from the head of the household to offer everyone in the household home-based HIV testing, in the same way that the Department of Health HIV teams do now. The team will give everyone that decides to participate an anonymous card so they can use the *Ukuphila kwami, ukuphila kwethu* research study clinics, or any Department of Health or mobile HIV testing clinics, if they do not wish to HIV test at home. All the HIV testing will be confidential and no one else will be able to learn someone else's HIV status. We will invite all those who find out they are positive, and any people who already know they are HIV positive to come to the *Ukuphila kwami, ukuphila kwethu* research study clinics or to continue to attend the local Department of Health clinics.

It is very important that people test for HIV regularly and repeatedly. To make sure we offer everyone this opportunity and also to make sure that we don't miss anyone who may get HIV during the course of the *Ukuphila kwami, ukuphila kwethu* research study, we will make sure that people can attend the study clinics or the Department of Health clinics for HIV tests and we will return to every household and seek permission to offer testing to people living there two more times during the next year.

The answers to these important questions will help researchers and the community to fight the HIV epidemic as well as to prevent other health problems. We can only find out the answers to these questions if many people agree to have their blood tested for HIV and then take-up the offer of ARV treatment.

WHO CAN TAKE PART IN THE STUDY?

Anyone can participate in the research who is aged 16 years or older, is able to understand the different parts of the study, how it may affect them, and able to provide consent to participate for themselves. A person can still participate even if they don't want to do an HIV test by answering a short questionnaire with one of the counselors. For now, we are only inviting people in this area to participate. In the future we hope to be able to make these opportunities available to people from across the Hlabisa sub-district. But of course, to get most out of participating, an individual needs to know what his/her HIV status is. Participants will be able to use the *Ukuphila kwami, ukuphila kwethu* research study clinics and have access to the ARV treatments and support that will be freely available there.

ARE THEIR ANY RISKS FOR PEOPLE WHO PARTICIPATE?

The team of *Ukuphila kwami, ukuphila kwethu* counsellors that visit households will explain in detail any potential risks before they ask anyone to agree to participate. But briefly, we describe what we think are the most important ones here. There may be some risks for individuals starting ARV treatment early. Taking ARV treatment is a life-long commitment and for it to work people need to take their ARV medication regularly and on time. Adhering to the recommendations of the clinic staff may be difficult, but it is very important that they continue to take the treatment to remain healthy. Our *Ukuphila kwami, ukuphila kwethu* teams in each of the research study clinics will have special training to help people to stick with their ARV treatment and to be able to support them in lots of different helpful ways.

There may be a small risk that ARV treatment causes other health problems for people who start them early. Because this is also a very important question, we will be monitoring people's health very carefully. This is one reason why we will build special research study clinics for people participating in *Ukuphila kwami, ukuphila kwethu*. Participants will be able to discuss any problems they may have with an experienced specially trained clinic team that includes counselors, nurses and a doctor

WHAT ARE THE BENEFITS TO BEING IN THE STUDY?

Of course as we already know there are many advantages to knowing your HIV status: People who know that they are HIV-negative have greater reason to take precautions to remain negative, while HIV-positive people can do things to help them prevent passing on HIV to their partners or babies. The *Ukuphila kwami, ukuphila kwethu* study team will be able to offer people opportunities to test using different services, whichever suits them best. Giving people different testing options, means that they can make the best decision for themselves taking account of whatever their specific needs are, for example, whether they have a concern about confidentiality or disclosure.

People who know they are HIV-infected can benefit from counselling and support, they can pay greater attention to healthy living, and they can access ARV treatments more easily which will increase their years of health. This is the main benefit for individuals, but we think it is also the biggest benefit for communities.

People who find out they are HIV positive or who are HIV-positive already and are already going to one of the Department of Health clinics, will be able to use the *Ukuphila kwami, ukuphila kwethu* research study clinics if they wish. They will be able to get the best possible care in these clinics. Their CD4 count (soldiers in the body that fight HIV) and HIV viral load (the number of HIV virus in the blood) test results will be explained to them by the nurse, or a counsellor or a doctor. This test is important to monitor the health of a person who is infected and to make sure that the treatment they are taking is working or not. Even though the same is done at the Department of Health clinics, what is different is that in our clinics we will be doing the test regularly. People will be able to monitor their own health more closely, and the *Ukuphila kwami, ukuphila kwethu* clinic teams can respond more quickly if something isn't right. People who choose to continue to attend the Department of Health clinics for their health will be asked for their records to be used by the study team to check if they are on HIV treatment and how they are responding to treatment. This will be part of the consent for the HIV counselling and testing. This is important in order to get the actual number of people receiving HIV care and treatment in the communities.

WHERE CAN YOU GET MORE INFORMATION?

The *Ukuphila kwami, ukuphila kwethu* research team is working closely with the Africa Centre's Community Engagement Office, a number of national and local NGOs, Hlabisa Hospital and with the local Department of Health Clinics to make sure people have all the information they need and answers to their questions. We are also working closely with the Africa Centre's Community Advisory Board (CAB), as well as with the municipal and traditional authorities and a number of local traditional healers, to make sure that people who need more information can get it easily.

If you need more information about the study, we recommend that you contact the Africa Centre Community Engagement Office directly (tel: 035 550 7500). Alternatively, any of the people who are mentioned on the list above will be able to refer you to someone at Africa Centre who can help.

Should you have any concerns that you feel the Africa Centre has not addressed to your satisfaction you can contact the Biomedical Research Ethics Committee of the University of KwaZulu-Natal or the South African Medicines Control Council. This trial is conducted in accordance with international guidelines for Good Clinical Practice in Clinical Trials and with the approval of:

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UKUPHILA KWAMI, UKUPHILA KWETHU'S SUCCESS IS UP TO ALL OF US

Ukuphila kwami, ukuphila kwethu is a very important opportunity for all of us to learn whether we can do something new and more effective to stop the spread of HIV in the community. The researchers at the Africa Centre involved in this study know it is a very big challenge both for themselves and for the community. But if it is to work, the *Ukuphila kwami, ukuphila kwethu* idea needs many people in the community to participate. This involves difficult and different decisions for each one of us. It is a very big challenge. But we also know that the potential benefits for all of us in this community are great. Slowing the spread of HIV is perhaps the greatest single thing we can each do in these times. As members of the *Ukuphila kwami, ukuphila kwethu* research team, we will aim to do our best for the community, and we encourage people from the community to consider carefully whether they feel they can benefit from participating in the *Ukuphila kwami, ukuphila kwethu* research study.

Professor Deenan Pillay, Africa Centre Director

INDIVIDUAL INFORMATION SHEET
(Home-Based Activities and HIV Testing)
English Version

TITLE OF THE RESEARCH STUDY:

Ukuphila kwami, ukuphila kwethu - Antiretroviral Treatment as Prevention (TasP) –
A cluster-randomized trial in Hlabisa sub-district, KwaZulu-Natal
ANRS 12249
Protocol V2.0 – 09/01/2014

Sponsor: ANRS - National AIDS Research Agency, Paris, France
Coordinating Centre: Africa Centre for Health and Population Studies,
University of KwaZulu-Natal
Somkhele, South Africa

This research study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (2 February 2012 and 6 July 2012) and the South African Medicines Control Council of the Department of Health (28 June 2012).

INTRODUCTION:

We would like to invite you to take part in a research study being conducted by Africa Centre. The name of the research study is "***Ukuphila kwami, ukuphila kwethu* - Antiretroviral Treatment as Prevention (TasP) – A cluster-randomized trial in Hlabisa sub-district, KwaZulu-Natal**".

Research studies are a way of answering important questions that could be important for people's health and well-being.

An *Ukuphila kwami, ukuphila kwethu* counselor should already have told you the basics of what the study involves. We would like you to read this Information Sheet or perhaps ask a friend to read it to you. It is important you understand what *Ukuphila kwami, ukuphila kwethu* involves, so you can make your own decision whether or not to take part. This Information Sheet is yours to keep. Please keep it somewhere safe. If in the future you are unsure about something, you can refer back to it. Or perhaps you may need to contact someone from the study for more information. You will find that information with the names and contact details of all the appropriate people are contained here.

Once you have read this Information Sheet, an *Ukuphila kwami, ukuphila kwethu* counsellor will sit with you, by yourself, in a private space and explain what taking part in *Ukuphila kwami, ukuphila kwethu* involves. If you choose to take part, the counsellor will ask you to sign, or make your mark, on two (2) Consent Forms. The first indicates that you are willing to take part in the *Ukuphila kwami, ukuphila kwethu* study. The second indicates that you agree to have an HIV test and is like the one used in the Department of Health clinics. But before we ask you to sign anything, it is important for you to know why the research study *Ukuphila kwami, ukuphila kwethu* is being done.

Please ask if there is anything that is not clear or you don't understand something or if you would like the counsellor to give you more information.

The most important things for you to know are that:

- We have asked permission from the household head to invite you to take part, but only you can decide for yourself whether or not you do. No one else can decide for you.
- You can decide to withdraw from the study at any time.
- If you decide not to take part, or change your mind and wish to withdraw, there will be no consequences for you or any members of your family or household.
- We will not tell anyone, in the household or anyone else, if you decide to take part or not, or if you decide to withdraw from the study in the future.
- If at any time you feel you have not been treated with appropriate respect, there is an independent complaints procedure and the counsellor will explain to you how that works before they ask you to sign the Consent Forms.

WHAT ARE WE TRYING TO LEARN IN *UKUPHILA KWAMI, UKUPHILA KWETHU*?

We know from previous Africa Centre research that HIV is a serious health problem in this area and that many people use the HIV testing services in the community and are taking the important step of learning their HIV status. We know many HIV infected people are taking ARV treatments, if they are eligible, and as a result many are recovering their health and leading nearly normal lives again. In most households in this area, one or more people have already accessed the HIV treatment and care programme provided by the local Department of Health clinics. From other Africa Centre research, we know many HIV-positive mothers who take ARV treatment during pregnancy, around the time of the birth and for months after, are having strong, healthy babies that can grow up HIV-free. But perhaps most importantly, we can all see that the number of people dying with AIDS is declining and this is very important for all of us, for all our families and the community. All together these different studies tell us that providing ARV treatments and helping people with HIV is important to help individuals and communities to remain strong and healthy. Many scientists around the world, including ones at the Africa Centre, think it is now time to take the next important step on the HIV prevention research journey.

This step involves testing whether we can further reduce the impact of HIV on the community by preventing HIV infected people passing on the infection to their partners.

We want to learn whether it is possible to reduce the number of people who become infected with HIV by increasing the number of people on ARV treatment, by offering people who know that they are HIV-positive ARV treatment as soon as they learn their HIV-positive status, rather than waiting until their CD4 count is low or they become sick.

WHAT DO WE KNOW ALREADY? AND HOW WILL THIS NEW APPROACH WORK?

ARV treatment works by helping our body to fight HIV by reducing the level of HIV in the body. To be effective and to ensure the best possible results, ARV treatment needs to be taken life-long, that means for the rest of one's life. After taking ARVs regularly for some time the level of HIV in the bodies becomes very low. HIV cannot be cured- it does not mean that these people will be cured- but if they continue to take treatment all the time, the level of HIV in their bodies will remain low. When the HIV level is very low, we think that it is much less likely that that person will pass on HIV to their HIV uninfected sexual partners. Our intervention may decrease transmission to those who do not have HIV. People who know they are not infected with HIV have a big reason to be careful so they remain uninfected, and those who have HIV can help by not infecting their partners. In a study done elsewhere, among sexual couples who

were in a stable relationship, it was found that within those stable couples treatment of the HIV infected partner reduced the risk of onward transmission to the uninfected partner.

Our question then is:
If this is what happens in a couple, what would happen if all the people in the community who have HIV learned their status and all those who are HIV-positive started treatment immediately while they are still well and living life normally? Would this mean that we could reduce the level of HIV in the blood in enough people in the community to reduce the number of new infections that happen?

This is the key question that the *Ukuphila kwami, ukuphila kwethu s*tudy aims to answer.

WHAT DOES THE *UKUPHILA KWAMI, UKUPHILA KWETHU* STUDY INVOLVE?

To answer this question, in the *Ukuphila kwami, ukuphila kwethu* study we need to undertake what is called a cluster-randomised trial. This is a special kind of research study where we divide the community into two groups. We make sure things are the same in both groups, but do one specific thing differently in one group to see what happens. Then after some time, we compare the two groups to see if there is a difference. If things become better, or if they become worse, in one group compared to the other, we can be sure it is because of what we have done, our intervention. Cluster-randomised trials are often very big research studies and they are the ***very best*** way for us to learn whether our idea to reduce the number of new HIV infections will actually work.

To start, we will make sure the two groups of communities are similar to each other in important ways. We will make sure each group of communities receive exactly the same treatment and care package as is provided in the Department of Health clinics. However, because this is a research study and we need to take extra care to make sure things are the same, so we will offer everyone the opportunity to access treatment and care for HIV and other conditions at special *Ukuphila kwami, ukuphila kwethu* study clinics. These clinics will be closer to people's homes, so that they don't need to travel far, and they will have specially trained clinic staff available so people won't have to wait long.

The *Ukuphila kwami, ukuphila kwethu* clinics are set-up in all the communities where the study is happening. At the *Ukuphila kwami, ukuphila kwethu* clinics, we will offer all people who know they have HIV infection medication to cure or prevent them getting TB (tuberculosis) if they need it. We will also make sure that we can give everyone from both groups of communities access to HIV counselling and testing services, HIV prevention services including condoms and lubricants, and monitoring of health and chronic diseases like BP (hypertension) and diabetes. However, one group of communities will be selected randomly, by chance, to be the place where we offer ARV treatment earlier, to people as soon as they know they are HIV-positive. In the other group of communities, we will be providing ARV treatment at a CD4 level (i.e. 350), when people are still healthy and have few symptoms of HIV infection. These criteria are the same as those of the Department of Health Clinics.

WHAT ARE THE *UKUPHILA KWAMI, UKUPHILA KWETHU* CLINICS?

The *Ukuphila kwami, ukuphila kwethu* clinics are new clinics that are set up in all the communities taking part in this study. The clinic buildings are either small Parkhomes like the ART facilities at the Department of Health clinics or Wendy houses supported by mobile clinics. Like the services at the Department of Health clinics, all services and medications in the

research clinics will be free of charge to patients. Some services will be available to everyone who takes part in the study. Although the *Ukuphila kwami, ukuphila kwethu* clinics will provide many of the same services as are available at the Department of Health clinics, they are not exactly the same. The services available at the *Ukuphila kwami, ukuphila kwethu* clinics include HIV ARV treatment and monitoring for people who are HIV-positive as well as screening for opportunistic infections. The clinics will also offer everyone treatment for, and prevention of, TB, HIV counselling and testing services, HIV prevention services including condoms and lubricant. In addition for HIV-positive people, there will be advice on reproductive health including family planning, screening for sexually transmitted infections (STI), monitoring of chronic disease conditions and support and referral to HIV community care and support services including social grants. If people need medical assistance for other problems, for example, for children's health problems, they will need to either use Department of Health clinics or the mobile services that operate in the area. Only people who live in the *Ukuphila kwami, ukuphila kwethu* communities taking part in the study can use these research study clinics.

WHAT ARE WE ASKING YOU TO DO NOW?

We are asking you to consider whether you would like to take part in the *Ukuphila kwami, ukuphila kwethu* study.

Taking part involves 3 things:

1) Firstly, today and every six months when we return to your homestead, the counsellor will ask you some questions. This takes about 15 minutes. The questions are about you, your general health, your attitudes and beliefs about HIV, your personal relationships and sexual partnerships. These are very important so that we can understand why things may turn out differently in the two groups of communities.
2) Secondly, today and every six months when we return to your homestead, the counsellor will ask your permission to obtain from you a very small blood specimen – 5 dots dried into a piece of paper. To do this requires a tiny prick of one of your fingers. Once the paper with the bloodspots is dry, the counselor will place it in an envelope. All the papers we collect will be stored in a laboratory and we only use it for other research studies relating to HIV.. Blood samples are very valuable and can help to answer lots of different questions, for example about new kinds of HIV tests or how the virus changes over time. All the samples will be tested for HIV antibodies, but of course we guarantee that confidentiality is kept because these samples are coded and the laboratory does not know your name or where you live.
3) Thirdly, today and every six months when we return to your homestead, the counsellor will ask you to consider taking the important step of learning your HIV status through a process of HIV counselling and testing (HCT). In order to be able to offer treatment to people, we first need to know who we should be offering it to. We can only do that by testing people and knowing for sure if someone is HIV-positive. You will be counselled separately about this, and asked to sign a separate Consent Form like the ones used in the Department of Health clinics indicating your agreement to have an HIV Test.

CONFIDENTIALITY AND PROTECTING YOUR PRIVACY

In all of the study activities we guarantee to keep all the information you provide private and confidential. We do this by making sure all our computer systems and databases are password-

protected. When we release any information concerning you to the researchers who work within *Ukuphila kwami, ukuphila kwethu* study, information that could identify you such as names and locations are removed, only code numbers are used instead. This applies to both the HIV test results as well as any other information that concerns you.

WHAT DO THE QUESTIONS THE COUNSELLOR WILL ASK INVOLVE?

The counsellor will ask you to give answers to a questionnaire. The questions are about your general health, your living arrangements, previous experience of HIV testing, personal relationships and sexual partnerships. The counselor will enter your answers on a questionnaire card. You may find some of the questions personal. But we ask that you please understand we would not ask these questions, if we did not know already that people's answers are often different from one another and that is what helps us to explain and understand important things about people's health and HIV. Be assured that the answers you give are confidential between you and the counsellor. The counsellors all have special training in maintaining confidentiality and will respect the trust that you are putting in them. There is nothing from your answers to the questions that could possibly identify you and no one can know your identity from looking at the form that we use for data capture. We hope knowing this extra information you will find it easier to answer these questions. When they are finished, the counsellors bring the questionnaire answers back to the Africa Centre and they will be entered into a database. This database has no names so nobody will be able to link your data and your name. The names of all participants are kept somewhere else secure and separate and can only be linked to people's answers through a code.

People who decide that they do not wish to test for HIV can still decide just to answer the counsellor's questions. This is very helpful to us. It also means that even if someone, for whatever reason, does not want to have an HIV test, they can still participate and help us to find important answers.

WHAT DOES GIVING A BLOOD SPECIMEN FOR STORAGE INVOLVE?

The process of giving blood for dry-blood spots is very easy and only slightly painful. The counsellor will prepare one finger to make sure it is properly clean. They will rub the finger a little and then prick it so it bleeds just a little bit. The counsellor will hold a piece of paper near your finger and direct 5 drops onto printed circles. The process takes less than 5 minutes. The paper will be sent to the Africa Centre and then to the laboratory in Durban. There will only be a code on the paper, so no one will be able to know who it comes from. Once at the lab, one spot will be tested for HIV, although whatever the result is the lab will not know who it has come from and they won't be able to tell you or anyone else the result. The result of this test and the unique code on it will go into the Africa Centre's database, without any names. The papers with the left over blood-spots we will keep separately and safely in a freezer. They are important to help us to develop new tests related to HIV in the future. If we want to do any tests on these samples in the future we will make sure we have the permission of the University of KwaZulu-Natal Biomedical Ethics Committee.

WHAT DOES HAVING AN HIV TEST INVOLVE?

The process of HIV testing will involve you and the *Ukuphila kwami, ukuphila kwethu* counsellor only, discussing in a private space and alone. The counsellor will do the pretest counseling, testing as well as post-test counselling with you. They will explain how the rapid HIV test works. The counsellor will ask you to sign or make your mark on a second consent

form before they begin. This form looks like the ones that are used in the Department of Health clinics and the home-based Department of Health testing programme. You can receive your result of your HIV test within about 15-20 minutes. The result of this test will be kept absolutely confidential. Apart from you, only the counsellor can link the result to you. In case you do not feel comfortable with the counsellor, if for example s/he is someone you know, you can request a different counsellor to come. The entire HIV counselling and testing process will take about 40 minutes and only you and the counsellor are present.

WHAT HAPPENS AFTER THAT?

After this visit, the *Ukuphila kwami, ukuphila kwethu* counsellors will visit this household every six months for the duration of the study so that everyone has an opportunity to test for HIV and those who have tested already can check their status again if they want to. We also want to make sure that anyone whose test result is HIV-positive can get treatment. We want to be able to invite everyone in the household to take part, including people who may have joined since the last visit.

When the *Ukuphila kwami, ukuphila kwethu* counsellors return they will seek permission again to offer testing to people. The counsellors will invite all household members and any new household members to test for HIV. The counsellors who return will not know who in the household has tested in previous rounds or what the result was. This is to protect people's confidentiality.

Anyone who already knows they are HIV-positive will be invited to participate at these follow-up visits the same way as all the household members. It will be their choice whether they decide to test again or not and whether they choose to disclose to members of the *Ukuphila kwami, ukuphila kwethu* study team that they already know that they are HIV-positive . This way there is no chance that someone's HIV status will be accidentally disclosed to anyone in the household if that person does not wish to do so.

WHAT IF I DON'T WANT TO TEST HERE AT HOME? OR I DON'T WANT TO TEST NOW?

The *Ukuphila kwami, ukuphila kwethu* counselors will be able to do an HIV test for everyone who decides they want to participate. But it is not required. Anyone who says they would like to participate in the research study will be given a card without any information about them on it, just a code. People who decide that they do not want to test at home can take this card to one of the *Ukuphila kwami, ukuphila kwethu* study clinics, or any Department of Health or mobile HIV testing clinic. The staff will only know that you come from one of the communities involved in the *Ukuphila kwami, ukuphila kwethu* study and will make sure you get good service and appropriate referral depending on your HIV test result. The services offered by the Department of Health for HIV testing are professional and confidential and no one else will be able to learn someone else's HIV status.

WHAT HAPPENS ONCE I LEARN MY HIV STATUS?

Anyone who finds out they are HIV-positive, or any people who already know they are HIV-positive will be invited to come to the *Ukuphila kwami, ukuphila kwethu* study clinics for their treatment and care, or if they prefer, they can attend the local Department of Health clinics. At the *Ukuphila kwami, ukuphila kwethu* clinics they will meet the members of local clinic team. The team will introduce themselves and register the person as a new patient. After that the clinic team will explain what happens and will ensure a person receives appropriate care. Any other

member of the communities taking part in *Ukuphila kwami, ukuphila kwethu* may also use the study clinics for HIV counseling and testing services, HIV prevention services, including condoms and lubricant. People who choose to continue to attend the Department of health clinics for their health will be asked for their records to be used by the study team to check if they are on HIV treatment and how they are responding to treatment. This will be part of the consent for the HIV counselling and testing. This is important in order to get the actual number of people receiving HIV care and treatment in the communities.

WHO CAN TAKE PART IN *UKUPHILA KWAMI, UKUPHILA KWETHU*?

Because the *Ukuphila kwami, ukuphila kwethu* team have come to your household that means the people in the household are eligible to participate. Anyone can participate who is 16 years or older, is able to understand the different parts of the study, how it may affect them, and able to provide consent to participate for themselves. A person can still participate even if they do not want to take a test for HIV by answering the questions and providing the anonymous dried bloodspots each time the *Ukuphila kwami, ukuphila kwethu* team returns to their household. In total we expect that 22000 people in the different communities will participate in this research study over the next 24 months. .

WHO WILL HAVE ACCESS TO MY INFORMATION?

No one except the senior members of the *Ukuphila kwami, ukuphila kwethu* study team will have access to the study data. All data will be anonymised (i.e. will not have names attached to it) and be kept on safe and secure password protected computers. From time to time it may be necessary to allow the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, monitors from the sponsors, ANRS, or from regulatory authorities in South Africa to have access to our anonymised study data to verify that we are handling the data correctly.

ARE THERE ANY RISKS FOR ME IF I PARTICIPATE?

The team of counsellors that visit each household and the clinic will explain in detail any potential risks to each person before they are asked to agree to participate.

There are, unfortunately, potential risks in having a blood test for HIV and knowing your HIV status: People who learn that they are HIV-positive may suffer from mental stress and depression as a result. If they tell other people their HIV status, they may also be stigmatized by their family and community and may be discriminated against – although this is illegal in South Africa. Occasionally, there are some HIV-infected people who are rejected by their partners, friends or family. This is the reason that we have made trained professional counsellors responsible to undertaking this part of the research study. There are teams of counselors at each of the *Ukuphila kwami, ukuphila kwethu* clinics, at the Africa Centre and at each of the Department of Health clinics who can provide confidential practical and emotional support. The counsellors can also give people helpful information and discuss with people who do test HIV-positive how to manage whom they disclose to and when it is appropriate to do so.

There may also be some risk for individuals starting ARV treatment early. Taking ARV treatment is a life-long commitment, and for these drugs to work properly people need to take their ARV medication regularly and on time, as recommended by the clinic staff. This practice of adhering may be difficult, but it is very important to continue to take the treatment to remain healthy and not become ill due to HIV or another condition like TB (tuberculosis). Our teams in

each of the study clinics will have special training to help people to stick with their ARV treatment and to support them in lots of different helpful ways.

There may be a small risk that ARV treatments cause other health problems for people who start them early. We know that taken as recommended ARV treatment works very well for people whose bodies are already battling HIV and who have low CD4 counts. But we are not completely sure about what happens when people take treatment when they have an almost normal CD4 level. Because this is such an important question we will be monitoring people's health very carefully. This is one reason why we have built special research study clinics for people participating in the *Ukuphila kwami, ukuphila kwethu* study. Participants will be able to have their health monitored frequently and be able to discuss any problems they may have with an experienced specially trained clinic team that includes counselors, nurses and a doctor.

WHAT ARE THE BENEFITS TO ME OF BEING IN THE STUDY?

Of course, as we already know, there are many advantages to knowing your HIV status: People who know that they are HIV-negative have greater reason to take precautions and remain negative. The study team will be able to offer people opportunities to HIV-test using different places, whichever one is best for them. Giving people different testing options, means that they can make the best decision for themselves taking account of whatever their specific needs are, for example, whether they have a concern about confidentiality or disclosure.

People who know they are HIV-positive can benefit from counseling and support, pay greater attention to healthy living, and access ARV treatments more easily, all of which will increase their years of health. This is the main benefit for individuals, but we think it is also the biggest benefit for communities.

People who find out they are HIV-positive, or who are HIV-positive already and go to one of the Department of Health clinics, will be able to come to the study clinics if they wish. They will be able to get the best possible care in these clinics. They will have their results explained to them by either, a nurse, counsellor or doctor. The tests are important to monitor an HIV infected person's health and to make sure that the ARV treatment they are taking is working properly. Although the same tests can be done in the Department of Health clinics, some will be done more frequently at the research study clinics, so people are able to monitor their own health more closely, and the *Ukuphila kwami, ukuphila kwethu* clinic team can respond more quickly if something isn't right.

We will be able to assist people to screen for TB at the *Ukuphila kwami, ukuphila kwethu* study clinics, although this will require some liaison with the Department of Health clinics in the area. When we know for certain whether or not someone has TB, we will be able to give them medication either to cure the TB or to prevent them getting it in the future. If we find some people who attend the *Ukuphila kwami, ukuphila kwethu* study clinics are having difficulty taking the ARV treatment regularly we will be able to provide support and practical ideas to help them. We will be able to do this on a one-on-one basis which isn't always possible at the Department of Health clinics. In the case where someone's ARV treatments are not working properly, we will be able to offer them a different sort of medication that will hopefully work better.

At the *Ukuphila kwami, ukuphila kwethu* study clinics we will also be able to give advice to women, who want to become pregnant to ensure that they prevent their baby getting HIV.

Anybody who wishes can see an HIV counsellor and will be able to have this service at the *Ukuphila kwami, ukuphila kwethu* study clinics, or at their home. Through ongoing counselling we hope to contribute to the reduction of stigmatization in the community. The counsellors will be there to support anyone who needs confidential advice about HIV or having a healthy lifestyle. The *Ukuphila kwami, ukuphila kwethu* counsellors are also trained to assist participants experiencing mental stress and depression for as long as support is required.

Participants will not receive any reimbursement or compensation for their participation as we believe that there are no additional costs for people who choose to participate.

WHERE CAN I GO TO GET MORE INFORMATION ABOUT *UKUPHILA KWAMI, UKUPHILA KWETHU* IN MY COMMUNITY?

The *Ukuphila kwami, ukuphila kwethu* study team is working closely with the Africa Centre's Community Engagement Team, some national and local NGOs, Hlabisa Hospital and with the local Department of Health clinics to make sure people have all the information they need and that their questions are always answered.

The *Ukuphila kwami, ukuphila kwethu* study team is also working closely with the Africa Centre's Community Advisory Board, as well as with the municipal and traditional authorities and a number of local traditional healers, to make sure that people who need more information can get it easily.

If you need more information about the study, contact:
Africa Centre Community Engagement Office Contact number: 035 550 7500).
If you wish to speak to the *Ukuphila kwami, ukuphila kwethu* study managers contact:
Dr Collins Iwuji, Trial Coordinator Contact number: 035 550 7683
Ms Nonhlanhla Okesola, Clinic Coordinator : Contact number :072 542 6522

Or alternatively, any of the people who are mentioned on the list above will be able to refer you to someone at Africa Centre who can help.

Should you have any concerns that you feel the Africa Centre has not addressed to your satisfaction you can contact the Biomedical Research Ethics Committee of the University of KwaZulu-Natal or the South African Medicines Control Council. This trial is conducted in accordance with international guidelines for Good Clinical Practice in Clinical Trials and with the approval of:

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Department of Health,
Private Bag X828,
PRETORIA 0001

SOUTH AFRICA
Fax: 27 (12) 395 8775
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WHAT IS THE INDEPENDENT COMPLAINTS PROCEDURE?

If at any time you or a member of your household feels they have not been treated respectfully or appropriately, you are free to make a complaint to those responsible for the *Ukuphila kwami, ukuphila kwethu study*. If you feel that you have suffered harm as a result of taking part in the study then you should first discuss this with the staff at the *Ukuphila kwami, ukuphila kwethu* clinic.

If you would like to speak to someone outside the research team at the Africa Centre you should contact: Community Liaison Office Manager on 035 550 7500.

The Africa Centre also has a Community Advisory Board (CAB) made up of community members. You can get a list of CAB members from the *Ukuphila kwami, ukuphila kwethu* clinic and can contact them if you have any concerns about the study or want to make any comments.

The research study staff are indemnified under insurance held by the University of KwaZulu-Natal or their host institution. The study is also insured in the event of a serious injury or adverse clinical event involving a trial participant by the trial sponsor (ANRS). Any complaint that may result in an insurance claim against the investigators, Africa Centre or the University should be addressed in the first instance to University of KwaZulu-Natal Biomedical Research Ethics Committee. If you feel that you have suffered harm because of the study or would like to know more about your rights as a research participant, you can also contact the University of KwaZulu-Natal Biomedical Research Ethics Committee at (031) 260 4495.

UKUPHILA KWAMI, UKUPHILA KWETHU'S SUCCESS IS UP TO ALL OF US

Ukuphila kwami, ukuphila kwethu is a very important opportunity for all of us to learn whether we can do more to stop the spread of HIV in the community. The researchers at the Africa Centre involved in this research study know it is a very big challenge both for themselves and for the community. But to work the *Ukuphila kwami, ukuphila kwethu* idea needs many people in the community to participate. This involves difficult and different decisions for each person. It is a very big challenge. But we also know that the potential benefits for all of us in this community are great. Slowing the spread of HIV is perhaps the greatest single thing we can each do in these times. As members of the *Ukuphila kwami, ukuphila kwethu* research team we will aim to do our best for the community, and we encourage people from the community to consider carefully whether they feel they can benefit from participating in this research study.

Professor Deenan Pillay Africa Centre Director

INTRODUCTION:

This leaflet explains an important research study that is being conducted in your area by the Africa Centre. It gives you information about the study, why it is important, what it involves, how you and the local community may benefit and how you can participate and support the study.
Please note that:

- Participation in this research is entirely voluntary;
- People can decide whether or not to take part and can decide to withdraw from the study at any time.
- There are no consequences for participants or members of their family or household if someone decides not to participate or to withdraw from the study.

WHO CAN TAKE PART IN THE STUDY?

Anyone can participate who is aged 16 years or older, is able to understand the different parts of the study, how it may affect them, and is able to provide consent to participate. A person can still participate even if they don't want to do an HIV test by answering a short questionnaire with one of the counselors. To get most out of participating, an individual needs to know his/her HIV status.

WHAT ARE WE TRYING TO LEARN?

We want to learn whether it is possible to reduce the number of people who become infected with HIV by increasing the number of people on ARV treatment in this area, by offering people who know that they are HIV-positive ARV treatment as soon as they learn their HIV-positive status, rather than waiting until their CD4 count is reduced or they become sick.

WHAT ARE WE PROPOSING TO DO?

To answer this question, the *Ukuphila kwami, ukuphila kwethu* research study will be what is called a **cluster-randomised trial.** We will divide the community into two groups. We will make sure things are exactly the same in both groups of communities, but do one specific thing differently in one group of communities to see what happens. Then we compare things between the two groups of communities over time. In our study clinics people will be given the opportunity to start ARV treatment earlier in the course of their infection. The study clinics will be located in your community and for most people they will be much closer than the DoH Clinics. However, before we can offer treatment to any more people, we will need to invite everyone that is willing, to come forward and take the important step of learning their HIV status through a process of HIV counselling and testing (HCT) that will be provided by trained counsellors of *Ukuphila kwami, ukuphila kwethu* in people's homes. All the HIV testing will be confidential and no one else will be able to learn someone else's HIV status.

It is very important that people test for HIV regularly and repeatedly to make sure that they get appropriate care as soon as they need it. To make sure we offer everyone this opportunity and also to make sure that we don't miss anyone who may get HIV during the course of the *Ukuphila kwami, ukuphila kwethu* research study we will return to people's homes and offer testing to them every six months.

WHAT DO WE KNOW ALREADY?

ARV treatment works by allowing our body's own ability to fight HIV to remain strong so it is able to reduce the level of HIV in the body. To be effective and to ensure the best possible results, ARV treatment needs to be taken life-long, that means for the rest of one's life. A recent study of couples where one partner was infected with HIV and the other was not, results showed that when the level of HIV in the blood of the infected partner was undetectable (i.e. very low) there was little chance of their HIV-negative partner becoming infected.

Our question then is:

If this is what happens in a couple, what would happen if all the people in the community who have HIV learned their status and all those who are HIV-positive started treatment immediately while they are still well and living life normally? Would this mean that we could reduce the level of HIV in the blood in enough people in the community to reduce the number of new infections that happen?

This is the key question that the *s*tudy aims to answer.

WHAT ARE THE BENEFITS?

The main benefit of this study is that we will be able to offer people better HIV care and closer to their homes. The intervention will reduce the likelihood of people who are HIV-negative to acquire the virus. People who know that they are HIV-negative have greater reason to take precautions to remain negative, while HIV-positive people can do things to help them prevent passing on HIV to their partners. The *Ukuphila kwami, ukuphila kwethu* study team will be able to offer people regular testing opportunities in their homes or refer them to the local clinic. Giving people different testing options means that they can make the best decision for themselves.

RISKS FOR PEOPLE WHO PARTICIPATE

There may be some risks for individuals starting ARV treatment early. Taking ARV treatment is a life-long commitment and for it to work people need to take their ARV medication regularly and on time. Adhering to the recommendations of the clinic staff may be difficult, but continuing to take the medication is important to remain healthy. There may be a small risk that ARV treatment causes other health problems for people who start them early. Some information from other research indicates there may be some risks linked to side effects people can experience. But our *Ukuphila kwami, ukuphila kwethu* teams in each study clinics will have special training to help people to stick with their ARV treatment and would be able to discuss these with people before they start treatment.

WHERE CAN YOU GET MORE INFORMATION?

You can contact the Africa Centre Community Engagement Office directly (tel: 035 550 7500) OR the BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Private Bag X 54001, Durban, 4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609 Email: BREC@ukzn.ac.za or the South African Medicines Control Council Tel; 012 395 8126 – Fax:012 395 8775

UKUPHILA KWAMI, UKUPHILA WETHU'S SUCCESS IS UP TO ALL OF US

Ukuphila kwami, ukuphila kwethu is an important opportunity for all of us to learn what we can do that's more effective to stop the spread of HIV. Researchers at the Africa Centre know it is a very big challenge both for themselves and for the community. But if we really want to know the answer many people in the community have to participate. Slowing the spread of HIV is perhaps the greatest single thing that each of us can do. We strongly encourage people to consider carefully what difference they will be making to the HIV epidemic in their community and whether they feel they can benefit from participating in the *Ukuphila kwami, ukuphila kwethu*.

Professor Deenan Pillay, Africa Centre Director

COMMUNITY EXPLANATION/INFORMATION SHEET
English Version

TITLE OF THE RESEARCH STUDY:

Ukuphila kwami, ukuphila kwethu - Antiretroviral Treatment as Prevention (TasP) – A cluster-randomized trial in Hlabisa sub-district, KwaZulu-Natal
ANRS 12249
Protocol V2.0 – 09/01/2014

Sponsor: ANRS - National AIDS Research Agency, Paris, France
Coordinating Centre: Africa Centre for Health and Population Studies, University of KwaZulu-Natal Somkhele, South Africa

Ethical approval: Biomedical Research Ethics Committee of the University of KwaZulu-Natal
02/02/2012 & 06/07/2012
South African Medicines Control Council Approval 28/06/2012

PARTICIPANT INFORMATION SHEET (CONTROL CLUSTERS)

English Version

TITLE OF THE RESEARCH STUDY:

Ukuphila kwami, ukuphila kwethu - Antiretroviral Treatment as Prevention (TasP) – A cluster-randomized trial in Hlabisa sub-district, KwaZulu-Natal
ANRS 12249
Protocol V2.0 - 09/01/2014

Sponsor: ANRS - National AIDS Research Agency, Paris, France
Coordinating Centre: Africa Centre for Health and Population Studies, University of KwaZulu-Natal
Somkhele, South Africa

This research study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (2 February 2012 and 6 July 2012) and the South African Medicines Control Council of the Department of Health (28 June 2012).

INTRODUCTION:

Thank you for taking the important step of coming to our research study clinic.

Today we would like to invite you to take part in the clinic-based part of the research study "***Ukuphila kwami, ukuphila kwethu* - Antiretroviral Treatment as Prevention (TasP) – A cluster-randomized trial in Hlabisa sub-district, KwaZulu-Natal**" that is being conducted by the Africa Centre.

We would like you to read this Information Sheet, or perhaps ask a friend to read it to you. It explains important information about the study that will be discussed with you. Once you understand the study, and you agree to take part, you will be asked to sign a Consent Form, or make a mark on the form in front of a witness.

This Information Sheet is yours to keep. Please try to keep it safe because it contains useful information that you may want to refer back to. If you need to contact someone from the study team, you will find the names and contact details of all the appropriate people at the end of this information sheet.

WHAT ARE WE TRYING TO LEARN IN *UKUPHILA KWAMI, UKUPHILA KWETHU*?

We want to learn whether it is possible to reduce the number of people who become infected with HIV, by increasing the number of people on ARV treatment. To do this we need to offer people who know that they are HIV-positive ARV treatment as soon as possible after they learn their HIV-positive status, rather than waiting until their CD4 count is low or they become sick.

We know that ARV treatment works by reducing the level of HIV in the body. To be effective and to ensure the best possible results, ARV treatment needs to be taken life-long, that means for the rest of one's life. After taking ARVs regularly for some time the level of HIV in people's bodies becomes very low. HIV doesn't disappear completely – people aren't cured – but as long as they continue to take ARVs regularly then the level of HIV should remain low. When the HIV level is very low we believe that a person is much less likely to pass on HIV to a partner. A

recent study of stable couples where one partner was infected with HIV and the other was not showed that when the level of HIV in the blood of the infected partner was undetectable (i.e. very low) there was very little chance of their HIV-negative partner becoming infected.

Following the results of this study, it is now very important to find out what would happen*, if all the people in the community who have HIV learned their status and all those who are HIV-positive start treatment immediately while they are still well and living life normally? Would this mean that we could reduce the level of HIV in the blood in enough people in the community to reduce the number of new infections that happen each day?*

WHO WILL TAKE PART?

Any adult aged 16 years or older, who comes from one of the study communities, who has tested for HIV, received their test result, knows that they are HIV-infected and comes to one of our *Ukuphila kwami, ukuphila kwethu* study clinics will be invited to participate.

WHAT DOES IT MEAN TO BE INVOLVED IN THIS STUDY?

If you agree to participate in the study you will receive your care at this study clinic. Your care will be the same as you would receive at any of the Department of Health clinics, but the number of times we do your blood tests will be slightly different:

Blood samples will be collected from you during some of the clinic visits (every 6 months if you do not start taking ARVs right away or 3 monthly for 6 months and then 6-monthly thereafter if you start taking ARVs. This is more often than in the Department of Health clinics, but is necessary so that we can monitor how your body is coping with the HIV infection. Some of the blood samples will go the laboratory at Hlabisa Hospital as would normally happen but at some visits an additional sample will be sent to the Africa Centre laboratory in Durban. An amount of blood from this sample will be stored at the Africa Centre laboratory in a freezer. It might be that during the study or once the study has finished we think of other tests that need to be done on these samples to help us understand certain findings from the study. If we want to do any tests on these stored samples we will ensure that we have permission from the University of KwaZulu-Natal Biomedical Ethics Committee.

MORE ABOUT THE STUDY DRUG – *ATRIPLA*

If you agree to participate in this study, we will check your CD4 count and if it is 350 or below or you have tuberculosis or are pregnant, we will offer you the opportunity to begin preparing to start taking ARV treatment immediately. If your CD4 level is higher than 350 we will offer you the opportunity come to this clinic for regular monitoring until such time as it is appropriate for you to start ARV treatment.

For people that are offered the chance to start ARV treatment immediately, this will involve completing the preparation sessions at the clinic which takes about two (2) weeks but can be done in one day if your CD4 count is very low. When you have completed these you will be given a drug called Atripla which is known as a 'triple combination' as it contains three (3) antiretroviral drugs in one tablet. The drugs are tenofovir, emtricitabine and efavirenz. You only need to take one tablet daily, rather than several tablets twice daily. This drug has been approved by the National Department of Health, and is available in public service clinics as Atroiza or Odimune. They contain exactly the same drugs as Atripla. It has an excellent record of strength, tolerability and safety.

All antiretroviral drugs have some side effects, but people taking *Atripla* generally experience few side effects. Common side effects include feeling dizzy, headaches and experiencing unusual dreams. Several patients complain of a rash, but this usually goes away without any change in treatment. Sometimes patients have diarrhoea and an upset stomach.

There are some more serious side effects that include kidney problems and more severe vomiting and muscle pains. You will be monitored carefully for these side effects when you are on treatment.

All people who come to the clinic, those who are on ARV treatment and those who have CD4 counts greater than 350 will be able to access other services at the clinic such as testing for STIs (sexually transmitted infections) and TB (tuberculosis), for example. The other services available at the clinic will be discussed with you by the nurse.

HOW LONG WILL THIS RESEARCH STUDY TAKE?

We anticipate that the study will be finished in 2016. Your participation in this study is completely voluntary and can start once you sign the Consent Form which the counsellor will explain to you. You may continue to be involved until the end of the study period or you may withdraw at any time. If you decide to withdraw from the study it is important that you still continue to take your ARV treatment. You would be able to access this from the Department of Health clinics in KwaZulu-Natal. After the study is complete, or if you decide to withdraw, you will be referred to the local Department of Health Clinics' treatment and care programme where you will continue to receive HIV care and treatment. All the medications used in the study are licensed and available in South Africa. The aim would be for you to receive the exact same medications you received in the study; otherwise it would be what is currently available in the local department of health clinics at the time of withdrawal or study closure.

WHAT WILL HAPPEN IF I DECIDE TO PARTICIPATE IN THIS PART OF THE STUDY?

Once you have read this Information Sheet, the *Ukuphila kwami, ukuphila kwethu* counsellor will sit with you, by yourself, in a private space and explain what taking part involves for you. If you do choose to take part, the counsellor will ask you to sign, or make your mark, on two (2) Consent Forms. The first indicates that you consent to take part in the *Ukuphila kwami, ukuphila kwethu* clinic-based study. The second consent form which is like the ones used in the Department of Health clinics indicates you agree to have your HIV care provided at this *Ukuphila kwami, ukuphila kwethu* study clinic. But before we ask you to sign anything, we will want to make sure you understand what being part of the study involves.

If you are not eligible to start on ARVs you will be asked to come to the study clinic again in about six (6) months for some blood tests and a check-up and to see if it is appropriate for you to start treatment at that point.

If you are eligible to start treatment, that means your CD4 count is 350 or less, or if you are already on ARVs and choose to move your HIV care to the research clinics, you will be asked to return to the clinic each month or every two months depending on your circumstance, and to come back earlier than this if you do not feel well or are worried about anything. At each visit the study nurse or the counsellor will ask you some questions about your health. If you have any symptoms you will be examined, as you would be in the Department of Health Clinics. If this is appropriate you will receive your supply of ARVs for the following month(s). If you need additional investigations or treatment for other illnesses that are not available at the study clinics, the study nurse will refer you appropriately. If you are taking ARVs you will have

samples of your blood taken regularly to check that your body is tolerating the antiretroviral drugs, and that the HIV in your body is falling as it should do. We will do these tests more frequently than is the case in the Department of Health clinics. We will ask your permission to link the information we collect about you during your study visits to information we have collected in your household. This will be done using a study code; as explained above personal details about you (e.g. name and physical address) will not be shared with people outside the clinic and medical facilities.

ARE THERE ANY RISK OF BEING IN THE STUDY?

There are no additional risks to your health of having your HIV treatment and care provided at the *Ukuphila kwami, ukuphila kwethu* study clinics as compared to the Department of Health Clinics.

All people treated with ARVs may develop side effects. In this trial most people will be starting treatment whilst they still feel well. There is a small possibility that you might experience some side effects, including the possibility of HIV virus becoming resistant to some of the ARVs in your medication combination. However we know that the side effects with *Atripla* are minimal, and we have talked about these already. We also know that people who take their ARV medications regularly are much less likely to develop any resistance. You will be monitored very carefully by the study nurses at your clinic visits, using clinical questions and examination and blood tests, to check your body is responding well and you are not developing any problems. If there are any problems these should be identified quickly, and we will manage them appropriately. A study physician, with expertise in HIV medicine, will also be available to help with any problems. During the trial you will be able to visit the study clinic at any time to seek help if you are worried.

IS THERE ANY BENEFIT BY BEING IN THE STUDY?

Starting ART is likely to mean that you will remain healthy and free from illnesses and complications associated with HIV for a lot longer. For example, we think that less people get TB (tuberculosis) if they start ART when their immune systems are still strong. Staying stronger for longer will mean that you are less likely to need admission to hospital for HIV-related illnesses.

There will be several trial clinics, most of which will be within 45 minutes walking distance of people's houses. As a trial participant you are free to use these clinics whenever you wish, even if you do not have a scheduled appointment. There will always be a nurse and/or a counsellor at the study clinic from Monday –Friday 9:00am-3:30pm, whom you will get to know very well during the trial. A few clinics will be open on Saturdays 9:00am-2:00pm depending on needs of participants.
If there is a problem that they cannot help with they will arrange for you to meet with one of the study doctors.

You will have regular blood tests taken like you would in the Department of Health clinics. This means that we can follow what is happening to your immune system and the HIV in your blood more frequently and detect earlier if there is a problem. The study staff will share these results with you and explain what they mean.

WHAT IF I DO NOT WANT TO TAKE PART?

Taking part in this study is entirely voluntary and there are no direct financial costs to you as a participant. If you decide not to take part, or decide to take part and later withdraw from the study and stop taking the ARVs, you will not be penalized in anyway. You will still be able to access normal health care at your Department of Health Primary Health Care Clinic and HIV treatment and care programme. You will continue to receive care in the ART programme and at the clinic.

WHO WILL HAVE ACCESS TO INFORMATION COLLECTED ABOUT ME AT THE CLINIC?

The information that is collected will be kept confidential. Only the *Ukuphila kwami, ukuphila kwethu* study researchers and staff will have access to this information and results. Your name and identity will not be revealed to anyone except to clinic staff. Once we have completed the study we will make the results available to all of the participants via newsletters, community presentations and presentations and education sessions with the Africa Centre Community Advisory Boards and the Africa Centre's Community Engagement Team. The results will also be made known to the Hlabisa hospital management and clinic based staff without revealing the identity of the individuals who participated in the study. They will also be made known to the National Department of Health as well as the Department of Health in KwaZulu-Natal. We will share our results with other scientists around the world in scientific publications and presentations at conferences.

WHERE CAN I GO IF I NEED TO GET GET MORE INFORMATION ABOUT *UKUPHILA KWAMI, UKUPHILA KWETHU* IN MY COMMUNITY?

The *Ukuphila kwami, ukuphila kwethu* study team is working closely with the Africa Centre's Community Engagement Team, some national and local NGOs, Hlabisa Hospital and with the local Department of Health clinics to make sure people have all the information they need and that their questions are always answered.

The *Ukuphila kwami, ukuphila kwethu* study team is also working closely with the Africa Centre's Community Advisory Board, as well as with the municipal and traditional authorities and a number of local traditional healers, to make sure that people who need more information can get it easily.

If you need more information about the study, contact:
Africa Centre Community Engagement Office, Contact number: 035 550 7500.
If you wish to speak to the *Ukuphila kwami, ukuphila kwethu* study managers contact:
Dr Collins Iwuji, Trial Coordinator, Contact number: 035 550 7683
Ms Nonhlanhla Okesola, Clinic Coordinator, Contact number: 072 542 6522

Or alternatively, any of the people who are mentioned on the list above will be able to refer you to someone at Africa Centre who can help.

WHAT IS THE INDEPENDENT COMPLAINTS PROCEDURE?

If at any time you feel you have not been treated respectfully or appropriately, you are free to make a complaint to those responsible for the *Ukuphila kwami, ukuphila kwethu study*. If you feel that you have suffered harm as a result of taking part you should first discuss this with the staff at the *Ukuphila kwami, ukuphila kwethu* clinic.

If you would like to speak to someone outside the research team at the Africa Centre you should contact: Community Liaison Office Manager on 035 550 7500.

The Africa Centre also has a Community Advisory Board (CAB) that is made up of community members. You can get a list of CAB members from the *Ukuphila kwami, ukuphila kwethu* clinic and can contact them if you have any concerns about the study or want to make any comments.
The research study staff are indemnified under insurance held by the University of KwaZulu-Natal or their host institution. The study is also insured in the event of a serious injury or adverse clinical event involving a trial participant. Any complaint that may result in an insurance claim against the investigators, Africa Centre or the University should be addressed in the first instance to University of KwaZulu-Natal Biomedical Research Ethics Committee. If you feel that you have suffered harm because of the study or would like to know more about your rights as a research participant, you can also contact the *University of KwaZulu Natal Research Ethics Committee at (031) 260 4495 or the South African Medicines Control Council at 012 395 8126*.

***UKUPHILA KWAMI*, *UKUPHILA KWETHU*'S SUCCESS IS UP TO ALL OF US**

Ukuphila kwami, ukuphila kwethu is a very important opportunity for all of us to learn whether we can do more to stop the spread of HIV in the community. The researchers at the Africa Centre involved in this research study know it is a very big challenge both for themselves and for the community. But to work the *Ukuphila kwami, ukuphila kwethu* idea needs many people in the community to participate. This involves difficult and different decisions for each person. It is a very big challenge. But we also know that the potential benefits for all of us in this community are great. Slowing the spread of HIV is perhaps the greatest single thing we can each do in these times. As members of the *Ukuphila kwami, ukuphila kwethu* research team we will aim to do our best for the community, and we encourage people from the community to consider carefully whether they feel they can benefit from participating in this research study.

Professor Deenan Pillay, Africa Centre Director

PARTICIPANT INFORMATION SHEET (INTERVENTION CLUSTERS)

English Version

TITLE OF THE RESEARCH STUDY:

Ukuphila kwami, ukuphila kwethu - Antiretroviral Treatment as Prevention (TasP) – A cluster-randomized trial in Hlabisa sub-district, KwaZulu-Natal
ANRS 12249
Protocol V2.0 – 09/01/2014

Sponsor: ANRS - National AIDS Research Agency, Paris, France
Coordinating Centre: Africa Centre for Health and Population Studies, University of KwaZulu-Natal
Somkhele, South Africa

This research study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (2 February 2012 and 6 July 2012) and the South African Medicines Control Council of the Department of Health (28 June 2012).

INTRODUCTION:

Thank you for taking the important step of coming to our research study clinic.

Today we would like to invite you to take part in the clinic-based part of the research study "***Ukuphila kwami, ukuphila kwethu* - Antiretroviral Treatment as Prevention (TasP) – A cluster-randomized trial in Hlabisa sub-district, KwaZulu-Natal**" that is being conducted by the Africa Centre.

We would like you to read this Information Sheet, or perhaps ask a friend to read it to you. It explains important information about the study that will be discussed with you. Once you understand the study, and you agree to take part, you will be asked to sign a Consent Form, or make a mark on the form in front of a witness.

This Information Sheet is yours to keep. Please try to keep it safe because it contains useful information that you may want to refer back to. If you need to contact someone from the study team, you will find the names and contact details of all the appropriate people at the end of this information sheet.

WHAT ARE WE TRYING TO LEARN IN UKUPHILA KWAMI, UKUPHILA KWETHU?

We want to learn whether it is possible to reduce the number of people who become infected with HIV, by increasing the number of people on ARV treatment. To do this we need to offer people who know that they are HIV-positive ARV treatment as soon as possible after they learn their HIV-positive status, rather than waiting until their CD4 count is low or they become sick.

We know that ARV treatment works by reducing the level of HIV in the body. To be effective and to ensure the best possible results, ARV treatment needs to be taken life-long, that means for the rest of one's life. After taking ARVs regularly for some time the level of HIV in people's bodies becomes very low. HIV doesn't disappear completely – people aren't cured – but as long as they continue to take ARVs regularly then the level of HIV should remain low. When the HIV level is very low we believe that a person is much less likely to pass on HIV to a partner. A

recent study of stable couples where one partner was infected with HIV and the other was not showed that when the level of HIV in the blood of the infected partner was undetectable (i.e. very low) there was very little chance of their HIV-negative partner becoming infected.

Following the results of this study, it is now very important to find out what would happen*, if all the people in the community who have HIV learned their status and all those who are HIV-positive start treatment immediately while they are still well and living life normally? Would this mean that we could reduce the level of HIV in the blood in enough people in the community to reduce the number of new infections that happen each day?*

WHO WILL TAKE PART?

Any adult aged 16 years or older, who comes from one of the study communities, who has tested for HIV, received their test result, knows that they are HIV-infected and comes to one of our *Ukuphila kwami, ukuphila kwethu* study clinics will be invited to participate.

WHAT DOES IT MEAN TO BE INVOLVED IN THIS STUDY?

If you agree to participate in the study you will receive your care at this study clinic. Your care will be same as you would receive at any of the Department of Health Clinics, but two (2) things will be slightly different.

(1) The first difference is that you will be offered the opportunity to start antiretroviral (ARV) treatment immediately without having to wait until your CD4 count is low enough for treatment to start as currently recommended in the South African National Department of Health. You will receive an antiretroviral drug called *Atripla*. This drug has been approved by the National Department of Health. One of the advantages of *Atripla* is that it is only one tablet but contains 3 antiretroviral drugs in it, so you only have to take one pill daily as opposed to several different medications. There is more information about *Atripla* below.

(2) Blood samples will be collected from you during some of the clinic visits (every 3 months for the first 6 months) after starting ARVs. This is a bit more often than in the Department of Health clinics, but it is necessary so that we can monitor how the ARVs are working and how your body is tolerating them. Some of the blood samples will go the laboratory at Hlabisa Hospital as would normally happen, but at some visits an additional sample will be sent to the Africa Centre laboratory in Durban. An amount of blood from this sample will be stored at the Africa Centre laboratory in a freezer. It might be that during the study or once the study has finished we think of other tests that need to be done on these samples to help us understand certain findings from the study. If we want to do any tests on these stored samples we will ensure that we have permission from the University of KwaZulu-Natal Biomedical Ethics Committee.

MORE ABOUT THE STUDY DRUG – *ATRIPLA*

If you agree to participate in this study, you will be offered the opportunity to begin preparing to start taking ARV treatment immediately. This will involve completing the preparation sessions at the clinic which takes about two (2) weeks. When you have completed this you will be given a drug called *Atripla* which is known as a 'triple combination' as it contains three (3) antiretroviral drugs in one tablet. The drugs are tenofovir, emtricitabine and efavirenz. You only need to take one tablet daily, rather than several tablets twice daily. This drug has been approved

by the National Department of Health and is available in public service clinics as Atroiza or Odimune. It has an excellent record of strength, tolerability and safety.

All antiretroviral drugs have some side effects, but people taking *Atripla* generally experience few side effects. Common side effects include feeling dizzy, headaches and experiencing unusual dreams. Several patients complain of a rash, but this usually goes away without any change in treatment. Sometimes patients have diarrhoea and an upset stomach.

There are some more serious side effects that include kidney problems and more severe vomiting and muscle pains. You will be monitored carefully for these side effects when you are on treatment.

All people who come to the clinic will be able to access other services such as testing for STIs (sexually transmitted infections) and TB (tuberculosis), for example. The other services available at the clinic will be discussed with you by the nurse.

HOW LONG WILL THIS RESEARCH STUDY TAKE?

We anticipate that the study will be finished in 2016.. Your participation in this study is completely voluntary and can start once you sign the Consent Form which the counsellor will explain to you. You may continue to be involved until the end of the study period or you may withdraw at any time. If you decide to withdraw from the study it is important that you still continue to take your ARV treatment. You will be able to access this from the Department of Health clinics in KwaZulu-Natal. After the study is complete, or if you decide to withdraw, you will be referred to the local Department of Health Clinics' treatment and care programme where you will continue to receive HIV care and treatment. All the medications used in the study are licensed and available in South Africa. The aim would be for you to receive the exact same medications you received in the study; otherwise it would be what is currently available in the local Department of Health clinics at the time of withdrawal or study closure.

WHAT WILL HAPPEN IF I DECIDE TO PARTICIPATE IN THIS PART OF THE STUDY?

Once you have read this Information Sheet, the *Ukuphila kwami, ukuphila kwethu* counsellor will sit with you, by yourself, in a private space and explain what taking part involves for you. If you do choose to take part, the counsellor will ask you to sign, or make your mark, on two (2) separate Consent Forms. The first indicates that you consent to take part in the *Ukuphila kwami, ukuphila kwethu* clinic-based study. The second consent form, which is like the ones used in the Department of Health clinics, indicates you agree to have your HIV care provided at this *Ukuphila kwami, ukuphila kwethu* study clinic. But before we ask you to sign anything, we will want to make sure you understand what being part of the study involves.
Once you are initiated on ART or if you are already on ARVs and choose to move to the research clinics for your care, you will be asked to come to the study clinic each month or every two months depending on your circumstance, and to come back earlier than this if you do not feel well or you are worried about anything. At each visit the study nurse will ask you some questions about your health and your drugs. If you have any symptoms you will be examined, as you would be in the Department of Health Clinics. You will receive your next supply of antiretroviral drugs for the following month(s). If you need additional investigations or treatment for other illnesses that are not available at the study clinics, the study nurse will refer you appropriately. You will have samples of your blood taken regularly to check that your body is tolerating the antiretroviral drugs, and that the HIV in your body is falling as it should do. We will do these tests more frequently than is the case in the Department of Health clinics. We will ask your permission to link the information we collect about you during your study visits to

information we have collected in your household. This will be done using a study code; as explained above personal details about you (e.g. name and physical address) will not be shared with people outside the clinic and medical facilities.

ARE THERE ANY RISK OF BEING IN THE STUDY?

There are no additional risks to your health by having your HIV treatment and care provided at the *Ukuphila kwami, ukuphila kwethu* study clinics as compared to the Department of Health Clinics.

All people treated with antiretroviral drugs may develop side effects. In this trial most people will be starting treatment at an earlier stage than they would do normally – in other words while they still feel well and the CD4 count is still high. There is therefore a small possibility that you might experience some side effects, including the possibility of HIV virus becoming resistant to some of the ARVs in your medication combination. However we know that the side effects with *Atripla* are minimal, and we have talked about these already. We also know that people who take their ARV medications regularly are much less likely to develop any resistance. You will be monitored very carefully by the study nurses at the clinic visits, using clinical questions and examination and blood tests, to check your body is responding well to the treatment and not developing any problems. If there are any problems these should be identified quickly, and we will manage them appropriately. A study physician, with expertise in HIV medicine, will also be available to help with any problems. During the trial you will be able to visit the study clinic at any time to seek help if you are worried.

IS THERE ANY BENEFIT BY BEING IN THE STUDY?

In the trial you may be starting ART earlier than you would do in the Department of Health HIV clinics. You may be starting drugs when your CD4 count is high and you are feeling well. There are a lot of potential advantages to this. Starting ART early is likely to mean that you will remain healthy and free from illnesses and complications associated with HIV for a lot longer than you would do if you were not on treatment. For example, we think that people will be less likely to get TB (tuberculosis) if they start ART earlier when their immune systems are still strong. Staying stronger for longer will mean that you are less likely to need admission to hospital for HIV-related illnesses.

There will be several trial clinics, most of which will be within 45 minutes walking distance of people's houses. As a trial participant you are free to use these clinics whenever you wish, even if you do not have a scheduled appointment. There will always be a counsellor and/or a nurse at the study clinic Monday-Friday 9:00am-3:30pm, whom you will get to know very well during the trial. A few clinics will be open on Saturdays 9:00am-2:00pm depending on needs of participants.
If there is a problem that they cannot help with they will arrange for you to meet with one of the study doctors.

You will have more regular blood tests taken than you would do in the Department of Health clinics. This means that we can follow what is happening to your immune system and the HIV in your blood more frequently and detect earlier if there is a problem. The study staff will share these results with you and explain what they mean.

WHAT IF I DO NOT WANT TO TAKE PART?

Taking part in this study is entirely voluntary and there are no direct financial costs to you as a participant. If you decide not to take part, or decide to take part and later withdraw from the study and stop taking the antiretrovirals, you will not be penalized in anyway. You will still be able to access normal health care at your Department of Health Primary Health Care Clinic and HIV treatment and care programme. You will continue to receive care in the ART programme and at the clinic.

WHO WILL HAVE ACCESS TO INFORMATION COLLECTED ABOUT ME AT THE CLINIC?

The information that is collected will be kept confidential. Only the *Ukuphila kwami, ukuphila kwethu* study researchers and staff will have access to this information and results. Your name and identity will not be revealed to anyone except to clinic staff. Once we have completed the study we will make the results available to all of the participants via newsletters, community presentations and presentations and education sessions with the Africa Centre Community Advisory Boards and the Africa Centre's Community Engagement Team. The study results will also be made known to the Hlabisa hospital management and clinic based staff without revealing the identity of the individuals who participated in the study. They will also be made known to the National Department of Health as well as the Department of Health in KwaZulu-Natal. We will share our results with other scientists around the world in scientific publications and presentations at conferences.

WHERE CAN I GO IF I NEED TO GET MORE INFORMATION ABOUT *UKUPHILA KWAMI, UKUPHILA KWETHU* IN MY COMMUNITY?

If you have any problems relating to your ARV medications you should first of all contact the *Ukuphila kwami, ukuphila kwethu* study clinic staff, who will make an urgent assessment and make a referral if that is necessary.

The *Ukuphila kwami, ukuphila kwethu* study team is working closely with the Africa Centre's Community Engagement Team, some national and local NGOs, Hlabisa Hospital and with the local Department of Health clinics to make sure people have all the information they need and that their questions are always answered.

The *Ukuphila kwami, ukuphila kwethu* study team is also working closely with the Africa Centre's Community Advisory Board, as well as with the municipal and traditional authorities and a number of local traditional healers, to make sure that people who need more information can get it easily.

If you need more information about the study, contact:
Africa Centre Community Engagement Office, Contact number: 035 550 7500.
If you wish to speak to the *Ukuphila kwami, ukuphila kwethu* study managers contact:
Dr Collins Iwuji, Trial Coordinator, Contact number: (035) 550 7683
Ms Nonhlanhla Okesola, Clinic Coordinator, Contact number: 072 542 6522

Or alternatively, any of the people who are mentioned on the list above will be able to refer you to someone at Africa Centre who can help.

WHAT IS THE INDEPENDENT COMPLAINTS PROCEDURE?

If at any time you feel you have not been treated respectfully or appropriately, you are free to make a complaint to those responsible for the *Ukuphila kwami, ukuphila kwethu study*. If you feel that you have suffered harm as a result of taking part you should first discuss this with the

staff at the *Ukuphila kwami, ukuphila kwethu* clinic. If you would like to speak to someone outside the research team at the Africa Centre you should contact: Community Liaison Office Manager on 035 550 7500.

The Africa Centre also has a Community Advisory Board (CAB) that is made up of community members. You can get a list of CAB members from the *Ukuphila kwami, ukuphila kwethu* clinic and can contact them if you have any concerns about the study or want to make any comments.

The research study staff are indemnified under insurance held by the University of KwaZulu-Natal or their host institution. The study is also insured in the event of a serious injury or adverse clinical event involving a trial participant. Any complaint that may result in an insurance claim against the investigators, Africa Centre or the University should be addressed in the first instance to University of KwaZulu-Natal Biomedical Research Ethics Committee. If you feel that you have suffered harm because of the study or would like to know more about your rights as a research participant, you can also contact the *University of KwaZulu-Natal Biomedical Research Ethics Committee at (031) 260 4495 or the South African Medicines Control Council at 012 395 8126.*

***UKUPHILA KWAMI, UKUPHILA KWETHU*'S SUCCESS IS UP TO ALL OF US**

Ukuphila kwami, ukuphila kwethu is a very important opportunity for all of us to learn whether we can do more to stop the spread of HIV in the community. The researchers at the Africa Centre involved in this research study know it is a very big challenge both for themselves and for the community. But to work the *Ukuphila kwami, ukuphila kwethu* idea needs many people in the community to participate. This involves difficult and different decisions for each person. It is a very big challenge. But we also know that the potential benefits for all of us in this community are great. Slowing the spread of HIV is perhaps the greatest single thing we can each do in these times. As members of the *Ukuphila kwami, ukuphila kwethu* research team we will aim to do our best for the community, and we encourage people from the community to consider carefully whether they feel they can benefit from participating in this research study.

Professor Deenan Pillay, Africa Centre Director

This English version is NOT for use in the field

Ukuphila kwami, ukuphila kwethu

Africa Centre TasP Trial

CE1
v31 Mar 2014

BSID
TasP ID
Visit Date
Fieldworker

PARTICIPANT SIGNATURE SHEET
INDIVIDUAL QUESTIONS AND DBS COLLECTION

Title of the research study:

Ukuphila kwami, ukuphila kwethu - Antiretroviral Treatment as Prevention (TasP) -A cluster-randomized trial in Hlabisa sub-district, KwaZulu-Natal
ANRS 12249
Protocol V2.0- 9 January2014
Sponsor: ANRS - National AIDS Research Agency, Paris, France
Coordinating Centre: Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa
This research study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal on 2 February 2012 and 6 July 2012.

Age of participant: ____ years If below 18 years, parent or guardian must sign to indicate their consent to the child's participation in the study.

Parent / guardian's name (print)	Parent / guardian's signature	Date
_____	_____	_____

Participation consent:

I have been told about the above research study by a trained counsellor. I understand my participation in this study is voluntary. No one can force me to participate.

I, _____ agree to participate in this research study being done by the Africa Centre. I have received and understood the study information sheet. I understand the benefits, difficulties and the implications for my family and myself of participating in this research study. I understand that the test for HIV is voluntary. I have been told where and when I can see a counsellor and obtain an HIV test if I do not want to have one today.

I consent to the following:

1) Answer the counsellor's questions about myself, my general health, my attitudes and beliefs about HIV, my personal relationships and sexual behaviour. This takes about 15 minutes.

2) Provide a very small blood specimen - 5 dots dried into a piece of paper. To do this requires a tiny prick of one of my fingers. Once the paper with the bloodspots is dry, the counsellors will place it in an envelope. All the papers collected will be stored in a laboratory and only used for other research studies relating to HIV. I understand that confidentiality is kept about these samples because they are coded and the laboratory does not know my identity.

3) Discuss with the counsellor about taking the important step of learning my HIV status through a process of HIV counseling and testing (HCT). I will be counseled separately about this, and asked to sign a separate consent form like the ones used in the Department of Health clinics indicating my agreement to have an HIV test. Having an HIV test today is not obligatory.

I know that I can leave the research study at any time without prejudice and that my treatment by the Health Services and by Africa Centre staff will be exactly the same whether or not I choose to take part. I also understand that I am not giving up any of my legal rights by signing this informed consent document.

Participant's name (print)	Participant's signature (Persons who cannot write may mark with X)	Date
_____	_____	_____
Name of staff member who administered consent (print)	Staff Member's signature	Date
_____	_____	_____
Witness' name (print) *	Witness' signature	Date
_____	_____	_____

Stick DBS Specimen Id barcode here

* Witness required only if the participant cannot write or if the participant asks for one.

This trial is conducted in accordance with international Guidelines for Good Clinical Practice in Clinical Trials and with the approval of both the University of KwaZulu-Natal Biomedical Research Ethics Committee (6 July 2012) and the SA Medicines Control Council (28 June 2012).

Contact details:
Biomedical Research Ethics Administration, University of KwaZulu-Natal, Research Office, Westville Campus, Govan Mbeki Building
Private Bag X 54001, Durban, 4000, KwaZulu-Natal. Tel: 27 31 2604769 - Fax: 27 31 2604609 - Email: BREC@ukzn.ac.za
SA Medicines Control Council, Department of Health, Private Bag X828, PRETORIA 0001. Fax: 27 12 395 8775; Email: nkambp@health.gov.za

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Ukuphila kwami, ukuphila kwethu

Africa Centre TasP Trial

CE2
v31 Mar 2014

BSID
TasP ID
Visit Date
Fieldworker

PARTICIPANT SIGNATURE SHEET
HOME-BASED HIV TESTING

Title of the research study:

Ukuphila kwami, ukuphila kwethu - Antiretroviral Treatment as Prevention (TasP) -A cluster-randomized trial in Hlabisa sub-district, KwaZulu-Natal
ANRS 12249
Protocol V2.0 - 9 January 2014
Sponsor: ANRS - National AIDS Research Agency, Paris, France
Coordinating Centre: Africa Centre for Health and Population Studies,
University of KwaZulu-Natal, Somkhele, South Africa
This research study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal on 2 February 2012 and 6 July 2012.

HIV testing consent:

I, …… hereby give my fully informed consent to be tested for HIV antibodies. I have been counselled by a trained HIV counsellor with knowledge of HIV issues. We have discussed the advantages and disadvantages of doing the test and I fully understand the implications of having a test and the impact it may have on my life. I understand that the test for HIV is voluntary and that I will receive my result today if I wish. I consent to being followed up should there be a need to refer me to another facility or facilitate attendance to the trial clinics to ensure that I have received all the necessary support and services available. This follow-up can take the form of a visit or a phone call from a member of the study team.

I understand that the study team may look at my clinic records to obtain limited clinical information concerning my HIV care for the purpose of this research.

I know that I can leave the research study at any time and refuse to receive my HIV test result without prejudice and that my treatment by the Health Services and by Africa Centre staff will be exactly the same whether or not I choose to take part. I also understand that I am not giving up any of my legal rights by signing this informed consent document.

_____	_____	_____
Participant's name (print)	Participant's signature (Persons who cannot write may mark with X)	Date
_____	_____	_____
Name of staff member who administered consent (print)	Staff Member's signature	Date
_____	_____	_____
Witness' name (print) *	Witness' signature	Date

* Witness required only if the participant cannot write or if the participant asks for one.

This trial is conducted in accordance with international Guidelines for Good Clinical Practice in Clinical Trials and with the approval of both the University of KwaZulu-Natal Biomedical Research Ethics Committee (6 July 2012) and the SA Medicines Control Council (28 June 2012).
Contact details:
Biomedical Research Ethics Administration, University of KwaZulu-Natal, Research Office, Westville Campus, Govan Mbeki Building
Private Bag X 54001, Durban, 4000, KwaZulu-Natal. Tel: 27 31 2604769 - Fax: 27 31 2604609 - Email: BREC@ukzn.ac.za
SA Medicines Control Council, Department of Health, Private Bag X828, PRETORIA 0001. Fax: 27 12 395 8775; Email: nkambp@health.gov.za

This English version is NOT for use in the field

Ukuphila kwami, ukuphila kwethu

Africa Centre TasP Trial

CE3
v31 Mar 2014

TasP ID
Clinic
Visit Date Y Y Y Y M M D D
Counsellor

PARTICIPANT SIGNATURE SHEET

RECEIVE ARV TREATMENT AND CARE

Title of the research study:

Ukuphila kwami, ukuphila kwethu - Antiretroviral Treatment as Prevention (TasP) -A cluster-randomized trial in Hlabisa sub-district, KwaZulu-Natal
ANRS 12249
Protocol V2.0 - 9 January 2014
Sponsor: ANRS - National AIDS Research Agency, Paris, France
Coordinating Centre: Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa
This research study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal on 2 February 2012 and 6 July 2012.

Patient Consent Form:

I, _____ have been educated/informed in three (3) ART lessons (literacy sessions), about the importance of taking my treatment appropriately.

I understand that ARVs do not cure HIV but if I take them appropriately they can help me to remain healthy much longer. I understand that I will be given, when possible and appropriate, a new drug combination called *Atripla*, which has been approved by the South African Department of Health. I understand ARV treatment is life-long and that I will need to take appropriate HIV medications for the rest of my life. I understand that the treatment can make certain changes in my body, and might cause side effects. I understand that on a daily basis I must take my treatment for it to be effective. I understand that if I have any problems with taking my ARVs that I should contact the clinic where I can speak to a nurse who will refer me to the clinic doctor if necessary.

I understand that I am free to leave the study at any time and that I will be able to continue to have my care provided at one of the Department of Health clinics. I understand that there is no cost to me for either the care provided by the research study or in the Department of Health clinics. My decision to leave the study will not affect the care I receive in the Department of Health clinic nor prejudice my relationship with the staff of the *Ukuphila kwami, ukuphila kwethu* study or the Africa Centre in any way.

_____	_____	_____
Participant's name (print)	Participant's signature (Persons who cannot write may mark with X)	Date
_____	_____	_____
Name of staff member who administered consent (print)	Staff Member's signature	Date
_____	_____	_____
Witness' name (print) *	Witness' signature	Date

* Witness required only if the participant cannot write or if the participant asks for one.

This trial is conducted in accordance with international Guidelines for Good Clinical Practice in Clinical Trials and with the approval of both the University of KwaZulu-Natal Biomedical Research Ethics Committee (6 July 2012) and the SA Medicines Control Council (28 June 2012).

Contact details:

Biomedical Research Ethics Administration, University of KwaZulu-Natal, Research Office, Westville Campus, Govan Mbeki Building
Private Bag X 54001, Durban, 4000, KwaZulu-Natal. Tel: 27 31 2604769 - Fax: 27 31 2604609 - Email: BREC@ukzn.ac.za

SA Medicines Control Council, Department of Health, Private Bag X828, PRETORIA 0001. Fax: 27 12 395 8775; Email: nkambp@health.gov.za

Title of the research study:

Ukuphila kwami, ukuphila kwethu - Antiretroviral Treatment as Prevention (TasP) -A cluster-randomized trial in Hlabisa sub-district, KwaZulu-Natal
ANRS 12249
Protocol V2.0 - 9 January 2014
Sponsor: ANRS - National AIDS Research Agency, Paris, France
Coordinating Centre: Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa
This research study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal on 2 February 2012 and 6 July 2012.

Participation consent:

I have been told about the above research study by a trained counsellor. I understand my participation in this study is voluntary. No one can force me to participate.

I, _____ agree to be part of the clinic component of this research study being done by the Africa Centre. I have received and understood the study information sheet. I have had the opportunity to ask questions about the study and have had answers to all of my questions.

I understand the implications of joining the study and that I may be asked additional information regarding my health and my treatment during study visits. I understand that the research and clinic study staff may need to look at my clinic records and that information from my clinic records will be used by the study team to answer questions about HIV and HIV treatment. I understand that there are no costs to me for the treatment and care provided either by the research study clinics or the Department of Health clinics.

I understand the benefits, difficulties and the implications for my family and myself of participating in this research study.

I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without affecting my medical care.

I consent to the following:

1) I agree to receive the offer of antiretroviral (ARV) treatment provided at this clinic, which specifically includes using a combination ARV medication called *Atripla*, which has the approval of the National Department of Health. I understand that I may be given ARVs (*Atripla*) at an earlier stage of my infection than might normally be the case in the routine care provided by the Department of Health clinics. I will discuss with the clinic staff whether *Atripla* is the most appropriate ARV medication for me. If it is not, I will be offered and alternative combination that is appropriate to my personal circumstances.

2) I agree to allow the nurses at the study clinic to collect a small blood specimen on some occasions (every 3 months) when I visit the clinic. I understand that this blood will be used to monitor how the ARVs are working to see how well my body is coping. I will receive the results of the tests and they will be explained to me.

3) I agree that the small amount of blood that remains after these tests are finished may be stored separately and safely in a freezer at the Africa Centre laboratory in Durban and that it may be used in the future for others studies about HIV. I also understand that before any further tests are done on this blood the scientists from the Africa Centre will obtain the permission of the Biomedical Research Ethics Committee of the University of KwaZulu-Natal.

I know that I can leave the research study at any time without prejudice and that I can access treatment and care for HIV at the Department of Health clinics. I understand that if I do this my treatment by the Department of Health Services and by the Africa Centre staff will remain exactly the same, whether or not I choose to take part. I understand that I am not giving up any of my legal rights by signing this informed consent document.

_____	_____	_____
Participant's name (print)	Participant's signature (Persons who cannot write may mark with X)	Date
_____	_____	_____
Name of staff member who administered consent (print)	Staff Member's signature	Date
_____	_____	_____
Witness' name (print) *	Witness' signature	Date

* Witness required only if the participant cannot write or if the participant asks for one.

This trial is conducted in accordance with international Guidelines for Good Clinical Practice in Clinical Trials and with the approval of both the University of KwaZulu-Natal Biomedical Research Ethics Committee (6 July 2012) and the SA Medicines Control Council (28 June 2012).

Contact details:

Biomedical Research Ethics Administration, University of KwaZulu-Natal, Research Office, Westville Campus, Govan Mbeki Building
Private Bag X 54001, Durban, 4000, KwaZulu-Natal. Tel: 27 31 2604769 - Fax: 27 31 2604609 - Email: BREC@ukzn.ac.za

SA Medicines Control Council, Department of Health, Private Bag X828, PRETORIA 0001. Fax: 27 12 395 8775; Email: nkambp@health.gov.za

Title of the research study:
Ukuphila kwami, ukuphila kwethu - Antiretroviral Treatment as Prevention (TasP) -A cluster-randomized trial in Hlabisa sub-district, KwaZulu-Natal
ANRS 12249
Protocol V2.0 - 9 January 2014
Sponsor: ANRS - National AIDS Research Agency, Paris, France
Coordinating Centre: Africa Centre for Health and Population Studies,
University of KwaZulu-Natal, Somkhele, South Africa
This research study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal on 2 February 2012 and 6 July 2012.

Participation consent:

I have been told about the above research study by a trained counsellor. I understand my participation in this study is voluntary. No one can force me to participate.

I, _____ agree to be part of the clinic component of this research study being done by the Africa Centre. I have received and understood the study information sheet. I have had the opportunity to ask questions about the study and have had answers to all of my questions.

I understand the implications of joining the study and that I may be asked additional information regarding my health and my treatment during study visits. I understand that the research and clinic study staff may need to look at my clinic records and that information from my clinic records will be used by the study team to answer questions about HIV and HIV treatment. I understand that there are no costs to me for the treatment and care provided either by the research study clinics or the Department of Health clinics.

I understand the benefits, difficulties and the implications for my family and myself of participating in this research study.

I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without affecting my medical care.

I consent to the following:

1) I agree to discuss with the clinic nurse whether I am eligible to receive the offer of antiretroviral (ARV) treatment provided at this clinic. I understand that treatment at this clinic specifically includes a combination ARV medication called *Atripla*, which has the approval of the National Department of Health. If I am eligible to start treatment now I will discuss with the clinic staff whether Atripla is the most appropriate ARV medication for me. If it is not, I will be offered an alternative combination of that is appropriate to my personal circumstances.

2) If I am not eligible to start ARV treatment now: to discuss with the clinic nurse the most appropriate ways that I can benefit from the care available at this research study clinic. This will include all the normal package of care and treatments that are provided at the Department of Health clinics.

3) I agree to allow the nurses at the study clinic to collect a small blood specimen on some occasions when I visit the clinic. I understand that this blood will be used either to monitor how the ARVs are working if I am taking ARVs or to see how well my body is coping with HIV (CD4 count). I will receive the results of the tests and they will be explained to me.

4) I agree that the small amount of blood that remains after these tests are finished may be stored separately and safely in a freezer at the Africa Centre laboratory in Durban and that it may be used in the future for others studies about HIV. I also understand that before any further tests are done on this blood the scientists from the Africa Centre will obtain the permission of the Biomedical Research Ethics Committee of the University of KwaZulu-Natal.

I know that I can leave the research study at any time without prejudice and that my treatment by the Department of Health Services and by the Africa Centre staff will remain exactly the same, whether or not I choose to take part. I understand that I am not giving up any of my legal rights by signing this informed consent document.

_____	_____	_____
Participant's name (print)	Participant's signature (Persons who cannot write may mark with X)	Date
_____	_____	_____
Name of staff member who administered consent (print)	Staff Member's signature	Date
_____	_____	_____
Witness' name (print) *	Witness' signature	Date

* Witness required only if the participant cannot write or if the participant asks for one.

This trial is conducted in accordance with international Guidelines for Good Clinical Practice in Clinical Trials and with the approval of both the University of KwaZulu-Natal Biomedical Research Ethics Committee (6 July 2012) and the SA Medicines Control Council (28 June 2012).

Contact details:

Biomedical Research Ethics Administration, University of KwaZulu-Natal, Research Office, Westville Campus, Govan Mbeki Building
Private Bag X 54001, Durban, 4000, KwaZulu-Natal. Tel: 27 31 2604769 - Fax: 27 31 2604609 - Email: BREC@ukzn.ac.za

SA Medicines Control Council, Department of Health, Private Bag X828, PRETORIA 0001. Fax: 27 12 395 8775; Email: nkambp@health.gov.za

This English version is NOT for use in the field

Ukuphila kwami, ukuphila kwethu

Africa Centre TasP Trial

CE6
v31 Mar 2014

TasP ID
Clinic
Visit Date Y Y Y Y M M D D
Interviewer

PARTICIPANT SIGNATURE SHEET

Social Science Clinic-based Interviewer-Administered Questionnaire

Title of the research study:

Ukuphila kwami, ukuphila kwethu - Antiretroviral Treatment as Prevention (TasP) -A cluster-randomized trial in Hlabisa sub-district, KwaZulu-Natal
ANRS 12249
Protocol V2.0 - 9 January 2014
Sponsor: ANRS - National AIDS Research Agency, Paris, France
Coordinating Centre: Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa
This research study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal on 26th September 2012.

Age of participant: ____ years If below 18 years, parent or guardian must sign to indicate their consent to the child's participation in the study.

Parent / guardian's name (print)	Parent / guardian's signature	Date
_____	_____	_____

Participation Consent:

I, _____ I have been told about the above research study by a trained counselor. I understand my participation in this study is voluntary. No one can force me to participate.

I agree to participate in this research study being done by the Africa Centre. I have received and understood the study information sheet. I have had the opportunity to ask questions about the study and have had answers to all my questions.

I understand the benefits, difficulties and the implications for my family and myself of participating in this research study.

I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without affecting my medical care.

I consent to answer the interviewer's questions about myself, my general health, my HIV treatment, my satisfaction with care, my attitude and beliefs about gender and violence, my personal relationships and sexual behaviour. This takes about 30-40 minutes.

I know that this interview will be entirely confidential and will not be shared with people involved in my treatment care at this Clinic.

I know that I can leave the research study at any time without prejudice and that my treatment by the Health Services and by Africa Centre staff will be exactly the same whether or not I choose to take part. I also understand that I am not giving up any of my legal rights by signing this informed consent document.

_____	_____	_____
Participant's name (print)	Participant's signature (Persons who cannot write may mark with X)	Date
_____	_____	_____
Name of staff member who administered consent (print)	Staff Member's signature	Date
_____	_____	_____
Witness' name (print) *	Witness' signature	Date

* Witness required only if the participant cannot write or if the participant asks for one.

The contact details of the Biomedical Research Ethics Committee are:
BIOMEDICAL RESEARCH ETHICS ADMINISTRATION, University of KwaZulu-Natal, Research Office, Westville Campus, Govan Mbeki Building
Private Bag X 54001, Durban, 4000, KwaZulu-Natal. Tel: 27 31 2604769 - Fax: 27 31 2604609 - Email: BREC@ukzn.ac.za

Ukuphila kwami, ukuphila kwethu

Africa Centre TasP Trial

PARTICIPANT SIGNATURE SHEET

INDIVIDUAL QUESTIONS AND DBS COLLECTION

Round 1

CZ1

v31 Mar 2014

BSID

TasP ID

Visit Date Y Y Y Y M M D D

Fieldworker

Isihloko Socwaningo:
Ukuphila kwami, ukuphila kwethu - Ukuvikela ngokusetshenziswa kwemishanguzo (TasP) -Ucwaningo olwenziwa ezigodini ezingaphansi kwesifunda sakwaHlabisa lungekho uhlelo oluqondile lokukhetha abantu, KwaZuluNatali
ANRS 12249
Uhlelo lwemithetho V2.0 - 9 January 2014
Umxhasi: ANRS - National AIDS Research Agency, Paris, France
Isikhungo esixhumanisayo: Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa
Lolucwaningo luphasiswe ikomidi elibhekelela amalungelo kwezocwaningo lwezempilo lase Nyuvesi yakwaZulu-Natali mhlaka - 2 Feb 2012 nangomhlaka 6 July 2012.

Ubudala ____ iminy Uma ingaphansi kuka-18, umzali noma umbheki kumele asayine ukuvumela ingane ukuthi ibambe

Igama lomzali /mbheki (Loba)	Ukusayina komzali / mbheki	Usuku

Iphepha lemvume lokubamba iqhaza:

Sengichazeliwe ngocwaningo olungenhla ngumaluleki oqeqeshiwe. Ngiyaqondisisa ukuthi ukubamba iqhaza kwami kulolucwaningo kungokuzikhethela kwami. Akekho namunye ongangiphoqelela ukubamba iqhaza.

Mina, _____ ngiyavuma ukuba yingxenye yocwaningo olwenziwa yi-Africa Centre. Ngilitholile iphepha lolwazi futhi ngaliqondisisa. Ngiyakuqonda ukuhlomula, ubunzima kanye nemthelela okungaba nawo emndenini wami nakimi ukuba yingxenye yaloluchwaningo. Ngiyaqonda ukuthi ukuhlolela igciwane le-HIV kungokuzikhethela kwami. Ngichazeliwe ukuthi ngingamubona kuphi nanini umaluleki ngihlolele i-HIV uma ngingathandi ukuhlolwa namuhla.

Ngiyavuma kulokhu okulandelayo:

1) Ukuphendula umaluleki imibuzo emayelana nami, isimo sempilo yami, indlela engicabanga ngayo, nezinkolelo zami nge-HIV, ubudlelwano enginabo nokuziphatha kwami ngezocansi. Lokhu kuzothatha imizuzu engevile kweyishumi nanhlanu.

2) Ukunikezela ngeconsi legazi - amaconsi amahlanu omisiwe esiqeshini esincane sephepha. Ukwenza lokhu kuzodinga ukuthi ngichofozwe kancane emunweni owodwa. Uma iphepha elinamaconsi egazi selomile, umaluleki uyobe eselifaka emvilophini. Wonke amaphepha aqoqiwe azobekwa e-laboratory ayosetshenziselwa kuphela olunye ucwaningo oluphathelene ne-HIV. Ngiyaqonda ukuthi ukuthathwa kwalama sampula egazi kugcineka kuyimfihlo ngoba kusetshenziswa amakhodi ne-laboratory angeke yazi ukuthi yimina.

3) Ukuxoxisana nomaluleki ngokuthatha igxathu elibalulekile lokwazi ngesimo sami se-HIV ngohlelo lokwalulekwa nokuhlolela i-HIV (HCT). Ngizokwalulekwa ngokwahlukile ngalokhu, ngisayine iphepha lemvume elifana nelisetshenziswa emitholampilo yoMnyango Wezempilo elizoveza ukuvuma kwami ukuhlolela i-HIV. Ukuhlolela i-HIV namuhla akusiyona impoqo.

Igama lobamba iqhaza (loba)	Obamba iqhaza uyasayina (Kongakwazi ukubhalo loba u X)	Usuku

Igama lomsebenzi onikezele ngephepha lemvume (loba)	Ukusayina komsebenzi	Usuku

Igama likafakazi (loba) *	Ufakazi uyasayina	Usuku

* Ufakazi udingeka kuphela uma obambe iqhaza engakwazi ukubhala noma ecela ukuba nofakazi.

Stick DBS Specimen Id barcode here

Lolucwaningo lwenziwa ngokulandela imigomo yomhlaba ye-Good Clinical Practice in Clinical Trials futhi luphasiswe yikomidi elibhekele amalungelo kwezocwaningo lwezempilo laseNyuvesi yaKwaZulu-Natali (Mhlaka 6 July 2012) nesigungu esilawula ngezemithi eNingizimu Africa (mhlaka 28 June 2012).

Imininingwane yekomidi:
Biomedical Research Ethics Administration, University of KwaZulu-Natal, Research Office, Westville Campus, Govan Mbeki Building
Private Bag X 54001, Durban, 4000, KwaZulu-Natal. Tel: 27 31 2604769 - Fax: 27 31 2604609 - Email: BREC@ukzn.ac.za
SA Medicines Control Council, Department of Health, Private Bag X828, PRETORIA 0001. Fax: 27 12 395 8775; Email: nkambp@health.gov.za

Ukuphila kwami, ukuphila kwethu

Africa Centre TasP Trial

CZ2

v28 April 2013

PARTICIPANT SIGNATURE SHEET

HOME-BASED HIV TESTING

BSID

TasP ID

Visit Date Y Y Y Y M M D D

Fieldworker

Isihloko Socwaningo:

Ukuphila kwami, ukuphila kwethu - Ukuvikela ngokusetshenziswa kwemishanguzo (TasP) -Ucwaningo olwenziwa ezigodini ezingaphansi kwesifunda sakwaHlabisa lungekho uhlelo oluqondile lokukhetha abantu, KwaZulu-Natali

ANRS 12249

Uhlelo lwemithetho V2.0 - 9 January 2014

Umxhasi: ANRS - National AIDS Research Agency, Paris, France

Isikhungo esixhumanisayo: Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa

Lolucwaningo luphasiswe ikomidi elibhekelela amalungelo kwezocwaningo lwezempilo lase Nyuvesi yakwaZulu-Natali mhlaka - 2 Feb 2012 nangomhlaka 6 July 2012.

Iphepha lemvume yokuhlolela i-HIV:

Mina, …… ngiyavuma ngokuphelele ukuthi ngihlolelwe isandulela ngculazi. Sengikhulumile nomaluleki oqeqeshiwe futhi onolwazi nge-HIV. Sixoxisene ngemiphumela yokuhlolwa kwegazi engaba mihle noma ibe mibi ngaqonda ngokuphelele imithelela engabakhona ngokuhlola empilweni yami. Ngiyaqonda ukuthi ukuhlolelwa i-HIV kungokokuzikhethela kwami futhi ngizothola imiphumela yami namuhlanje uma ngifuna. Ngiyavuma ukulandelelwa uma kunesidingo sokuba ngidluliselwe kwesinye isikhungo noma ngikhuthazwe ukuhambela imitholampilo yocwaningo ukuqinisekisa ukuthi ngikuthola konke ukwesekwa nezinsiza ezikhona. Lokhu kulandelelwa kungaba ngokuvakashelwa noma ukushayelwa ucingo ilungu lethimba locwaningo.

Ngiyaqonda ukuthi ithimba locwaningo lingabheka imiininingwane yami eqoshiwe yasemtholampilo ukuthola ulwazi lozokwelashwa olufushane mayelana nokunakekelwa kwami kwesandulelangculazi nokuhambisana nalolucwaningo.

Ngiyaqonda ukuthi ngingalushiya ucwaningo noma ingasiphi isikhathi futhi nginganqaba ukuthatha imiphumela yami yesandulela ngculaza ngaphandle kokucwaswa ngokwenzenjalo kanti futhi nokuphathwa kwami ngabasebenzi bezempilo nabakwa Africa Centre kuzofana uma ngivuma noma nginqaba ukubamba iqhaza. Ngiyaqonda futhi ukuthi alikho ilungelo engililahlayo ngokusayina lelifomu lemvume.

_____	_____	_____
Igama lobamba iqhaza (loba)	Obamba iqhaza uyasayina (Kongakwazi ukubhalo loba u X)	Usuku
_____	_____	_____
Igama lomsebenzi onikezele ngephepha lemvume (loba)	Ukusayina komsebenzi	Usuku
_____	_____	_____
Igama likafakazi (loba) *	Ufakazi uyasayina	Usuku

* Ufakazi udingeka kuphela uma obambe iqhaza engakwazi ukubhala noma ecela ukuba nofakazi.

Lolucwaningo lwenziwa ngokulandela imigomo yomhlaba ye-Good Clinical Practice in Clinical Trials futhi luphasiswe yikomidi elibhekele amalungelo kwezocwaningo lwezempilo laseNyuvesi yaKwaZulu-Natali (mhlaka 6 July 2012) nesigungu esilawula ngezemithi eNingizimu Africa (mhlaka 28 June 2012).

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SA Medicines Control Council, Department of Health, Private Bag X828, PRETORIA 0001. Fax: 27 12 395 8775; Email: nkambp@health.gov.za

Ukuphila kwami, ukuphila kwethu

Africa Centre TasP Trial

PARTICIPANT SIGNATURE SHEET

RECEIVE ARV TREATMENT AND CARE

TasP ID
Clinic
Visit Date Y Y Y Y M M D D
Counsellor

Isihloko Socwaningo:

Ukuphila kwami, ukuphila kwethu - Ukuvikela ngokusetshenziswa kwemishanguzo (TasP) -Ucwaningo olwenziwa ezigodini ezingaphansi kwesifunda sakwaHlabisa lungekho uhlelo oluqondile lokukhetha abantu, KwaZulu-Natali
ANRS 12249
Uhlelo lwemithetho V2.0 - 9 January 2014
Umxhasi: ANRS - National AIDS Research Agency, Paris, France
Isikhungo esixhumanisayo: Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa
Lolucwaningo luphasiswe ikomidi elibhekelela amalungelo kwezocwaningo lwezempilo lase Nyuvesi yakwaZulu-Natali mhlaka - 2 Feb 2012 nangomhlaka 6 July 2012.

Iphepha lemvume lobambe iqhaza:

Mina, _____ sengifundisiwe/sengichazeliwe ngezifundo ezintathu (3) zakwa ART (isession yokufunda), ngokubaluleka kokuthatha amaphilisi ami ngendlela.

Ngiyaqonda ukuthi imishanguzo ayiyilaphi i-HIV kodwa uma ngiwasebenzisa ngendlela angangisiza ukuthi angigcine ngiphilile isikhathi eside. Ngiyaqonda ukuthi uma kufanele, kungenzeka nginikezwe iphilisi elisha elibizwa ngokuthiwa *i-Atripla*, eliphasiswe uMnyango wezempilo waseNingizimu Africa. Ngiyaqonda ukuthi imishanguzo eyokusetshenziswa impilo yakho yonke, futhi kuzodingeka ukuthi ngiyithathe ngendlela impilo yami yonke. Ngiyazi ukuthi imishanguzo ingadala ushintsho emzimbeni wami, futhi ingadala ukugula. Ngiyazi ukuthi njalo kuzomele ngidle imishanguzo ukuze isebenze kahle. Ngiyazi ukuthi uma ngiba nenkinga ngokudla imishanguzo ngingaxhumana nomtholampilo lapho ngingakhuluma nomhlengikazi ongangidlulisela kudokotela womtholampilo uma kunesidingo.

Ngiyaqonda ukuthi ngikhululekile ukuthi ngingashiya lolucwaningo nanomangasiphi isikhathi nokuthi ngizoqhubeka ngikwazi ukuthola usizo emtholampilo yoMnyango wezempilo. Ngiyaqonda ukuthi angikhokhi lutho ngosizo engiluthola emtholampilo wocwaningo noma engiluthola emtholampilo yoMnyango wezempilo. Isinqumo sami sokushiya ucwaningo angeke sibenomthelela omubi osizweni engilutholayo emtholampilo yoMnyango wezempilo noma ukucwaswa kobudlelwano bami nabasebenzi bocwaningo lwe-Ukuphila kwami, ukuphila kwethu noma base-Africa Centre noma ngayiphi indlela.

_____	_____	_____
Igama lobamba iqhaza (loba)	Obamba iqhaza uyasayina (Kongakwazi ukubhalo loba u X)	Usuku
_____	_____	_____
Igama lomsebenzi onikezele ngephepha lemvume (loba)	Ukusayina komsebenzi	Usuku
_____	_____	_____
Igama likafakazi (loba) *	Ufakazi uyasayina	Usuku

* Ufakazi udingeka kuphela uma obambe iqhaza engakwazi ukubhala noma ecela ukuba nofakazi.

Lolucwaningo lwenziwa ngokulandela imigomo yomhlaba ye-Good Clinical Practice in Clinical Trials futhi luphasiswe yikomidi elibhekele amalungelo kwezocwaningo lwezempilo laseNyuvesi yaKwaZulu-Natali (mhlaka 6 July 2012) nesigungu esilawula ngezemithi eNingizimu Africa (mhlaka 28 June 2012).

Imininingwane yekomidi:

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SA Medicines Control Council, Department of Health, Private Bag X828, PRETORIA 0001. Fax: 27 12 395 8775; Email: nkambp@health.gov.za

Ukuphila kwami, ukuphila kwethu

Africa Centre TasP Trial

PARTICIPANT SIGNATURE SHEET

PARTICIPATE IN CLINIC-BASED RESEARCH (INTERVENTION CLUSTERS)

TasP ID
Clinic
Visit Date Y Y Y Y M M D D
Counsellor

Isihloko Socwaningo:

Ukuphila kwami, ukuphila kwethu - Ukuvikela ngokusetshenziswa kwemishanguzo (TasP) -Ucwaningo olwenziwa ezigodini ezingaphansi kwesifunda sakwaHlabisa lungekho uhlelo oluqondile lokukhetha abantu, KwaZulu-Natali
ANRS 12249
Uhlelo lwemithetho V2.0 - 9 January 2014
Umxhasi: ANRS - National AIDS Research Agency, Paris, France
Isikhungo esixhumanisayo: Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa
Lolucwaningo luphasiswe ikomidi elibhekelela amalungelo kwezocwaningo lwezempilo lase Nyuvesi yakwaZulu-Natali mhlaka - 2 Feb 2012 nangomhlaka 6 July 2012.

Iphepha lemvume lobambe iqhaza:

Sengichazeliwe ngocwaningo olungenhla ngumaluleki oqeqeshiwe. Ngiyaqondisisa ukuthi ukubamba iqhaza kwami kulolucwaningo kungokuzikhethela kwami. Akekho namunye ongangiphoqelela ukubamba iqhaza.

Mina, _____ ngiyavuma ukuba yingxenye yocwaningo olwenziwa emitholampilo i-Africa Centre. Ngilitholile iphepha lolwazi futhi ngaliqondisisa. Ngilitholile nethuba lokubuza imibuzo mayelana nocwaningo ngathola izimpendulo futhi zayoyonke imibuzo yami.

Ngiyaqonda ukuthi kusho ukuthini ukubayingxenye yalolucwaningo, nokuthi ngingabuzwa eminye imibuzo ephathelene nesimo sami sezempilo nesimayelana nemishanguzo uma bevekashile abacwaningi. Ngiyaqonda ukuthi abasebenzi bocwaningo nabasemtholampilo bangadinga ukubuka imininingwane yami yezempilo egcinwe emtholampilo ukuphendula imibuzo mayelana ne-HIV nokwelashwa kwe-HIV. Ngiyaqonda futhi ukuthi akukho mali engizoyikhokhela ukuthola imishanguzo noma ukukhokhela usizo engiluthola emitholampilo yocwaningo noma eMnyango wezempilo.

Ngiyakuqonda ukuhlomula, ubunzima kanye nomthelela okungaba nawo emndenini wami nakimi ukuba yingxenye yalolucwaningo.

Ngiyaqinisekisa ukuthi ukubamba iqhaza kwami kungokokuzikhethela kwami futhi ngingashiya nanoma yinini lokho kungaphazamisi indlela engithola ngayo usizo kwezempilo.

Ngiyavuma kokulandelayo:

1) Ngiyavuma ukuthola imishanguzo (ARVs) enikezelwa kulo mtholampilo, okubalwa umshanguzo oyinhlanganisela obizwa ngokuthiwa *i-Atripla*, ophasiswe uMnyango wezempilo kaZwelonke. Ngiyaqonda ukuthi nginganikwa imishanguzo (*Atripla*) nganeno kwesikhathi esijwayelekile sokunikezelwa kwemishanguzo nokunakekelwa okwenziwa emitholampilo yomnyango wezempilo. Ngizoxoxisana nabasebenzi bomtholampilo ukuthola ukuthi *i-Atripla* ingumshanguzo ongangilungela yini mina. Uma ingangilungele, ngizonikezwa elinye eliyinhlanganisela elisilungele isimo sami.

2) Ngiyavuma ukuvumela abahlengikazi emtholampilo wocwaningo ukuthi bathathe isampula elincane legazi ngezinye izikhathi (njalo emva kwezinyanga ezingu-3) uma ngiza emtholampilo. Ngiyaqonda ukuthi leligazi lizosetshenziselwa ukubhekisisa ukuthi imishanguzo isebenzakanjani nokuthi umzimba wami uyakwazi yini ukuwabekezelela. Ngizoyithola imiphumela futhi ngizochazelwa ngayo.

3) Ngiyavuma ukuthi leligazi elincane elizosala uma lokhu kuhlolwa sekuqediwe lingabekwa lodwa endaweni ephephile eyisiqandisi e-laboratory yase-Africa Centre eThekwini nokuthi lingasetshenziswa esikhathini esizayo ukwenza olunye ucwaningo nge-HIV. Ngiyaqonda futh ukuthi ngaphambi kokuthi leligazi lihlolwe ososayensi bakwa-Africa Centre bazocela imvume ekomidini elibhekelene namalungelo kwezocwaningo lwezempilo lase Nyuvesi yakwaZulu-Natal.

Ngiyaqonda ukuthi ngingalushiya ucwaningo noma isiphi isikhathi futhi angeke ngicwaswe ngokwenze njalo kanti futhi nokuphathwa kwami ngabasebenzi bezempilo nabakwa Africa Centre akuzukwehluka uma ngivuma noma nginqaba ukubamba iqhaza. Ngiyaqonda futhi ukuthi alikho ilungelo lami engililahlayo ngokusayina lelifomu lemvume.

_____ Igama lobamba iqhaza (loba)	_____ Obamba iqhaza uyasayina (Kongakwazi ukubhalo loba u X)	_____ Usuku
_____ Igama lomsebenzi onikezele ngephepha lemvume (loba)	_____ Ukusayina komsebenzi	_____ Usuku
_____ Igama likafakazi (loba) *	_____ Ufakazi uyasayina	_____ Usuku

* Ufakazi udingeka kuphela uma obambe iqhaza engakwazi ukubhala noma ecela ukuba nofakazi.

Lolucwaningo lwenziwa ngokulandela imigomo yomhlaba ye-Good Clinical Practice in Clinical Trials futhi luphasiswe yikomidi elibhekele amalungelo kwezocwaningo lwezempilo laseNyuvesi yaKwaZulu-Natali (mhlaka 6 July 2012) nesigungu esilawula ngezemithi eNingizimu Africa (mhlaka 28 June 2012).

Imininingwane yekomidi:

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Ukuphila kwami, ukuphila kwethu

Africa Centre TasP Trial

PARTICIPANT SIGNATURE SHEET

PARTICIPATE IN CLINIC-BASED RESEARCH (CONTROL CLUSTERS)

CZ5
v31 Mar 2014

TasP ID
Clinic
Visit Date Y Y Y Y M M D D
Counsellor

Isihloko Socwaningo:

Ukuphila kwami, ukuphila kwethu - Ukuvikela ngokusetshenziswa kwemishanguzo (TasP) -Ucwaningo olwenziwa ezigodini ezingaphansi kwesifunda sakwaHlabisa lungekho uhlelo oluqondile lokukhetha abantu, KwaZulu-Natali
ANRS 12249
Uhlelo lwemithetho V2.0 - 9 January 2014
Umxhasi: ANRS - National AIDS Research Agency, Paris, France
Isikhungo esixhumanisayo: Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa
Lolucwaningo luphasiswe ikomidi elibhekelela amalungelo kwezocwaningo lwezempilo lase Nyuvesi yakwaZulu-Natali mhlaka - 2 Feb 2012 nangomhlaka 6 July 2012.

Iphepha lemvume lobambe iqhaza:

Sengichazeliwe ngocwaningo olungenhla ngumaluleki oqeqeshiwe. Ngiyaqondisisa ukuthi ukubamba iqhaza kwami kulolucwaningo kungokuzikhethela kwami. Akekho namunye ongangiphoqelela ukubamba iqhaza.

Mina, _____ ngiyavuma ukuba yingxenye yocwaningo olwenziwa i-Africa Centre. Ngilitholile iphepha lolwazi futhi ngaliqondisisa. Ngilitholile nethuba lokubuza imibuzo mayelana nocwaningo ngathola izimpendulo futhi zayoyonke imibuzo yami.

Ngiyaqonda ukuthi kusho ukuthini ukubayingxenye yalolucwaningo, nokuthi ngingabuzwa eminye imibuzo ephathelene nesimo sami sezempilo nesimayelana nemishanguzo uma bevakashile abacwaningi. Ngiyaqonda ukuthi abasebenzi bocwaningo nabasemtholampilo bangadinga ukubuka imininigwane yami yezempilo egcinwe emtholampilo ukuphendula imibuzo mayelana ne-HIV nokwelashwa kwe-HIV. Ngiyaqonda futhi ukuthi akukho mali engizoyikhokhela ukuthola imishanguzo noma ukukhokhela usizo engiluthola emitholampilo yocwaningo noma eMnyango wezempilo.

Ngiyakuqonda ukuhlomula, ubunzima kanye nemthelela okungaba nawo emndenini wami nakimi ukuba yingxenye yalolucwaningo.
Ngiyaqinisekisa ukuthi ukubamba iqhaza kwami kungokokuzikhethela kwami futhi ngingashiya nanoma yinini lokho kungaphazamisi indlela engithola ngayo usizo kwezempilo.

Ngiyavuma kokulandelayo:

1) Ngiyavuma ukuxoxisana nomhlengikazi wasemtholampilo mayelana nokuthi ngikulungele yini ukuthola imishanguzo (ARVs) enikezelwa kulo mtholampilo. Ngiyaqonda ukuthi lemishanguzo iyinhlanganisela ebizwa ngokuthiwa *i-Atripla* ephasiswe umnyango wezempilo. Ngizoxoxisana nabasebenzi bomtholampilo ukuthola ukuthi *i-Atripla* ingumshanguzo ongangilungela yini mina. Uma ingangilungele, ngizonikezwa elinye eliyinhlanganisela elisilungele isimo sami.

2) Uma ngingalungele ukuqala imishanguzo manje: ukuxoxisana nomhlengikazi wasemtholampilo izindlela eziyizo engingazuza ngazo ngosizo olutholakala kulomtholampilo wocwaningo. Lokhu kubala lonke usizo olujwayelekile olutholakala emtholampilo yoMnyango wezempilo.

3) Ngiyavuma ukuvumela abahlengikazi emtholampilo wocwaningo ukuthi bathathe isampula elincane legazi ngezinye izikhathi uma ngiza emtholampilo. Ngiyaqonda ukuthi leligazi lizosetshenziselwa ukubhekekisisa ukuthi imishanguzo isebenzakanjani nokuthi amasosha omzimba wami (CD4 count) ayakwazi yini ukuwabekezelela. Ngizoyithola imiphumela futhi ngizochazelwangayo.

4) Ngiyavuma ukuthi leligazi elincane elizosala uma lokhu kuhlolwa sekuqediwe lingabekwa lodwa endaweni ephephile eyisiqandisi e-laboratory yase-Africa Centre eThekwini nokuthi lingasetshenziswa esikhathini esizayo ukwenza olunye ucwaningo nge-HIV. Ngiyaqonda futhi ukuthi ngaphambi kokuthi leligazi lihlolwe ososayensi bakwa-Africa Centre bazocela imvum-e ekomidini elibhekelene namalungelo kwezocwaningo lwezempilo lase Nyuvesi yakwaZulu-Natal.

Ngiyaqonda ukuthi ngingalushiya ucwaningo noma isiphi isikhathi futhi angeke ngicwaswe ngokwenze njalo kanti futhi nokuphathwa kwami ngabasebenzi bezempilo nabakwa Africa Centre akuzukwehluka uma ngivuma noma nginqaba ukubamba iqhaza. Ngiyaqonda futhi ukuthi alikho ilungelo lami engililahlayo ngokusayina lelifomu lemvume.

_____	_____	_____
Igama lobamba iqhaza (loba)	Obamba iqhaza uyasayina (Kongakwazi ukubhalo loba u X)	Usuku
_____	_____	_____
Igama lomsebenzi onikezele ngephepha lemvume (loba)	Ukusayina komsebenzi	Usuku
_____	_____	_____
Igama likafakazi (loba) *	Ufakazi uyasayina	Usuku

* Ufakazi udingeka kuphela uma obambe iqhaza engakwazi ukubhala noma ecela ukuba nofakazi.

Lolucwaningo lwenziwa ngokulandela imigomo yomhlaba ye-Good Clinical Practice in Clinical Trials futhi luphasiswe yikomidi elibhekele amalungelo kwezocwaningo lwezempilo laseNyuvesi yaKwaZulu-Natali (mhlaka 6 July 2012) nesigungu esilawula ngezemithi eNingizimu Africa (mhlaka 28 June 2012).

Imininingwane yekomidi:

Biomedical Research Ethics Administration, University of KwaZulu-Natal, Research Office, Westville Campus, Govan Mbeki Building
Private Bag X 54001, Durban, 4000, KwaZulu-Natal. Tel: 27 31 2604769 - Fax: 27 31 2604609 - Email: BREC@ukzn.ac.za

SA Medicines Control Council, Department of Health, Private Bag X828, PRETORIA 0001. Fax: 27 12 395 8775; Email: nkambp@health.gov.za

Ukuphila kwami, ukuphila kwethu

Africa Centre TasP Trial

CZ6 m6
v16 Oct 2012

PARTICIPANT SIGNATURE SHEET

Social Science Clinic-based Interviewer-Administered Questionnaire (m6)

TasP ID
Clinic
Visit Date Y Y Y Y M M D D
Intereviewer

Isihloko Socwaningo:

Ukuphila kwami, ukuphila kwethu - Ukuvikela ngokusetshenziswa kwemishanguzo (TasP) -Ucwaningo olwenziwa ezigodini ezingaphansi kwesifunda sakwaHlabisa lungekho uhlelo oluqondile lokukhetha abantu, KwaZulu-Natali
ANRS 12249
Uhlelo lwemithetho V2.0 - 9 January 2014
Umxhasi: ANRS - National AIDS Research Agency, Paris, France
Isikhungo esixhumanisayo: Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa
Lolucwaningo luphasiswe ikomidi elibhekelela amalungelo kwezocwaningo lwezempilo lase Nyuvesi yakwaZulu-Natali nangomhlaka 26th September 2012.

Ubudala ___ iminy Uma ingaphansi kuka-18, umzali noma umbheki kumele asayine ukuvumela ingane ukuthi ibambe

_____	_____	_____
Igama lomzali /mbheki (Loba)	Ukusayina komzali / mbheki	Usuku

---

Imvume yokubamba iqhaza:

Mina, _____ ngitsheliwe mayelana nocwaningo olungenhla ngumeluleki oqeqeshiwe. Ngiyaqonda ukuthi ukubamba kwami iqhaza kulolucwaningo kungokokuzikhethela. Akekho ongangiphoqa ukuthi ngibambe iqhaza.

Mina ngiyavuma ukubamba iqhaza kulolucwaningo olwenziwa i-Africa Centre. Ngilutholile futhi ngaluqonda ulwazi olumayelana nocwaningo. Ngilitholile ithuba lokubuza imibuzo mayelana nocwaningo futhi ngazithola izimpendulo zayo yonke imibuzo yami.

Ngiyaqinisekisa ukuthi ukubamba kwami iqhaza kulolucwaningo kungokokuzikhethela ngokupheleleyo nokuthi ngingayeka noma inini ngaphandle kokubeka ukunakekelwa kwami kwezempilo engcupheni.

Ngiyakvuma ukuphendula imibuzo mayelana nami, isimo sami sezempilo, ukuthola kwami ukwelashwa kwe-HIV, ukugculiseka kwami ngokunakekelwa kwami, imibono yami kanye nenkolelo mayelana nobulili kanye nodlame, ubudlelwano bami kanye nokuzibandakanya kwami ocansini. Loku kuthatha imizuzu engu-30-40.

Ngiyazi ukuthi lokukubuzwa kuyimfihlo ngokupheleleyo futhi angeke kuze kuxoxwe nomuye umuntu osebenza ekunakekelweni kwami kulomtholampilo.

_____	_____	_____
Igama lobamba iqhaza (loba)	Obamba iqhaza uyasayina (Kongakwazi ukubhalo loba u X)	Usuku
_____	_____	_____
Igama lomsebenzi onikezele ngephepha lemvume (loba)	Ukusayina komsebenzi	Usuku
_____	_____	_____
Igama likafakazi (loba) *	Ufakazi uyasayina	Usuku

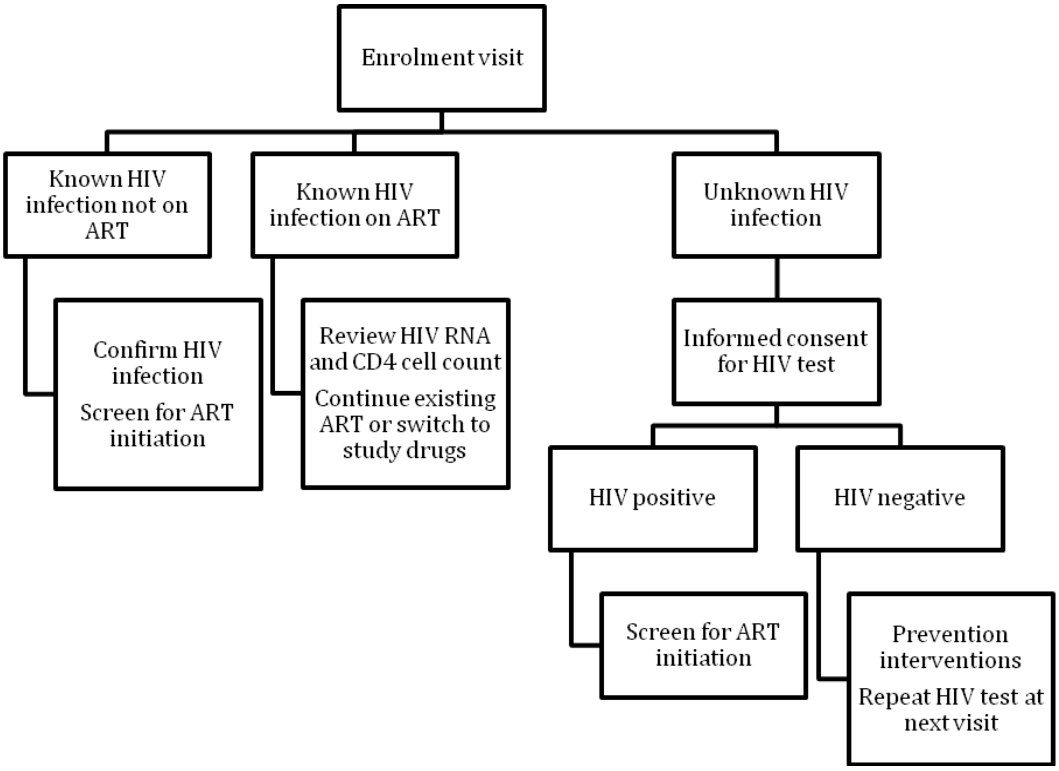
* Ufakazi udingeka kuphela uma obambe iqhaza engakwazi ukubhala noma ecela ukuba nofakazi.

Izindlela ongaxhumana ngazo nekomidi elimele indlela elungile yokwenziwa kocwaningo:

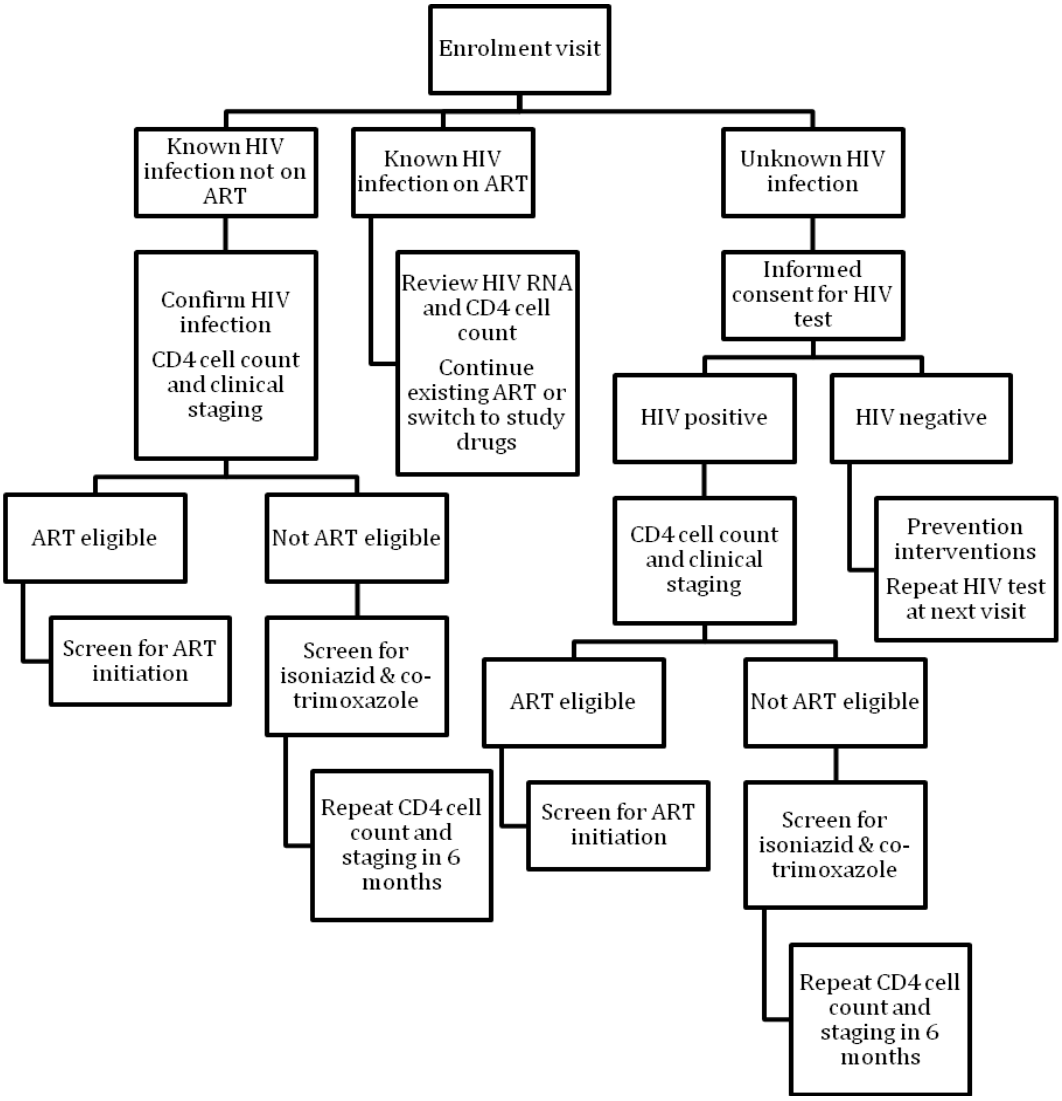
BIOMEDICAL RESEARCH ETHICS ADMINISTRATION, University of KwaZulu-Natal, Research Office, Westville Campus, Govan Mbeki Building Private Bag X 54001, Durban, 4000, KwaZulu-Natal, SOUTH AFRICA. Tel: 27 31 2604769 - Fax: 27 31 2604609 - Email: BREC@ukzn.ac.za

15.5 Appendix 5. Follow-up algorithms

15.5.1 Intervention clusters



15.5.2 Control clusters



15.6 Appendix 6. Insurance certificate

Biomedicinsure
EQUATEUR EN ASSURANCES

Parc d'Innovation Bretagne sud
C.P. 142 - 56038 VANNES CEDEX
Tel. +33(0)2 97 69 19 19
Fax +33(0)2 97 69 11 11
biomail@biomedic-insure.com

HDI GERLING
Insurance of SA Limited
P O Box 66, Saxonwold , 2132
Tel: +27 11 340 0100
Fax: +27 11 447 4981

Certificate of Insurance

Named Insured:
INSERM ANRS
101, Rue de Tolbiac
75013
PARIS

This is to certify that policies of insurance listed below have been issued to the insured named above and are in fore at this time. Notwithstanding any requirement, term or condition of any contract or other document with respect ot which this certificate may be issued or may pertain, the insurance afforded by the policies described herein is subject to all the terms exclusions and conditions of such policies

Type of Insurance	Policy-Nr.:	Expiration Date	Limits of Liability in ZAR	
	01475192-14051		Per Tested Person:	Per Trial
Clinical Trial Insurance		31.12.2016	R 1,000,000	R 30,000,000

[X] Clinical Trial in South Africa

Deductible:
R 3,000 each and every incident

Overall Insurance Limit per Trial:
R 30,000,000

All terms and conditions as per quote of: **09 January 2012**

No. of tested persons	**750**
Sponsor:	**INSERM ANRS** **101, Rue de Tolbiac** **75013** **PARIS**
Study title:	**A cluster randomised trial comparing the impact of immediate versus WHO recommendations guided ART initiation on HIV incidence The ANRS 12249 TasP (Treatment as Prevention) trial in Hlabisa Sub-district, Kwa-Zulu Natal, South Africa**
Protocol number:	**ANRS 12249**
Study duration	**10 January 2012 to 31 December 2016**

Cancellation:
Should any of the above described policies be cancelled before expiration date thereof, the issuing insurer will endeavour to mail ten days written notice to the below named certificat holder, but failure to mail such notice shall impose no obligation or liability of any kind upon the company.
This certificate is issued as a matter of information only and confers no rights upon the certificate holder. This certificate does not amend, extend or alter the coverage afforded by the policies listed above

Insurer:

HDI GERLING
HDI-Gerling Insurance of South Africa Limited
3rd Floor, 20 Baker Street, Rosebank 2196
P O Box 66, Saxonwold 2132
Telephone: +27 (0) 11 340 0100
Telefax: +27 (0) 11 447 4981
Authorised Financial Services Provider 9489
Reg No. 1998/009418/06

HDI-Gerling Insurance of South Africa Ltd

Name and Address of Certificate Holder:

To whom it may concern

15.7 Appendix 7. UKZN Biomedical Research Ethics Committee approval letter

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI

RESEARCH OFFICE
BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 260-4609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx

06 July 2012

Prof. M-L Newell
Africa Centre for Health & Population Studies
Mtubatuba
3935

Dear Prof Newell

PROTOCOL: A cluster randomised trial to evaluate the effectiveness of antiretroviral treatment immediately on HIV diagnosis on reducing HIV incidence: the Treatment as Prevention trial in Hlabisa sub-district, rural KwaZulu-Natal. REF: BFC104/11

The Biomedical Research Ethics Committee (BREC) has considered the abovementioned application.

The study was provisionally approved by a sub-committee of the Biomedical Research Ethics Committee on 02 February 2012 pending a response from the Medicine Controls Council. Your responses dated 29 June 2012 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 06 July 2012.

This approval is valid for one year from **06 July 2012.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The following Committee members were present at the meeting that took place on 13 December 2011:

Professor Doug Wassenaar. Chair
Professor Viren Rambiritch, Pharmacology
Professor Steven Collings, Psychiatry
Dr R Govender, Family Medicine
Dr Tim Hardcastle, Surgery - Trauma
Dr Z Khumalo - KZN Health (External)
Professor Dennis Pudifin, Medicine
Professor Chris Rout, Department of Anaesthesia
Dr Divendra Singh, Department of Anaesthesia
Professor Joyce Tsoka-Gwegweni, School of Medicine
Mrs T Makhanya, External
Professor Rajendra Bhimma - Paediatrics & Child Health
Professor Anne Coutsoudis - Paediatrics & Child Health
Professor Jerome Singh - Legal Representative

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

PROFESSOR D R WASSENAAR
Chair: Biomedical Research Ethics Committee