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, KwaZulu-Natal, South Africa

ANRS 12249 TasP Protocol
version 1.2 • 8 March 2012
phase 1 (2011-2013) and phase 2 (2013-2016)

Modification from the Version 1.1 dated 03/06/2011:
Approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal for the control clusters on 02/02/2012.
Granted full approval by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal on 06/07/2012.

Registration number in http://clinicaltrials.gov: NCT01509508
Registration number in the South African National Trial Register: DOH-27-0512-3074

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**Agence Nationale de Recherches sur le Sida et les hépatites virales - ANRS**

**Director:** Prof. Jean-François Delfraissy

**Atripla® to be used in the trial will be provided by Merck & Co.**
Abstract

Title: A cluster randomised trial comparing the impact of immediate versus WHO recommendations guided ART initiation on HIV incidence. The ANRS 121249 TasP (Treatment as Prevention) trial in Hlabisa sub-district, KwaZulu-Natal, South Africa

Background: More than twenty-five 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 (SA).

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 over a period of 24 months.

Setting: The trial will be conducted in Hlabisa sub-district, Umkhanyakude district, Northern KwaZulu-Natal, SA. This rural setting of 1430 km² 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 end 2010, about 15,000 HIV-infected people eligible for treatment had been initiated on ART; patients’ treatment eligibility is determined by SA guidelines.

Design: A cluster-randomised trial with 2×17 clusters will be conducted within the Hlabisa sub-district, covering a total population of 42 500 inhabitants aged 16 years and above, of whom an estimated 34 000 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 regular (first 6 months, then 4 months) 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. Current funding from ANRS is restricted to the first phase (of 24 months) during which the trial will take place in four (2×2) clusters, with three rounds (6 months, 4 and 4 months) of home-based testing and
surveillance according to the trial protocol, but which 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 30 clusters. Possible amendments to the trial 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 will be included in 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. Pregnant women in the first trimester and those trying to conceive will be offered the choice to substitute EFV to nevirapine (NVP) or Lopinavir/ritonavir. Participants with pre-existing chronic kidney disease (creatinine clearance <50ml/min) will be provided with zidovudine (ZDV) rather than TDF and the drug dosage will be adapted when appropriate (as per current SA guidelines).

**Follow-up:** The treatment and follow-up period for HIV-infected patients is 24 months. During the first phase, follow-up will be curtailed 24 months after the start of the trial, which means patients will be treated between 7 and 19 months.

**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 24 months 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 over 14 months of follow-up; 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 will take place over six years (2011-2016). The first phase will take 24 months, with a planning stage (September 2011 – February 2012), enrolment in the first four (2×2) clusters in a six-month period (March – August 2012 inclusive), two consecutive rounds of testing of four months each (September 2012 – April 2013). Data analysis and review of results will be performed during 2013 to inform decision-making regarding process and procedures in the expanded trial.

Sample size: A fully parameterised, deterministic mathematical model demonstrates that a 30% reduction in cumulative HIV incidence (5% versus 3.5%) in HIV-negative participants over two years should be feasible across a wide range of parameter space. Sample size calculations indicate that 34 clusters (17 in each arm), with 1 250 consenting participants >15 years of age in each cluster (N=42 500; 34 000 HIV-negative), are required to achieve this objective. The first phase will be conducted on 5 000 participants in four 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 OMS sur l'incidence du VIH. L’essai ANRS 12129 TASP (traitement par la prévention) dans le sous-district de Hlabisa, KwaZulu-Natal, Afrique du Sud.

Contexte : Vingt-cinq 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 sur 24 mois.


Méthodologie : Un essai randomisé en grappes (« clusters ») sera conduit dans le sous-district de Hlabisa au sein de 2x16 grappes comprenant un total de 42 500 individus âgés de plus de 15 ans, 34 000 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. Le financement par l’ANRS ne concerne que la première phase de l’étude (24 mois) qui sera conduite dans quatre (2×2) grappes : trois cycles de dépistage à domicile (de 6, 4 et 4 mois) seront conduits, toutes les procédures du protocole seront mises en œuvre mais 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 30 autres grappes. 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 combinerà le tenofovir (TDF) + l’emtricitabine (FTC) + l’efavirenz (EFV) en une prise par jour. Les femmes dans leur premier trimestre de grossesse et celles désirant concevoir pourront remplacer l’EFV par la Névirapine (NVP) ou le Lopinavir/ritonavir (LVR/r). Pour les individus souffrant de maladie chronique du rein (clearance de la créatinine <50ml/min) le TDF sera remplacé par la Zidovudine (ZDV), selon les recommandations sud-africaines.

Suivi : La durée de traitement et de suivi pour les patients infectés par le VIH est 24 mois. Durant la première phase, la période de suivi stoppant 24 mois après le début de l’essai, les patients seront suivis entre 7 et 19 mois.

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 données 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 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’événements
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 après 14 mois de suivi chez les personnes séronégatives et 11 mois en moyenne chez les personnes séropositives 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.


**Taille de l’échantillon** : Un modèle mathématique déterministe et entièrement paramétré a montré la faisabilité sur deux ans d’une réduction de 30% de l’incidence cumulée du VIH (5% vs.3.5%) au sein de participants séronégatifs. Les calculs de taille d’échantillon suggèrent que 34 grappes (17 dans chaque bras) comprenant 1 250 participants de plus de 15 ans dans chaque grappe (N=42 500, 34 000 personnes séronégatives au début de l’essai) sont nécessaires pour répondre à cet objectif. La première phase portera sur 5 000 personnes dans quatre 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.
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<table>
<thead>
<tr>
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<th>Definition</th>
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<tr>
<td>3TC</td>
<td>Lamivudine</td>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>ANRS</td>
<td>Agence Nationale de Recherches sur le SIDA et les hépatites virales</td>
</tr>
<tr>
<td>ART</td>
<td>AntiRetroviral Treatment</td>
</tr>
<tr>
<td>ARV</td>
<td>AntiRetroViral (drug)</td>
</tr>
<tr>
<td>bd</td>
<td>Twice daily</td>
</tr>
<tr>
<td>BIA</td>
<td>Budget Impact Analysis</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CAB</td>
<td>Community Advisory Board</td>
</tr>
<tr>
<td>CAR</td>
<td>Clinic Activity Report</td>
</tr>
<tr>
<td>CAP</td>
<td>Consumer Advisory Panel</td>
</tr>
<tr>
<td>CBC</td>
<td>Clinic Baseline Visit (Counsellor) questionnaire</td>
</tr>
<tr>
<td>CEA</td>
<td>Cost-Effectiveness Evaluation</td>
</tr>
<tr>
<td>CFU</td>
<td>Clinic Follow-Up (Counsellor) questionnaire</td>
</tr>
<tr>
<td>CHE</td>
<td>Clinic History and Examination questionnaire</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>d4T</td>
<td>Stavudine</td>
</tr>
<tr>
<td>DBS</td>
<td>Dried Blood Spot</td>
</tr>
<tr>
<td>DoH</td>
<td>Department of Health</td>
</tr>
<tr>
<td>DSA</td>
<td>Demographic Surveillance Area</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
</tr>
<tr>
<td>EFV</td>
<td>Efavirenz</td>
</tr>
<tr>
<td>FDC</td>
<td>Fixed-Dose Combination</td>
</tr>
<tr>
<td>FTC</td>
<td>Emtricitabine</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practices</td>
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</table>
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
IQ1-IQ3  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
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>QALY</td>
<td>Quality-Adjusted Life Years</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Clinical Trial</td>
</tr>
<tr>
<td>SA</td>
<td>South Africa</td>
</tr>
<tr>
<td>SAB</td>
<td>Scientific Advisory Board</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SC</td>
<td>Steering Committee</td>
</tr>
<tr>
<td>SCB</td>
<td>Social Science Clinic-based Baseline questionnaire</td>
</tr>
<tr>
<td>SCC</td>
<td>Social Science Clinic-based Counsellor-administered questionnaire</td>
</tr>
<tr>
<td>SCI</td>
<td>Social Science Clinic-based Interviewer-administered questionnaire</td>
</tr>
<tr>
<td>SCS</td>
<td>Social Science Clinic-based Survey (SCB + SCC + SCI)</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>STI</td>
<td>Sexually Transmitted Infection</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TDF</td>
<td>Tenofovir disoproxyl fumarate</td>
</tr>
<tr>
<td>THR</td>
<td>TasP Household registration questionnaire</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>VCT</td>
<td>Voluntary Counselling and Testing (HIV)</td>
</tr>
<tr>
<td>VL</td>
<td>Viral Load (HIV plasma RNA measurement)</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization (Switzerland)</td>
</tr>
<tr>
<td>XDR TB</td>
<td>Extensively Drug-Resistant Tuberculosis</td>
</tr>
<tr>
<td>ZDV</td>
<td>Zidovudine</td>
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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, with limited numbers in KZN having been circumcised to date (Personal communication, Jan 2011, Dr Kevi Naidu). 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 recently publicised preliminary results of the NIH-sponsored trial HPTN 052 (clinicaltrials.gov identifier NCT00074581) show that ART reduces by 96% transmission 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/mm³ 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). Furthermore, it is recommended that pregnant women not yet eligible for ART should either receive Zidovudine (ZDV) monotherapy from the start of the second trimester of pregnancy and single dose Nevirapine (NVP) during labour and delivery (option A) or HAART combination therapy (option B) for the prevention of mother-to-child transmission of HIV (PMTCT). Breastfed infants should then receive NVP post-exposure prophylaxis during the breastfeeding period up to one year (option A) whereas breastfeeding women receiving option B up to delivery should continue to receive HAART throughout the breastfeeding period. In formulating these recommendations high value was placed on avoiding deaths, disease progression and likely HIV transmission (19). The 2010 SA guidelines were amended in August 2011 to broaden treatment eligibility to start at 350 CD4 cells for all HIV infected people, those with WHO stage 3 or 4 disease and those with multi-drug resistant or extensively-resistant tuberculosis (MDR or XDR TB) (see Appendix 15.1 and 15.2).

Although the shift towards widening the ART indications has been substantial since the previous 2006 guidelines, two clinical trials are already 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). It is likely that the results of these trials, which are not expected to yield early results before the end of 2012, will broaden ART indications to improve individual benefits even further.

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 (20).

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 (21, 22), have led to the development of other innovative forms of HIV testing such as mobile clinics that take testing services to people. In 2006 WHO and UNAIDS put forward the concept of Provider-Initiated Testing and Counselling (PITC) (23). PITC is defined as 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 etc. PITC has been established in some settings including the TB clinics in the Hlabisa HIV Treatment and Care programme (see section 2.3) with very high levels (90%) of uptake. PICT has also been evaluated in the Africa Centre’s mobile clinic and home-based VCT programme, the latter being particularly popular, and is being evaluated in other programmes elsewhere (24-26).

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 in order to reach the goal of 15 million people tested by mid-2011 (AFP, 11 March 2010). 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?

A recently published report of results from 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” (27). Two accompanying commentaries addressed how and whether this was feasible to deliver in the ‘real world’ (28, 29). 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). More recently, 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 (30). 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).
The available evidence for the choice of the appropriate study medication is reviewed in Appendix 15.3. An Atripla®-like regimen (efavirenz [EFV] 600 mg / tenofovir disoproxyl fumarate [TDF] 300 mg / emtricitabine [FTC] 300 mg once daily preferably in fixed-doses combinations (FDC) is clearly a suitable candidate for the purpose of this protocol, and in line with the current SA first-line regimen.

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” (30).

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

Randomised controlled trials are the gold standard for establishing the efficacy of a health intervention. In the Treatment as Prevention (TasP) trial the primary outcome to be compared does not involve the subjects who receive the intervention, but rather their sexual contacts. Conventional individual randomization of individuals would necessitate tracing all their sexual contacts, an option which is not realistic. A less sophisticated approach would consist of a simple comparison of HIV incidence, before and after expansion of an ART programme. However, many other factors besides introduction of treatment may change from "before" to "after", introducing bias and incorrect attributions of causality to any observed change in incidence. Hence the choice of a cluster-randomised trial as the best design for TasP, further discussed below.

We provided in section 1.1 a summary of the growing evidence, from observational data and mathematical modelling, for the potential of ART to prevent HIV transmission at the population level. However, what is lacking is a randomised trial in an appropriate population under ‘real-life’ circumstances 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 90% of new HIV infections occur.

TasP will be a cluster-randomised controlled trial (RCT), with communities used as the units for randomisation. The cluster randomized design is considered the gold standard to investigate the effect of public health interventions delivered at the community level (31). Furthermore, the highest degree of scientific evidence will be required to inform public health decisions on this matter and non-randomized studies would not meet the criteria.
that are now required in the formulation of public health recommendations and guidelines (32).

Given the high incidence of HIV in the proposed trial population (33) and the recently-demonstrated high uptake of voluntary counselling and testing (ML Newell personal communication) this represents a unique opportunity to test the efficacy of this intervention in a real-world situation using a gold-standard approach. Further in a study that measures HIV transmission, an individual-based trial is clearly not appropriate. A discordant couples design was discussed but was not considered suitable given the high levels of sexual partnership concurrency in the area - 26% among males on average and exceeding 70% among males in some communities (34). This would bias the result of any couple-based intervention towards the null hypothesis. In other word, the cluster design is chosen to minimize the contamination when clusters coincide with predominant sexual networks (35). A cluster-randomized design also leverages the key strengths (already outlined in Appendix 15.4 of the proposal) of the Africa Centre vital to the successful implementation of a trial of this size. These include (but are not limited to) the Africa Centre demographic information system (containing a wealth of social, demographic, behavioural and geographical data on local communities in the sub-district collected for over a decade), the existing community engagement structures and excellent community relations as well as theAfrica Centre’s geographical information system - one of the most comprehensive in Africa.

1.4 Trial phases

The investment of both financial and human resources to prepare and conduct a cluster-randomized trial is substantial. Furthermore, there are uncertainties in designing the trial interventions and applying them to half of the clusters. We will thus proceed in a two-phase approach:

- The first phase will be conducted in a selected number of clusters (n=4, approx. ⅛th of total sample size, 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), funding may be sought specifically for implementation of the protocol in the remaining clusters (n=30, 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 km² 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
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 971,556 individuals estimated to have been receiving ART in December 2009 (36). 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 (37). There remains, however, a large unmet need for treatment, with an estimated coverage in mid-2008 of approximately 40% of those eligible for treatment (38), although this varies across districts.

The delivery of ART in the public sector is guided by the Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment and the National Antiretroviral Treatment (39, 40). Until early 2010, HIV-infected adults were eligible for ART if CD4 cell count <200 cells/mm³ 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/mm³, and in August 2011 these guidelines were further extended to eligibility starting at 350 for all HIV infected people in addition to those with WHO stage 3 or 4 disease or those with MDR or XDR TB (see Appendix 15.2).

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 (41). 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 40,000 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 (41).

Programmatic outcomes have been examined and published and are comparable with other programmes in sub-Saharan Africa. For individuals on ART, retention in care at one year was 84.0% and mortality in the first year was 10.9% (42). Retention in care for HIV-infected individuals prior to ART eligibility was relatively poor with fewer than 50% returning for CD4 monitoring within one year (43).

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. Appendix 15.4 provides detailed information about the Africa Centre, its infrastructure and presents some recent relevant research findings. 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 proposed 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 proposed trial area contains eight of the 17 fixed primary health care clinics in the sub-district.

Among activities relevant to the present proposal, the Africa Centre provides reliable estimates of the local HIV prevalence across Hlabisa sub-district as summarized in Figure 2. These estimates are informed by the data from the HIV surveillance in the Africa Centre DSA (bottom corner under the blue rivers line), and data from antenatal clinics (from the HIV treatment data base – number of pregnant women tested per clinic, and number found to be HIV positive at antenatal test). We used a validated geographic information system (GIS) model of travel time to clinic (44) to divide the sub-district into discrete clinic catchment areas. For the six clinics in the surveillance area (where we have detailed data available), we then used a Poisson regression to analyse the relationship between antenatal prevalence and population-based prevalence (for each clinic's catchment population) in 2008. We also incorporated distance to nearest primary or secondary road (log-transformed) as an additional predictor variable. We then used the coefficients from this relationship to predict population-based prevalence in the clinic catchments that were located outside the surveillance area. Estimates of numbers of individuals infected were obtained using a detailed demographic and GIS dataset obtained in 1999 (45) projecting the numbers forward to 2008 based on the growth rate observed in the surveillance area over the same period.
The research of the Africa Centre in terms of demographic surveillance (population studies) and treatment and care (clinical studies) are supported by an evolving programme of social and behavioural science studies (see www.africacentre.com). The main focus is on the development and evaluation of biomedical and structural interventions targeting neglected and hard-to-reach groups within the local population (e.g. men, youth, orphans and vulnerable children). Recently, the Africa Centre has begun an exploratory study to examine the acceptability of different modes of providing HIV testing and community education requirements in advance of the large-scale community trial such as the one being proposed here.
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 WHO guidelines, on the reduction in incidence of new HIV infections in the general population in the same setting over a period of 24 months.

3.1.2 Specific objectives

Among all participants

- To compare the acceptability and feasibility over a 24 month period 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 over 24 months of follow-up 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, over 24 months of follow-up 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 of first phase

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.

Among all participants

- To estimate the acceptability and feasibility over a 14 months period 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 over a 7-19 months follow-up period (see section 7.3.2)
- To estimate HIV testing experience, ART knowledge and perception, self-reported adherence to ART, quality of life, over a 7-19 months follow-up period (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 over 14 months in the four 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 necessary, after a year in the field in a limited number of clusters, 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). Funding will be provided by the ANRS as the trial sponsor.

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=5000) and a limited number of clusters (2×2, see section 8).

Within these 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 7-19 months depending on the time of entry in the trial (first or third HIV testing rounds, see Figure 4).

Trial outcomes of the first phase (see section 7) will be measured after one year of follow-up on average and presented to the SAB and DSMB.

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), funding may be sought specifically for implementation of the protocol in the remaining clusters (n=30, see section 8) in the second phase.

Four HIV testing rounds of six months each will then be conducted in all 30 clusters. HIV-infected participants will be followed for 24 months and at the end of the trial, will be transferred to the Hlabisa ART programme.

All trial outcomes will be measured at 24 months.

4.2 Trial timelines
Figure 3 summarises the timeline of the overall trial, first and second phase.
Figure 3
Timeline for the overall TasP trial
4.2.1 First phase (24 months, 2011-2013)

- September 2011 – February 2012: Preparation of the trial, recruitment and training of staff, logistics, ethics application, liaison with Department of Health.
- March – August 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.).
- September 2012 – April 2013: Two further rounds of HIV testing of four months each
- April to August 2013: 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 up to the 24 months planned for each individual (see section 6.4).

Figure 4 summarises the timeline for the first phase of the trial.

**Figure 4**
Timeline for the first phase of the ANRS 12249 TasP trial

4.2.2 Second phase (2013-2016)

- Preparation of the trial in the 30 new clusters (three months)
- Enrolment in the 30 (2×15) clusters (six months) and follow-up (24 months to achieve incidence outcome) in the 34 clusters
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 5 below.

**Figure 5**
Description of the different components of the TasP trial

<table>
<thead>
<tr>
<th>Cluster randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 Control Clusters</td>
</tr>
<tr>
<td>17 Intervention Clusters</td>
</tr>
</tbody>
</table>

- **Component 1: test**
  - HIV testing
  - Prevention services
  - 21 250 pers. (17 000 HIV neg.)
  - Phase 1: 2 500 pers. (2 000 HIV neg.)

- **Component 2: treat**
  - ARV treatment according to WHO guidelines
  - 2 125 HIV pos. individuals treated
  - Phase 1: 250 HIV pos. individuals treated

- **Component 1: test**
  - HIV testing
  - Prevention services
  - 21 250 pers. (17 000 HIV neg.)
  - Phase 1: 2 500 pers. (2 000 HIV neg.)

- **Component 2: treat**
  - “Immediate ARV treatment regardless of CD4 counts
  - 4 250 HIV pos. individuals treated
  - Phase 1: 500 HIV pos. individuals treated

* expected number of subjects within the 34 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 WHO guidelines will be offered ART.
6. Trial conduct

6.1 Preparing the community

A detailed community entry, education and trial promotion strategy that builds on the Africa Centre’s extensive community engagement programme will be finalized based on the preparatory field work 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.

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 (Figure 6).

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 1) complete the Tasp home-based individual questionnaire (IQ1), see section 7.4.1, and/or anonymous sampling of blood for HIV surveillance, and/or 2) undergo confidential HIV counselling and testing (see section 6.2.2 below). Individual
household members may participate to the trial by agreeing to either component alone (the individual questionnaire and/or HIV testing) or both components together (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 IQ1 is described section 7.4.1 and Table 7.

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).

In subsequent rounds the same procedures will apply, and the counsellors will not know who has tested in the earlier rounds. All participants will be offered repeat HIV testing and asked to complete the follow-up TasP home-based individual questionnaires (IQ2 and IQ3) (see section 7.4.1 and Table 7).

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 multiple visits each year (i.e. twice in the first year of the trial and then three times in each year of follow-up) 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 used will be G-ocean, and the confirmatory test will be Determine. 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.

HIV-infected participants will all be referred to the trial clinic for further assessment as to their treatment eligibility (see section 6.4 below).

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 SA guidelines at the DoH clinics and other facilities.

Figure 6 summarises the home-based procedures at each round of testing.
6.2.3 Referral 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 clinic to confirm a participant’s correct identity and their correct service eligibility (i.e. treatment, care and prevention or VCT and prevention).

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

Rates of male circumcision among participants in the Africa Centre’s HIV surveillance are low. 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. The plan involves the setting up of mobile surgical facilities (in ‘camps’) where the procedure is performed by a trained physician 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. Male circumcision is also available from private medical practitioners in the area and is covered by some employees’ medical-aids schemes.

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. Any reported symptom will prompt referral to the nearest fixed primary health care clinic for syndromic treatment, as per SA policy – this will be facilitated with a standardised referral form. 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 (D-15)

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 (within two weeks – 15 days of diagnosis). 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 new 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 2). 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 the pre-assessment visit, at D-15, to review this pre-therapeutic assessment and, if indicated, initiate treatment at M0.

In both clusters, patients refusing ART will be asked to consent to 6-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. Participants choosing to continue follow-up from their normal provider will be asked to consent to 6-monthly reviews and to provide permission for additional clinical information obtained from their provider to be used in the trial. 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% sample by week block. During these times, samples collected from patients attending the clinics for 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 as per the 2010 WHO guidelines (18), and in line with the August 2011 amendment to the SA (see Appendix 15.2) if:

- CD4 count ≤ 350 cells/mm3 irrespective of clinical symptoms
- WHO clinical stage 3 or 4 irrespective of CD4 count
- MDR or XDR TB

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 summarized in appendix 15.1.

The standard first-line drug regimen for HIV-infected participants, will be in both arms the fixed drug combination (FDC) Tenofovir (TDF – 245 mg) + Emtricitabine (FTC – 200 mg) + Efavirenz (EFV – 600 mg) or Atripla® once daily.
The trial treatment will be adapted for participants with the following conditions (specificities to be developed in the trial procedures):

- Chronic kidney disease (creatinine clearance < 50 ml/min): ZDV will be given rather than TDF (see appendix 15.1) and the drug dosage will be adapted when appropriate.
- Tuberculosis co-infection at time of treatment initiation: TB treatment to be started approximately 2 weeks prior to ARV initiation, as per standard South African TB/HIV guidelines
- Ongoing first line treatment failure: ZDV + 3TC + LPV/r (see appendix 15.1)
- Ongoing first line treatment using d4t: patients should remain so if they are happy and stable on d4T, however should they find it difficult to adhere then they will be offered to gradually switch to TDF-based regimen (possibly using Atripla®)
- Pregnant women and women willing to conceive: substitute NVP (or LPV/r if CD4 ≥ 250) for EFV

Table 1

<table>
<thead>
<tr>
<th>Clinical indication</th>
<th>Antiretroviral drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard first-line regimen</td>
<td>TDF + FTC + EFV (Atripla)</td>
</tr>
<tr>
<td>Renal impairment (CrCl &lt; 50ml/min)</td>
<td>AZT (substitute for TDF)</td>
</tr>
<tr>
<td>Tuberculosis co-infection at ARV initiation</td>
<td>ARV to be initiated approximately 2 weeks after anti-TB treatment initiation</td>
</tr>
<tr>
<td>Pregnant first trimester or no reliable contraception &amp; CD4 &lt; 250</td>
<td>NVP (substitute for EFV)</td>
</tr>
<tr>
<td>Pregnant first trimester or no reliable contraception &amp; CD4 ≥ 250</td>
<td>LPVr (substitute for EFV)</td>
</tr>
<tr>
<td>Standard second-line regimen*</td>
<td>AZT + 3TC + LPVr</td>
</tr>
<tr>
<td>Second-line regimen (HBV co-infected)</td>
<td>AZT + 3TC + TDF + LPVr</td>
</tr>
</tbody>
</table>

The following drugs will be available from the KwaZulu-Natal Provincial Department of Health if a treatment adaptation is needed:

- Tenofovir (TDF): 245 mg od
- Lamivudine (3TC): 300mg od
- Efavirenz (EFV): 600 mg nocte
- Nevirapine (NVP): 200 mg od (14 days) then bd
- Zidovudine (AZT): 300 mg bd

6.4.3.2 Supply

During the first phase, and for the full 24 months follow-up period of all HIV-infected participants, Atripla® will be provided by MSD. All other drugs will be provided by the KwaZulu-Natal Provincial Department of Health according to the standard of care.

By the time the second phase of the trial begins, it is likely that Atripla® will be approved as a first-line drug in the South African public sector. If not, arrangements will be made to secure provision of the drug until completion of the trial.
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 throughout the trial. 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 (M0)

ART initiation will take place at M0, ideally within four weeks of HIV testing OR 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 15.7 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 M0 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 24 months, from M0 to M24 (see Table 1).

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.

During the first phase, all HIV-infected participants will be followed-up between 7 and 19 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 24 months within the second phase.
6.4.4.3 ART follow-up visits (M1 to M24)

- **Participants receiving ART**
  Participants receiving ART will be reviewed by the trial nurse monthly when they collect their medication. Assessments will include the following as indicated in Table 1:

  **Clinical evaluation (monthly)**
  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, M18 and M24 (counting from entry into care), regarding specific topics according to visits (see Table 2). 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 2 is presented the distribution of topics to be asked either by the counsellor or interviewer.
Table 2
Topics of Social science clinic-based survey, by questionnaire

<table>
<thead>
<tr>
<th>Topic</th>
<th>Baseline†</th>
<th>M6</th>
<th>M12</th>
<th>M18</th>
<th>M24</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing experience</td>
<td>C</td>
<td></td>
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<td></td>
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<tr>
<td>Economic situation</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Health expenditures</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>ART perception and decision</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Disclosure and couple</td>
<td>C</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Social and community support</td>
<td>C</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
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<tr>
<td>ART knowledge</td>
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<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
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<tr>
<td>Sexual behaviour</td>
<td></td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Self-reported adherence to ART*</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>HIV Quality of Life</td>
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<td>I</td>
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<td>I</td>
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<tr>
<td>Stigma and discrimination</td>
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<td>I</td>
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<tr>
<td>Satisfaction with care</td>
<td></td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
</tbody>
</table>

C: counsellor-administered questionnaire;  
I: independent interviewer-administered questionnaire;  
† D-15 to M0;  
* 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 SA treatment guidelines, see section 7.3.2.5)
- Objective, technical (monthly): pill count
- Objective, biological (quarterly): viral load plus resistance test in case of 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 assessment (M3, M6, M12, M18, M24)

Viral Load will be taken at 3 months after initiation and then 6-monthly to identify adherence issues and instigate adherence support where needed (Table 3). CD4 will be assessed six-monthly (point of care). The other laboratory tests and schedules are presented in Table 3.

Other screening (monthly as required):

Sputum will be collected for TB investigation (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 2).
- 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.

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

Participants on ART who prefer to remain within the Hlabisa HIV treatment and care programme will be asked permission to be assessed by the trial nurse as per trial protocol (trial nurses will attend the nearest fixed clinic once a week). The relevant data will be collected from these patients to complete the trial CRFs (CHE, CFU).

6.4.4.4 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.
### Table 3: Follow-up calendar for HIV-infected participants eligible to ART

#### Consent
- M0

#### Medical history
- M0

#### Nurse
- Physical examination
  - M1, M2, M3, M4, M5, M6, M7, M8, M9, M10, M11, M12, M13, M14, M15, M16, M17, M18, M19, M20, M21, M22, M23, M24
- Weight, height
  - M0
- WHO clinical staging
  - M0
- Morbidity/hospitalization
  - M0
- TB/STI screening (if appropriate)
  - M0
- CD4 point of care
  - M0
- ART initiation
  - M0

#### Adherence monitoring
- M0

#### Laboratory
- HIV VL
  - M0
- Genotyping
  - as clinically indicated, in case of confirmed virological failure
- CD4 counts (quality control)
  - M0
- Haematology
  - M0
- Biochemistry (U&Es, LFTs)
  - M0
- HBsAg
  - M0
- Beta hCG
  - M0
- Urinalysis
  - M0
- Plasma storage (-80°C)
  - M0
- Blood volume (ml)

#### Clinic-based survey
- HIV testing experience
  - M0
- ART perception, decision
  - M0
- Disclosure and couple
  - M0
- Social and community support
  - M0
- Stigma and discrimination
  - M0
- Health expenditure
  - M0
- Economic situation
  - M0
- Sexual behaviour
  - M0
- ART knowledge
  - M0
- Self-reported ART adherence
  - M0
- HIV quality of life
  - M0
- Satisfaction with care
  - M0

**Note:** The same pattern of follow-up for HIV-infected participants will be replicated within the second phase of the trial.

**TB:** Tuberculosis; **STI:** Sexually Transmitted Infections; **ART:** Antiretroviral Treatment; **VL:** Viral Load; **U&Es:** Urea and Electrolytes test; **LFT:** Liver function tests.
Table 4
Follow-up calendar of HIV-infected participants not eligible for ART

<table>
<thead>
<tr>
<th></th>
<th>M0</th>
<th>M6</th>
<th>M12</th>
<th>M18</th>
<th>M24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent</td>
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<tr>
<td>Medical history</td>
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<td><strong>Nurse</strong></td>
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<td>Physical examination</td>
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<td>Weight, height</td>
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<tr>
<td>WHO clinical staging</td>
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<td>Morbidity/hospi</td>
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<td>TB/STI screening if appropriate</td>
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<tr>
<td>CD4 point of care</td>
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<td><strong>Laboratory</strong></td>
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<tr>
<td>Beta hCG</td>
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<tr>
<td><strong>Clinic-based survey</strong></td>
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<tr>
<td>HIV testing experience</td>
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<td>ART perception</td>
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<td>Disclosure and couple</td>
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<td>Social and community support</td>
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<td>Stigma and discrimination</td>
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<td>Health expenditure</td>
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<td>Economic situation</td>
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<td>Sexual behaviour</td>
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<td>ART knowledge</td>
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<td>HIV quality of life</td>
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<tr>
<td>Satisfaction with care</td>
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</tbody>
</table>

M0 = date of entry into care
TB: Tuberculosis; STI: Sexually Transmitted Infections; ART: Antiretroviral Treatment
Note: the same pattern of follow-up for HIV-infected participants will be replicated within the second phase of the trial.

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. Pregnant women in the first trimester and women trying to conceive will be offered the choice to substitute NVP (or LPV/r if CD4 ≥ 250) for EFV. This strategy will be adapted should international and national guidelines evolve.
6.4.5.2 Toxicity and treatment failure

In case of toxicity or intolerance, single drug substitutions will be allowed, as per SA guidelines (46). 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 three months apart (as per current SA national guidelines) (46). 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 SA 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 15.5).

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/mm³.
- Multivitamins (1 tablet od) supplementation will be provided to HIV-infected participants on ART in the intervention and control clusters as per SA 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 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, M18, M24) according to the schedule presented table 1

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 4 clusters for the first phase within 34 clusters during the overall trial.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition, indicators</th>
<th>Comparison</th>
<th>Tool</th>
<th>See</th>
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</thead>
<tbody>
<tr>
<td><strong>General population level</strong></td>
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<tr>
<td>HIV incidence</td>
<td>* Results of DBS, molecular epidemiology findings (clusters), primary resistance</td>
<td>IC vs.CC</td>
<td>IQ</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>* Results of cBED during first phase only</td>
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<tr>
<td></td>
<td>* Incidence estimates corrected by socio-demographic characteristics</td>
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<tr>
<td>Acceptability of initial HIV counselling and testing</td>
<td>* HIV testing history at baseline</td>
<td>IC vs.CC</td>
<td>IQ</td>
<td>7.3.1.1</td>
</tr>
<tr>
<td></td>
<td>* Attitudes towards HIV testing at baseline and at 12 months</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>* Different estimates of coverage/uptake of HIV testing per method of calculation, per round and according to time interval</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>* Social determinants of HIV testing uptake at individual and community levels (at baseline then cumulative and/or at 12 months)</td>
<td></td>
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<tr>
<td>Prevention practices</td>
<td>* Circumcision uptake over time</td>
<td>IC vs.CC</td>
<td>IQ</td>
<td>7.3.1.2</td>
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<tr>
<td></td>
<td>* Contraceptive use and pregnancies over time</td>
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<tr>
<td>Sexual behaviours</td>
<td>* Sexual partnerships patterns over time, dishinhibition</td>
<td>IC vs.CC</td>
<td>IQ, SCS</td>
<td>7.3.1.2</td>
</tr>
<tr>
<td></td>
<td>* Safe sex and condom use over time</td>
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<tr>
<td></td>
<td>* Conjugal relationships (disclosure, unions, communication)</td>
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<tr>
<td>Quality of life</td>
<td>* Quality of life at baseline and over time</td>
<td>IC vs.CC</td>
<td>IQ, SCS, CAP, IDI</td>
<td>7.3.1.3</td>
</tr>
<tr>
<td>Household health care expenditures</td>
<td>* Cost analysis</td>
<td>IC vs.CC</td>
<td>THR, HHI, IQ, SCS, CRF</td>
<td>7.3.1.4</td>
</tr>
<tr>
<td>Treatment/care cost and cost-effectiveness</td>
<td>* Economic impact of HIV infection on the household welfare (health care use and health care expenditures)</td>
<td></td>
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<tr>
<td></td>
<td>* Budget impact</td>
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<tr>
<td>Community awareness</td>
<td>* Stigma toward PLWHA, perception of stigma</td>
<td>IC vs.CC</td>
<td>IQ, SCS, IDI</td>
<td>7.3.1.5</td>
</tr>
<tr>
<td></td>
<td>* Perception about ART preventing HIV infection</td>
<td></td>
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<tr>
<td>Outcome</td>
<td>Definition, indicators</td>
<td>Comparison</td>
<td>Tool</td>
<td>See</td>
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<td>----------------------------------------------</td>
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<tr>
<td><strong>HIV-infected participants</strong></td>
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<tr>
<td>Acceptability / uptake entry into care</td>
<td>* Expectations and perceptions of early treatment over time</td>
<td>IC vs.CC</td>
<td>IQ, HHI, CRF, SCS, CAR</td>
<td>7.3.2.1</td>
</tr>
<tr>
<td></td>
<td>* Knowledge of HIV care and treatment</td>
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<td></td>
<td>* Time to initiation of treatment</td>
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<tr>
<td></td>
<td>* Modalities of entry into care (health structures used)</td>
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<tr>
<td></td>
<td>* Socio-cultural and economic determinants of entry into care</td>
<td></td>
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<tr>
<td>Therapeutic success</td>
<td>* Patterns of retention and referral over time and their determinants</td>
<td>IC vs.CC</td>
<td>SCS, CRA</td>
<td>7.3.2.2</td>
</tr>
<tr>
<td>Programme retention</td>
<td>* Patterns of retention and referral over time and their determinants</td>
<td>IC vs.CC</td>
<td>SCS, CRA</td>
<td>7.3.2.3</td>
</tr>
<tr>
<td>Morbidity, mortality and treatment</td>
<td>* Mortality and severe morbidity (leading to hospitalization)</td>
<td>IC vs.CC</td>
<td>CRF, SCS, IQ</td>
<td>7.3.2.4</td>
</tr>
<tr>
<td></td>
<td>* Tuberculosis (incidence)</td>
<td></td>
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<tr>
<td></td>
<td>* Other morbidity events (infectious or not) by CD4 strata</td>
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<tr>
<td></td>
<td>* Immunological and virological response</td>
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<tr>
<td></td>
<td>* Socio-economic determinants of response to treatment</td>
<td></td>
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<tr>
<td></td>
<td>* First-line treatment, durability, switches to second-line treatment, adverse events leading to drug discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>* Hepatitis B co-infection</td>
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<tr>
<td>Adherence to ART</td>
<td>* Estimates, patterns and measurement of adherence over time</td>
<td>IC vs.CC</td>
<td>CRF, SCS, IDI, CAP</td>
<td>7.3.2.5</td>
</tr>
<tr>
<td></td>
<td>* Determinants of adherence by CD4 strata</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquired HIV drug resistance</td>
<td>* Prevalence and incidence of acquired and transmitted drug resistance</td>
<td>IC vs.CC</td>
<td>CRF</td>
<td>7.3.2.7</td>
</tr>
<tr>
<td>Virological failure</td>
<td>* Persistent VL &gt; 1000 copies/ml</td>
<td>IC vs.CC</td>
<td>CRF</td>
<td>6.4.5.2</td>
</tr>
<tr>
<td>Toxicity</td>
<td>* Monitoring of renal dysfunction (TDF), liver function (NVP), teratogenicity (EFV)</td>
<td>IC vs.CC</td>
<td>CRF</td>
<td>6.4.5.2</td>
</tr>
<tr>
<td>Vertically-acquired HIV infection</td>
<td>* Uptake of PMTCT intervention(s) and relation with care program</td>
<td>IC vs.CC</td>
<td>CRF</td>
<td>7.3.2.6</td>
</tr>
<tr>
<td></td>
<td>* Pregnancy outcomes with Efavirenz first-line ART and transmission</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>* Overall HIV paediatric testing/treatment patterns in sample</td>
<td></td>
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</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition, indicators</th>
<th>Comparison</th>
<th>Tool</th>
<th>See</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health care system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experience of care</td>
<td>* Training and experience in HIV care, working conditions, practices and knowledge about ART management</td>
<td>IC vs.CC</td>
<td>SCS, SS CAR</td>
<td>7.5.1</td>
</tr>
<tr>
<td>Characterisation of health facilities and activity</td>
<td>* Type of health services, clientele, human resources, working times, technical equipment, HIV-care organization &lt;br&gt; * Unit costs of the resources used</td>
<td>IC vs.CC</td>
<td>CAR, SS</td>
<td>7.4.3</td>
</tr>
<tr>
<td>Budget impact</td>
<td>* Impact of TasP (level of coverage, rate of ART switches, drug prices) on health care system</td>
<td>IC vs.CC</td>
<td>CAR, THR, IQ, HHI, SCS</td>
<td>7.5.2</td>
</tr>
</tbody>
</table>

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) <br>CAR: Clinic Activity Report; SS: Specific Survey.

### 7.2 Primary outcome

HIV incidence over a 24 months period (14 months for the first phase) will be measured using two approaches:

**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, i.e. during three HIV testing rounds between baseline and 18 months. HIV testing will follow the standard South Africa DBS protocols used in the Africa Centre population-based HIV surveillance in past years (47). For the first phase of the trial, the duration of the three testing rounds will be six, then four and four 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.

**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 (48) and is thus an appropriate measure of HIV incidence at baseline for a community randomized control trial. Moreover, some of the calibration problems encountered in applications of the BED assay in other settings (49), 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 24 months follow-up

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 measurement are planned for at M0 (i.e. date of entry into care for treatment ineligible patients and any of the pre-treatment visits for ART-eligible participants), M6, M12, M18 and M24 (see Table 3 and Table 4). A quality of life module will be designed using standardised validated instruments appropriate to the context and culture of the participant population. Candidate scales for possible consideration are:
  - 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 (50). 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 (51). 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 (52). This face-to-face questionnaire includes 33 items regarding the occurrence of different events which may have happened 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 (53, 54). This instrument has been found to discriminate between different health states amongst PLWHA and has been validated in isiZulu formats (55, 56).

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 IQ2 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-pocket 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 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 IQ1, IQ2 and IQ3 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 and 24 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.

All events included in the secondary outcomes must be reported in both the intervention and control clusters for the duration of the trial. All events will be reported immediately after a working diagnosis of the event has been made according to the locally-used clinical procedures.

7.3.2.5 Adherence

Adherence will be measured three monthly after enrolment (i.e. at M3, M6, M9, M12, M15, M18, M21, M24) 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 (Chaiyachati et al. 2011). This tool, using visual analogue scale, pill identification test and pill count, will be included in CRF and CFU questionnaires.

However, as non-adherence was rarely reported and as the questions used performed poorly in identifying patients with treatment failure (Chaiyachati et al. 2011), we will test an additional scale constructed to limit both recall and social desirability bias and which has been tested in different settings (Boyer et al. 2011; Carrieri et al. 2001; Chesney et al. 2000; Spire et al. 2008). 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 (Carrieri et al. 2001) 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 (Oyugi et al. 2007) and has already been tested in another context (Boyer et al. 2011). This second measure of ART adherence will be surveyed each 6 months (i.e. at M6, M12, M18 and M24) and included in the Social science clinic-based interviewer-administered questionnaire (SCI).

7.3.2.6 Pediatric 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 recently 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 (60).

In the trial intervention clusters all HIV-infected women will be on ART irrespective of the CD4 count or the clinical stage; those who wish to become pregnant or become pregnant whilst on HAART will be switched to a regimen that is known to have no teratogenic properties as per WHO guidelines. In the control clusters, women who are not yet eligible for HAART will be managed according to the best available PMTCT guidelines approved by the SA national authorities (currently option A has per WHO guidelines for the pregnant women – antepartum AZT as early as 14 weeks of gestation + single-dose NVP at the onset of labour – and their offspring – daily NVP from birth until a minimum of four weeks and until one week after all exposure to breast milk has ended). Women in the control clusters will be managed in the primary health care clinics as per routine PMTCT guidelines by the DoH.

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. Any vertically infected infant will be referred to the Hlabisa HIV Treatment and Care Programme (61) for initiation of HAART in line with current SA paediatric guidelines.

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 three 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.

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).

The exact format of survey instruments in the second phase will depend on results and experience in the first phase and are thus not described here.
Table 7
Data collection during the HIV testing rounds, among the general population: Household and individual questionnaires (first phase of the trial)

<table>
<thead>
<tr>
<th>Table 7</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Home-based Household questionnaire</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household head verbal consent</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Household composition and socio-economic characteristics</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Changes in household composition (including in-out migrations/mortality/newly eligible)</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>Home-based Individual questionnaire</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual consent for questionnaire</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Knowledge/beliefs about HIV infection</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Knowledge/expectations about treatment</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Lifetime HIV testing history</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>HIV testing attitudes/beliefs</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Uptake of testing opportunities</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Self-reported knowledge of HIV status</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Disclosure of HIV status</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Sexual partnerships</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Condom use</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Contraceptive use</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Circumcision status</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Risk behaviours (alcohol etc.)</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Stigma towards PLWHA</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Health care use</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Health care expenditure</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>Home-based HIV testing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual consent for DBS and/or HIV testing</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>DBS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Home HIV counselling and testing (rapid test)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

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 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), M6, M12, M18 and M24 visits as illustrated in Table 2. 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 a baseline (CBC) and follow up CRF (CFU) to be completed by the counsellors and a combined history and clinical examination CRF (CHE) 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 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. These key intermediate, logistical outcomes of the first phase can then feed directly into the delivery of the second phase.

### 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 convened 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 (62, 63). Such factors have been shown to have an impact on human performance and may jeopardize quality of care, as well as HIV treatment delivery (64).

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 (65). 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 and Figure 7). Randomisation will occur at the start of the first phase.

The trial area consists of 211 local areas (neighbourhoods). These were aggregated into 48 clusters of between one and six contiguous neighbourhoods comprising an average of 1250 individuals >15 years of age. Clusters were designed to encompass social networks based on earlier studies in the DSA (38), 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 (>9km² in area). This meant that the number of individuals in peri-urban clusters were larger than their rural counterparts. The sample size calculations demonstrated that 34 clusters of 1250 participants were required (see section 8.2.6 below). Therefore, 34 contiguous communities bordering the Africa Centre’s surveillance area will be included in the trial.

Adjacent communities representing relatively distinct social and sexual networks were grouped together to form the units of randomization (median population ≥15 = 1450; median area = 19 km²). 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 (31). 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 4300 participants ≥15 years of age and median size of 48 km². 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 km². Extrapolating from these results, we are confident that only a very small proportion of trial participants will have sexual partners outside these ‘super-clusters’ (median size=48 km²). 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. As outlined in section 8.2.6 below however, contamination was taken into account in our original sample size calculations by mathematical modelling using conservative assumptions.

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

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† 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 (66. Tanser F, Lesueur D, Solarsh G, Wilkinson D. HIV heterogeneity and proximity of homestead to roads in rural South Africa: an exploration using a geographical information system. Trop Med Int Health. 2000 Jan;5(1):40-6.).
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 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).

For the first phase, four (2×2) clusters will be selected at random from the full randomisation list of 34 clusters. These clusters will however have to meet the following criteria; two rural and two peri-urban clusters, two adjacent intervention and two adjacent control clusters (to constitute “super clusters”), areas of differing HIV prevalence, clusters that are relatively close to the Africa Centre. The distribution of the remaining 28 clusters between, the intervention and control arms will remain confidential until the end of the first phase.

### 8.2 Modelling exercise and sample size calculation

#### 8.2.1 Principles of the model

We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) International model to project TasP trial outcomes for the two trial arms. The CEPAC International model is a state-transition, Monte Carlo simulation of HIV disease, screening and treatment. Details regarding the model structure have been previously described (67-69). Model output included the relative difference in cumulative HIV incidence, HIV prevalence, and the cumulative risk of mortality and active TB in HIV-infected participants in the intervention arm compared to the control arm at two years.

We used sensitivity analyses to examine the stability of results and to identify input parameters that had the greatest impact on the difference in cumulative HIV incidence at two years.

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ii Note: This research was funded by the National Institute of Allergy and Infectious Diseases (R01 AI058736) and the Agence Nationale de Recherches sur le SIDA et les hépatites virales (ANRS 12136, ANRS 12212).
8.2.2 Model input parameters

Model input parameters were derived from Africa Centre data when possible (Table 8).

Table 8
Base case model input parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base case value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV prevalence at trial start</td>
<td>20%</td>
<td>Welz et al., AIDS 2007 (70)</td>
</tr>
<tr>
<td>Prior diagnosis and ART in prevalent participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed, already on ART</td>
<td>20.0%</td>
<td>Cooke et al, BMC 2010 (71)</td>
</tr>
<tr>
<td>Diagnosed, not yet on ART</td>
<td>33.3%</td>
<td>Houlihan et al., IJE 2010 (41)</td>
</tr>
<tr>
<td>Undiagnosed</td>
<td>46.7%</td>
<td>Calculated</td>
</tr>
<tr>
<td>Age at baseline, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed, already on ART</td>
<td>35 (10) years</td>
<td>Houlihan et al., IJE 2010 (41)</td>
</tr>
<tr>
<td>Diagnosed, not yet on ART</td>
<td>30 (10) years</td>
<td>Houlihan et al., IJE 2010 (41)</td>
</tr>
<tr>
<td>Undiagnosed</td>
<td>30 (10) years</td>
<td>Assumption</td>
</tr>
<tr>
<td>Initial CD4 of prevalent participants, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed, already on ART</td>
<td>278 (146) cells/μL</td>
<td>Mutevedzi et al., Bull WHO 2010 (42)</td>
</tr>
<tr>
<td>Diagnosed, not yet on ART</td>
<td>401 (190) cells/μL</td>
<td>Houlihan et al., IJE 2010 (41)</td>
</tr>
<tr>
<td>Undiagnosed</td>
<td>372 (199) cells/μL</td>
<td>Model initialization</td>
</tr>
<tr>
<td>Internal migration*</td>
<td>0.0%</td>
<td>Assumption</td>
</tr>
<tr>
<td>HIV screening performance with each round of testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV test offer</td>
<td>89.8%</td>
<td>Tanser et al., IJE 2008 (72)</td>
</tr>
<tr>
<td>Test acceptance (among those offered)</td>
<td>38.2%</td>
<td>Tanser et al., IJE 2008 (72)</td>
</tr>
<tr>
<td>Linkage to care upon diagnosis (among those accepting the test)</td>
<td>72.0%</td>
<td>Houlihan et al., IJE 2010 (41)</td>
</tr>
<tr>
<td>ART efficacy, 1st and 2nd line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA suppression at 24 weeks</td>
<td>80.4%**</td>
<td>Touré et al., AIDS 2008 (73)</td>
</tr>
<tr>
<td>Treatment failure after 24 weeks</td>
<td>15.6/100 PY</td>
<td>Touré et al., AIDS 2008 (73)</td>
</tr>
<tr>
<td>Loss to follow-up on ART</td>
<td>3.7%/year</td>
<td>Mutevedzi et al., Bull WHO 2010 (42)</td>
</tr>
<tr>
<td>Secondary HIV transmission (index case)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary infection</td>
<td>67.8/100 PY</td>
<td>Wawer et al., JID 2005 (74)</td>
</tr>
<tr>
<td>Chronic infection, by HIV RNA</td>
<td>0.16 – 9.03/100 PY</td>
<td>Attia et al., AIDS 2009 (11)</td>
</tr>
</tbody>
</table>

* Internal migration is defined as mixing between the intervention and control clusters. This could result from relocation from one type of cluster to another or from sexual mixing between clusters of different types. We used weighted averages of model outcomes to estimate the impact of internal migration in sensitivity analyses.

** Consistent with Mutevedzi et al., Bull WHO 2010 (42) and Barth et al., Lancet Infect Dis 2010 (75)
8.2.3 Base case results

Compared to the control arm, the intervention arm resulted in a 47.2% decrease in cumulative HIV incidence at two years as well as a 3.7% decrease in HIV prevalence, a 34.3% decrease in the cumulative risk of mortality in HIV-infected patients, and a 15.9% decrease in the cumulative risk of active TB in HIV-infected patients.

8.2.4 One-way sensitivity analyses

We used one-way sensitivity analyses to identify the changes in model input parameters that would result in a decrease in cumulative HIV incidence at two years of less than 47.2%. These included:

- Decreases in the mean initial CD4 of prevalent participants who were undiagnosed or diagnosed but not yet on ART before the trial start;
- Decreases in the percentage of trial participants diagnosed before the trial start;
- Decreases in the probability of test acceptance and of linkage to care upon HIV diagnosis;
- Increases in internal migration between the control and intervention clusters;
- Earlier initiation of ART in the control arm (based on 2009 WHO guidelines not yet implemented in SA).

Table 9 shows results for these parameter changes. Changes in other parameters (the mean initial CD4 of prevalent patients who are diagnosed and already on ART, rates of background HIV testing [e.g., client-initiated screening or screening in patients with symptoms], the ART failure rate, the probability of loss to follow-up on ART, and absolute levels of transmission risk by HIV RNA) had little impact on the difference in cumulative HIV incidence at two years in the intervention arm compared to the control arm.

Table 9
Base case results and selected one-way sensitivity analyses

<table>
<thead>
<tr>
<th></th>
<th>% Δ in cumulative HIV incidence at two years (intervention vs. control arm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>-47.2</td>
</tr>
<tr>
<td>Sensitivity analyses</td>
<td></td>
</tr>
<tr>
<td>Initial CD4 of undiagnosed, prevalent participants decreased by 50%</td>
<td>-36.4</td>
</tr>
<tr>
<td>Initial CD4 of diagnosed, prevalent participants not yet on ART decreased by 50%</td>
<td>-35.4</td>
</tr>
<tr>
<td>Percentage of prevalent participants diagnosed before trial start decreased by 50%</td>
<td>-40.8</td>
</tr>
<tr>
<td>Probability of test acceptance decreased to 10%</td>
<td>-38.1</td>
</tr>
<tr>
<td>Probability of linkage to care upon diagnosis decreased to 10%</td>
<td>-36.5</td>
</tr>
<tr>
<td>Internal migration increased to 20%</td>
<td>-31.3</td>
</tr>
<tr>
<td>ART in the control arm initiated at CD4 ≤ 350/μL or with stage III-IV disease</td>
<td>-35.0</td>
</tr>
</tbody>
</table>
Table 10

<table>
<thead>
<tr>
<th>Probability of linkage to care upon HIV diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
</tr>
<tr>
<td>100%</td>
</tr>
<tr>
<td>90%</td>
</tr>
<tr>
<td>80%</td>
</tr>
<tr>
<td>70%</td>
</tr>
<tr>
<td>60%</td>
</tr>
<tr>
<td>50%</td>
</tr>
<tr>
<td>40%</td>
</tr>
<tr>
<td>30%</td>
</tr>
<tr>
<td>20%</td>
</tr>
<tr>
<td>10%</td>
</tr>
</tbody>
</table>

*The 20% internal migration scenario is presented here as an extreme situation for the purpose of exploring the model.*

### Methodological and statistical considerations

**TasP ANRS 12249 Protocol**

- **Table 10** Relative decrease in cumulative incidence at two years in the intervention arm compared to the control arm as a function of 4 key model input parameters: 1) Test acceptance, 2) Linkage to care upon HIV diagnosis, 3) Internal migration, and 4) ART initiation criteria in the control arm.
8.2.5 Multi-way sensitivity analyses

We used multi-way sensitivity analyses to identify combinations of parameter values for test acceptance, linkage to care upon HIV diagnosis, internal migration, and ART initiation criteria in the control arm that would lead to decreases in cumulative HIV incidence of at least 30% in the intervention arm compared to the control arm. These combinations are highlighted in green in Table 10.

8.2.6 Sample size calculation based on model assumptions

The base case scenario of this modelling exercise is helpful to understand the two-year possible effect of the TasP intervention and favours its field testing in this population. Sensitivity analyses confirm this finding in most scenarios. Longer-term effects have not been explored; while they could lead to different results, they are likely to be dependent on those achieved in the first two years.

In summary, a fully parameterised, deterministic mathematical model demonstrates that a 30% reduction in cumulative HIV incidence (3.5 versus 5%) in HIV-negative participants over two years should be feasible across a wide range of parameter space.

Underlying statistical parameters to derive from these assumptions a sample size calculation are as follows: a 90% power to detect this difference, an alpha-type-one error of 5% (two-tailed) and an allowance of 20% of trial participants lost to follow up. We assume also a coefficient of variation of 0.25 to account for within-group variation between clusters. The cluster size variability correction was not included in the calculation because the clusters were designed to be of approximately equal population size. Sample size calculations using the recommended formula for cluster sampling (31) indicate that 34 clusters (17 in each arm), with 1 250 participants 16 years or older in each cluster (N=42 500, including 34 000 HIV-negative), are required to achieve this objective.

We acknowledge that even with the design we have proposed which will reduce inter-arm contamination (due to migration) to an absolute minimum, contamination can never be eliminated altogether. For this reason to inform our sample size calculations we explicitly incorporated parameters around inter-arm contamination into the model. For example, using a one-way sensitivity analysis, our model predicts that >30% reduction in cumulative HIV incidence could still be achieved with 20% of trial participants either having partners in communities in the other arm of trial (or outside of the trial area for communities in the intervention arm) or migrating between arms. This figure of 20% represents an extreme scenario and the real value is likely to be considerably less than this. It is worth noting here that if a TasP-like public health programme was to be rolled out across the country, there would still be considerable heterogeneity in levels of coverage of treatment and thus the design as outlined in the protocol is close to a real-world test of the hypothesis. Further, because detailed sexual behaviour data (including location of partner) will be collected as part of the trial, we will be able to control for this in the secondary analyses. Finally, contamination should lead to an underestimation of the effect of the intervention (higher incidence than expected in intervention groups and lower incidence than expected in control groups in the hypothesis that the intervention is effective). Therefore, any demonstration of the efficacy of the intervention will give the lower bound of its effect.

The calculations in terms of HIV-infected participants put on treatment are as follows. Each cluster has 1 400 adults, of whom 1 250 (80%) are estimated to consent to trial participation. Of these 1 250, an estimated 250 (20%) will be HIV-infected.
During the first phase, the 4 pilot clusters will comprise 1 000 HIV-infected participants:

- 500 in control communities of whom 250 would be eligible for treatment according to the current SA guidelines of 350 CD4 cells (Note: based on the information from the Hlabisa Treatment programme, it is estimated that 50% of HIV-infected individuals will have a CD4 count below 350)
- 500 in intervention clusters of whom 250 would be eligible according to the SA guidelines and 250 would fall outside the national guidelines but will be offered treatment within the trial

So in the context of a full treatment coverage, with a 100% acceptance of treatment, a total of 750 patients will be on treatment within the first phase of the trial, 500 who would be eligible and another 250 who would not yet be eligible as per SA guidelines.

For the full trial, within 34 clusters, among the 42 500 participants, an estimated 8500 will be HIV-infected. A total of 6375 patients will be on treatment (4250 who would be eligible and 2125 who would not be eligible yet as per SA guidelines).

Of note, the current uptake of treatment among all HIV-infected participants in the surveillance area has been measured at 21% (71). We can assume therefore that 20% of all HIV-infected participants in the trial area are already on treatment.

- In the control arm, 850 (20%) of the 4250 HIV-infected participants are already on treatment and an additional 1275 would need to be put on treatment because they are eligible.
- In the intervention arm, 850 of the 4250 HIV-infected participants are already on treatment and another 3400 would need to be put on treatment because they are HIV-infected.

Thus during the entire course of the trial, an estimated $6375 - 1700 (8500 \times 20\%) = 4675$ patients will initiate treatment (including $2125 > 350$ in the intervention clusters).

### 8.3 Randomization

Randomisation will be performed by the trial statisticians (F. Tanser, R. Thiebaut). Random numbers will be computer generated for all 32 communities in the trial area using MapInfo 10.0. Communities will be randomly allocated in equal measure to control and intervention communities (16:16). To minimise the degree of between-cluster variation, communities will be stratified on the basis of predicted HIV prevalence. Randomisation will be carried out within each stratum to derive an equal number of control and intervention communities per stratum. Figure 7 shows an example of such a randomisation. By chance, contiguous communities randomised to the same arm of the trial will ‘cluster’ together. In this example, groupings of contiguous communities (randomised to the same arm of the trial) have a median of 4 300 people >15 years of age. These larger groupings of communities further reduce the potential for inter-arm contamination in the trial population.
8.4 Plan of analysis

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

The first phase aims to evaluate acceptability and feasibility of the trial. Criteria for discontinuation have been defined according to the modelling work performed in preparation of this trial. The key parameters modifying the impact of the intervention are: prevalence of undiagnosed HIV infection, HIV incidence, CD4 level of HIV-infected participants who are undiagnosed or diagnosed but not yet on ART, ART initiation criteria in the control arm, migration, test acceptance and the linkage to care. The last three parameters are those associated with the intervention. Simulations from the model show the impact of the variation of those parameters. For example, with an internal migration rate of 15% and a test acceptance above 40%, the rate of patients treated after a
positive testing should be above 10% to allow a decrease of more than 30% of the cumulative incidence at two years. We thus provide the thresholds for deciding whether the trial should continue (in addition to feasibility and acceptability) based on the probability of reaching the main outcome defined as a decrease of 30% or more of the 2-year cumulative HIV incidence.

The following criteria apply for not continuing from the first to the second phase:

a) 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.

We will use the model developed in collaboration with Ken Freedberg’s group (Massachusetts General Hospital, Boston, USA) in preparation for the TasP protocol to evaluate the power of the TasP trial. The model has informed the design of the trial and sample size calculations. We will update the parameter assumptions with information collected during the first phase to determine the feasibility of the full TasP trial. 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).

b) 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 (76). 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 (77). 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 (78) 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.

With regard to the randomization, strata will be defined on the basis of predicted HIV prevalence (see Figure 2 page28). Clusters will be stratified according to 5% prevalence intervals (<15, 15-20, 20-25, >25). With regard to the sample size calculation, clustering was taken into account by the coefficient of variation (=0.25), the value of which was based on the values used in other randomized trials in Africa with HIV incidence as the outcome measure (79). This coefficient of variation is necessarily conservative. For instance, a coefficient of variation of 0.2 would have led to 30 000 population (24 clusters) needed. By stratifying on the basis of estimated HIV prevalence, we expect to minimize inter-arm variation in HIV incidence. The sample size calculation is very conservative and will be further adjusted on the basis of the results of the first phase of the trial. 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: (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:

- 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


iii 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.
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 anytime 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 / Study Steering Group

All SAE will be reported to the UKZN Biomedical Research Ethics Committee, the trial DMSB, Study Steering group 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 8 below summarises the trial oversight organisation.

Figure 8
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 Principal 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 two project leaders (one in South Africa and one in France), the local trial coordinator and any relevant participants to discuss specific issues. The CT undertakes the day-to-day 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 leaders.
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 is composed as follows:

**Chair:**
- Professor Patrick YENI

**Members:**
- Mr Nathan FORD (NGO representative)
- Professor Hakima HIMMICH (Infectious Disease)
- Professor Papa SALIF SOW (Infectious Disease)
- Professor Helen Weiss (Biostatistics)

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. The SAB is composed as follows (preliminary list, to be updated):

**Chair:**
- Professor Bernard HIRSCHEL

**Members of the study:**
- BARNIGHAUSEN Till
- CALMY Alexandra
- DABIS François
- IMRIE John
- IWUJI Collins
- LERT France
- MOATTI Jean-Paul
- NEWELL Marie Louise
- ORNE-GLIEMANN Joanna
- TANSER Frank

**International experts:**
- ANGLARET Xavier - Université de Bordeaux II, France; **Epidemiology - Methodology**
- COOVADIA Hoosen - Durban, KwaZulu-Natal, South Africa; **Clinic**
- GIRAUDEAU Bruno - Inserm, Tours, France; **Biostatistics**
- GORNA Robin - International AIDS Society, Switzerland; **Public Health - Social sciences**
- GRANICH Reuben - OMS, Genève, Switzerland; **Institutional representative**
- MOLINA Jean-Michel - Hôpital Saint-Louis, Paris, France; **Clinic**
- MORRIS Lynn - Cape Town, South Africa; **Virology**
- VENTER François - Durban, KwaZulu-Natal, South Africa; **Clinic**
- Dr ZUNGU Sibongile - Johannesburg, South Africa; **Institutional representative**

**Community representatives** (non-voting members):
- FLEUTELOT Eric - Sidaction, France
- GOEMAERE Eric - MSF, Johannesburg, South Africa
Sponsor representatives (non-voting members):
- BAZIN Brigitte
- DIALLO Alpha
- REKACEWICZ Claire

Pharmaceutical company representative (non-voting member):
- Representative from MSD and GILEAD, which will provide drugs for the trial, are invited to attend the SAB as observer.

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 feedback 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 will be submitted for approval to the Biomedical Research Ethics Committee of the University of KwaZulu-Natal and for health authorities’ authorisation. The KwaZulu-Natal Department of Health in South Africa.

The final version of this protocol will be approved and signed by the two Coordinating Investigators and the Sponsor (cf. signatures on page 1). It will be also signed by all the investigators participating in the trial as listed on page 2 (the ANRS 12249 TasP Trial Team) before its implementation (see Appendix 15.8).

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 15.5).

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 15.6), 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 15.6. 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.

The table of correspondence (only in paper form) will be kept under lock and key by the principal investigator (South). 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 (principal investigators, ANRS trial monitors, DSMB statistician) at the discretion of the trial principal 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. 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 principal 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 15.9.
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 leaders. Only the coordinating investigators, the project leaders 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. Any member of the Study Steering Group from South Africa (Africa Centre), France (INSERM U897/ISPED, INSERM U108, INSERM U912, CEPED UMR196, EA 3620), Switzerland (Hôpital Cantonal) and USA (CEPAC and Massachusetts General Hospital) 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 them 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 followed included or persons 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 and funder is ANRS (“The French National Agency for Aids and Viral Hepatitis Research (ANRS) is the sponsor and funder of the trial phase I.”);
- the source of funding if co-financing and/or if different from the sponsoring;
- the pharmaceutical company which provided drugs (“Trial conducted with the support of MERCK & Co. Inc and Gilead Sciences.”).
14. References


50. Duracinsky M, A.C., Lalanne C, Hermann S, Lau L, Lecoeur S, et al., editors. Differences in Heath-related Quality of life (HRQL) measured by the PROQOL-HIV, a new specific instrument developed across cultures. 5th IAS Conference on HIV Pathogenesis Treatment and Prevention; 2009; Cape Town, South Africa.


15. Appendices

15.1 Appendix 1. Summary of National Department of Health Adult HIV management guidelines (2010)

First-line drug regimens
- TDF + 3TC/FTC + EFV
- TDF + 3TC/FTC + NVP
- ZDV + 3TC + EFV
- ZDV + 3TC + NVP

NVP preferred for pregnant women, women of child-bearing age not on reliable contraception, and patients on psychoactive drugs

ZDV to be used if contra-indication to TDF (creatinine clearance < 50ml/min)

TB co-infection
- First-line regimen should be EFV-based
- ART should be initiated as soon as patient is tolerating their TB therapy. Ideally within 2-4 weeks
- If on LPV/r, dose should be doubled to 800/200mg (4 tabs) twice daily

Criteria for switch to second-line regimen
- Virological failure defined as viral load >1000 copies/ml on two occasions at least 3 months apart, despite good adherence and intensive adherence support

Second-line drug regimens
- ZDV + 3TC + LPV/r (if failed on TDF-based regimen)
- TDF + 3TC + LPV/r (if failed on AZT or d4T-based regimen)

If HBsAg positive, continue TDF (i.e. ZDV + TDF + 3TC + LPV/r)
ATV/r can be substituted for LPV/r if uncontrolled diabetes mellitus, hypercholesterolaemia, or severe GI intolerance of LPV/r

Co-trimoxazole
- Indicated if CD4 count ≤ 200 cells/mm³ or stage II, III or IV disease
- Dosage 800/160 mg (2 tablets) once daily
- Continued until CD4 > 200 cells/mm³

Isoniazid preventive therapy
- Indicated in all patients with no TB symptoms or signs, regardless of ART use
- Tuberculin skin test not required
- Includes pregnant women and participants with past history of TB treatment
- Contraindicated if active liver disease or alcohol misuse
- Adult dosage 5 mg/kg (max. 300 mg) for 6 months
- Pyridoxine 25 mg once daily should be prescribed
15.2 Appendix 2. Revised National Department of Health Adult HIV eligibility criteria (2011)
15.3 Appendix 3. 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 WHO guidelines (2009) and SA guidelines (2010 – amended 2011) suggests initiating ART when the CD4 cell count falls below the 350 cells / mm³ 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 (80). 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 (81).

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 Registryiv 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

iv APR: http://www.apregistry.com/index.htm
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 (82).

As the main limitation for a wider use of EFV in resource-limited settings is the fact that about 60% of patients are female and in child-bearing age, this information of EFV-pregnancy tolerability is critical.

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. A revision of the pregnancy indication for use of EFV is in revision by the International AIDS Society.

Additionally, the pregnancy rate in South Africa (including Hlabisa district) is low and contraceptive are well accepted and taken.

- **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 (83). It is therefore essential that drug supply is not interrupted and adherence ensured.

- **Availability**

There is no patent protection for EFV or for 3TC in India. TDF patent decision by the Indian patent office is still pending. Atripla® is already included in the EML established in 2007 by WHO. Of note, South Africa is changing its first line ART regimen in 2010 to this Atripla-like combination but not in FDC.

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 (84). 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 (85). 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.
15.4 Appendix 4. Overview of the Africa Centre for Health and Population Studies

The Africa Centre Demographic Information System (ACDIS)

ACDIS is the most comprehensive demographic surveillance system in Africa and was established to ‘describe the demographic, social and health impact of the HIV epidemic in a population going through the health transition’ and to monitor the impact of intervention strategies on the epidemic. South Africa’s political and economic history has resulted in highly mobile urban and rural populations, coupled with complex, fluid households. In order to successfully monitor the epidemic it was necessary to collect longitudinal demographic data (e.g. mortality, fertility, migration) on the population and to mirror this complex social reality within the design of the demographic information system. To this end, three primary subjects are observed longitudinally in ACDIS: physical structures (e.g. homesteads, clinics and schools), households and individuals. The information about these subjects, and all related information, is stored in a single MS-SQL Server database, in a truly longitudinal way - i.e. not as a series of cross-sections.
Figure 9
Map showing the location of the demographic surveillance area (DSA) within the Hlabisa sub-district of the Umkanyakude district of KwaZulu-Natal

The surveillance area (Figure 9) is located near the market town of Mtubatuba in the Umkanyakude district of KwaZulu-Natal. The area 438 km² in size and includes a population of approximately 90,000 people who are members of approximately 11,000 households. The population is almost exclusively Zulu-speaking. The area is typical of many rural areas of South Africa in that while predominantly rural, it contains an urban township and informal peri-urban settlements. The area is characterized by large variations in population densities (20-3000 people per km²). In the rural areas, homesteads are scattered rather than grouped. Most households are multi-generational and range with an average size of 7.9 (sd = 4.7) members. Despite being a predominantly rural area, the principle source of income for most households is waged employment and state pensions rather than agriculture. Approximately 77% of households in the surveillance area have access to piped water and toilet facilities respectively.

To fulfil the eligibility criteria for the ACDIS cohort, individuals must be a member of a household within the surveillance area but not necessarily resident within it. Crucially this means that ACDIS collects information on resident and non-resident members of...
households (Figure 10) and makes a distinction between membership (self-defined on the basis of links to other household members) and residency (residing at a physical structure within the surveillance area at a particular point in time). Individuals can be members of more than one household at any point in time (e.g. polygamously married men whose wives maintain separate households). As of December 2006, there were 85,855 people under surveillance of whom 33% were not resident within the surveillance area. Obtaining information on non-resident members is vital for a number of reasons. Most importantly, understanding patterns of HIV transmission within rural areas requires knowledge about patterns of circulation and about sexual contacts between residents and their non-resident partners.

**Figure 10**

Age and sex profile of the surveillance population by residency, 31st December 2009 (n=56,791 residents and 29,164 non-residents)

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**Population-based HIV sero-surveillance and sexual behaviour survey**

Nested within the ACDIS cohort is the population-based HIV cohort. Between 2003 and 2006 (3 rounds of data collection), all women aged 15-49 years and men aged 15-54 years resident in the surveillance area were eligible for HIV testing. However, starting in 2007, eligibility was extended to cover all residents aged ≥15 years of age. In addition to the resident sample, a 12.5% stratified sample of non-residents (‘migrants’) is also included in each round of data collection. These non-resident trial participants are sampled randomly into equally sized strata by sex and frequency of their presence pattern within the surveillance area (e.g. returns at month end). Approximately 10,000 individuals consent to HIV testing per year and 170 seroconversions (round 2 – 5) per year are observed in HIV negative individuals. In total the Africa Centre’s HIV surveillance has identified 770 seroconversions among 9,614 individuals over 23,136
A summary of data collected as part of the survey is given (Table 11).

**Table 11**
Summary of data collected as part of the HIV surveillance and sexual behaviour survey

<table>
<thead>
<tr>
<th>Topic</th>
<th>Types of information</th>
<th>Frequency</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV status</td>
<td>HIV status</td>
<td>Annual</td>
<td>2003-2006: women 15-49 years, men 15-54 years</td>
</tr>
<tr>
<td></td>
<td>Reason for refusing test</td>
<td>2003/4, 2005/6/7/8</td>
<td>2007/8 women and men 15 years and older</td>
</tr>
<tr>
<td>Sexual behaviour</td>
<td>Pregnancy history</td>
<td>Annual</td>
<td>2000-2003 women 15-49 years only.</td>
</tr>
<tr>
<td></td>
<td>Contraceptive use</td>
<td>2003/4, 2005/6/7/8</td>
<td>2003-2006: women 15-49 years, men 15-54 years</td>
</tr>
<tr>
<td></td>
<td>Sexual activity (including partnership concurrency, partner age differences)</td>
<td>2007/8 women and men 15 years and older</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Attitudes to condom use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knowledge and perceived risk</td>
<td>Knowledge of ART and perceived HIV risk</td>
<td>Annual</td>
<td>2003/4: women 15-49 years, men 15-54 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2003/4, 2005/6/7/8</td>
<td></td>
</tr>
</tbody>
</table>

Teams of two trained fieldworkers visit each eligible individual in his or her household on an annual basis. If a subject is absent, the field workers make up to four repeat visits to the same household. If a subject no longer lives in the household, the field worker hands the case to a specially trained tracking team that attempts to find the individual in his or her new residence which may be as far as Johannesburg or Durban. After written informed consent, field workers collect blood by finger prick and prepare dried blood spots for HIV testing according to the Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO) Guidelines for Using HIV Testing Technologies in Surveillance. HIV status is determined by antibody testing with a broad based HIV-1/HIV-2 ELISA (Vironostika® HIV-1 Microelisa System (Biomérieux, Durham, North Carolina, USA) followed by a confirmatory ELISA (Wellcozyme HIV 1+2 GACELISA; Murex Diagnostics Benelux B.V., Breukelen, The Netherlands). In an effort to reduce social potential biases in the sexual behaviour interview, fieldworkers are always of the same sex as the respondent and are never from the community in which the respondent lives.

In addition, HIV test results can be obtained confidentially in a number of counselling centres which have been set up for that purpose in the survey area. A linked, anonymous voluntary HIV testing system with pre- and post-result counselling using confidential personal pin numbers and handheld computers for result communication has also been established.

### The Africa Centre Geographical Information System

Since its inception the Africa Centre has developed and maintained geographical information systems (GIS) capacity that allows the spatial analysis of any of the variables collected. The GIS is the most comprehensive and sophisticated of all demographic surveillance sites in Africa. All 12,000 homesteads and facilities in the trial area have been mapped by fieldworkers using differential global positioning systems (to an accuracy of < 2m) and the homesteads database is continuously updated as new homesteads are built as part of the ongoing surveillance programme. As well as being used for operational purposes, the Africa Centre has achieved recognition for the novel application of GIS and spatial methodologies to a diverse range of public health
problems. These have included the measurement of access to and planning of primary health care, measurement of spatial patterns of HIV prevalence and HIV-related mortality, TB DOT treatment coverage and TB case clustering, childhood vaccination coverage and patterns of urinary schistosomiasis among school children in the sub-district. The geographical database can be used to construct important georeferenced explanatory and confounding community variables associated with HIV outcomes including basic demographics, education levels, household assets, sexual behaviour and socioeconomic status.

**Linkage with the sub-district HIV treatment and care programme**

The Africa Centre partners with the Department of Health in the PEPFAR-funded ART programme in the government hospital and 17 peripheral primary health care clinics in the surrounding area. Ethical approval has been obtained for linkage between the HIV/ARV cohort and demographic and behavioural information in the ACDIS and HIV surveillance database to quantify the association between ART roll-out and sexual risk behaviour and HIV transmission within households and communities. Approximately half of the 10,500 patients currently on ART reside in the surveillance area and this database will continue to expand as more patients are enrolled into the treatment programme.

**The Africa Centre’s virology laboratory and bioinformatics unit**

The Africa Centre’s virology laboratory is based at the Nelson R. Mandela School in Durban. Equipment is available to perform automated viability cell count on whole blood or breast milk (Guava Technologies®), first & second line HIV-1 antibody detection (ELISA reader EL×800) and quantification of HIV-1 RNA on plasma and dried blood spots (The Nuclisens Easy-Q-Biomérieux). The semi-automated silica-based nucleic acid extraction method (MiniMag), enables isolation of nucleic acid to be used on alternative platforms, such as real-time PCR assays and sequencing reactions. In addition, a real-time PCR platform (Bio-Rad MiniOpticon) has been established in the laboratory and equipment to perform automated electrophoresis for determination of quantity, purity and integrity of extracted DNA, RNA and protein (Bio-Rad Experion).

The laboratory generates HIV sequences using in-house methods as well as resistance genotyping using the FDA approved Viroseq method. All of the sequences are generated locally in the ABI 3100 sequencer machine. The laboratory has 10 minus-80°C ultra-freezers and 9 minus-20°C chest freezers in a dedicated sample storage room on site. All six laboratory scientific staff members have completed a training course in Good Clinical Laboratory Practice. One staff member has also completed a training course in compliance with International Air Transport Association (IATA).

Previous results produced by the virology laboratory and bioinformatics unit was used to: characterize HIV-1 subtype C complete genomes in South Africa, determine the level of HIV-1 ART drug resistance prevalence in our research area, determine difference in fitness of local subtype C strains and estimate the migration of HIV-1 strains from South Africa to neighbouring countries and vice-versa. In addition, the bioinformatics unit is responsible for the development of open source bioinformatics software application, including a number of widely used software applications, such as the REGA HIV-1 genotyping tool (300,000 users to date) the GDE-Linux integrated interface for the analysis of HIV-1 molecular data (downloaded by 450 academic institutes) and the first HIV-1 proteomics resource worldwide. The bioinformatics unit contains all major software applications needed in the analysis to HIV sequence data using a phylodynamics framework and has its own website where all open-access publications and software produced are made freely available (http://www.bioafrica.net). (See technique lists of
laboratory tests and bioinformatics software applications in the scientific infrastructure section).

**Strengths of the Africa Centre dataset**

The use of ACDIS as a comprehensive sampling frame for the HIV cohort eliminates many of the problems commonly affecting surveys e.g. errors with household listing and selection and allows a quantification of the effects of non-participation on HIV prevalence estimates. All data collected by the HIV survey can be linked anonymously to other demographic, socio- and household-economic and health and behavioural data collected by the demographic information system.

The longitudinal design and collection of data for both resident and non-resident members and relationships to households is a key strength of the demographic information system and HIV testing platforms. Understanding of the population is enhanced by data about household dynamics, population mobility, inter- and intra-household relationships and social networks. Using a different set of eligibility criteria for individual enumeration rather than standard census definitions provides an opportunity to examine the coverage and the representation in the census of the full set of individuals who are integrally part of the population. To our knowledge, no other HIV survey has been able to track non-resident members of rural households to their migration destinations. Extension of the eligibility criteria for the HIV survey into the older age groups (>50 years) from 2007 is a further strength and has generated important knowledge on the impact of the HIV epidemic in these neglected age groups.

Another key strength of the Africa Centre is the production of detailed comprehensive information at different levels: the community, the household and the individual. Few, if any, sites in Africa have this degree of depth or breadth of information. A further strength lies in the opportunity to quickly evaluate the impact of the ART programme on demographic and behavioural indicators collected in ACDIS and its impact on HIV incidence.

**Key Findings**

ACDIS data has been extensively used to provide empirical evidence about the demographic and social impact of the HIV epidemic in a severely affected, largely rural population. HIV/AIDS has considerably increased mortality rates in the trial population and significantly reduced life expectancy at birth. By 2000, the probability of dying between the ages 16 and 60 years was estimated at 58% for women and 75% for men. However, a recent study has suggested that the upward trend in mortality rates is being reversed by the ART programme which has contributed significantly to an increase in life expectancy. Studies using the verbal autopsies show that the leading cause of death is AIDS, followed by non-communicable diseases. In 2000, AIDS caused 73% and 61% of the female and male deaths respectively among the 15-44 age group.

The Africa Centre’s population-based HIV survey is the first of its kind in South Africa to investigate the prevalence of HIV in a rural area among residents and non-residents. It shows some of the highest population-based HIV prevalence rates ever documented worldwide (especially when considering that this relates to 15 years into the epidemic). In 2004, HIV prevalence peaked at 51% (95% CI 47-55%) among women aged 25-29 year old and 44% (95% CI 38-49%) in men aged 30-34.(70) Non-resident men were nearly twice as likely (adjusted OR = 1.8) to be infected than their resident counterparts; the corresponding ratio for women was 1.5.(70)
Recent work

We recently used data (563 new HIV infections observed in 16,256 person-years) from the population-based longitudinal HIV surveillance at the Centre to test whether HIV incidence in the study community changed from 2003 through 2007. We find that HIV incidence neither decreased nor increased, but remained constant over the time period at the high level of 3.4 per 100 person-years (95% confidence interval 3.1 – 3.7).

We confirmed the high HIV incidence levels in this community with a different approach in a different sample. We used longitudinal data from the HIV surveillance to calibrate a test to distinguish recent from non-recent HIV infections in a cross-section (the BED IgG-Capture Enzyme Immunoassay or cBED assay). We then applied the cBED assay to estimate HIV incidence based on the earliest available cross-section in the surveillance and compared the results to the longitudinal estimates. The two estimation approaches yield essentially the same results with overlapping narrow uncertainty bounds. Related to cross-sectional approaches to measure HIV incidence, we published, submitted, and presented further work, including a comparison of distal determinants of HIV infection, using longitudinal and cBED assay-based cross-sectional analysis.

We further used data from a questionnaire on partnership patterns conducted in 2003/4 from 2,699 males and a novel GIS methodology to construct community-specific measures of both the prevalence of partnership concurrency and mean numbers of concurrent partners. The overall prevalence of concurrency was 28%. In univariate and multivariate Weibull regression (controlling for age, sex, education-level, wealth tertile, urban locale, marital status, and community-specific HIV prevalence) using both the prevalence of partnership concurrency and the overall mean numbers of concurrent partners as explanatory variables we found no evidence of a relationship between levels of concurrent partnerships in a community and risk of HIV acquisition (p values > 0.50).
The Africa Centre’s Scientific Infrastructure

The Africa Centre headquarters in Somkhete/Mtubatuba has space for 188 computer stations, including a dedicated data centre. The Centre employs more than 600 people, mostly fieldworkers or based in the primary health care clinics in the sub-district. The data centre provides the following services:

- **Document production.** Two high speed, high volume printers are used to produce data collection documents.
- **Document management.** A team of eight archivists manage document distribution, reception and archiving. All documents are tracked through individual document numbers using barcode scanners. The Centre has started the process of converting to digital archiving to be accomplished by mid-2011.
- **Data entry.** By a team of data typists using data entry systems ranging from EpilInfo for a few small studies to custom developed data entry systems for larger studies, including the surveillance. Quality control is the responsibility of the data collection supervisor, as well as a formally trained quality control manager.

The Centre has its own registered academic domain (www.africacentre.com). The computer server room at the Centre has dedicated access control, power, environmental and fire protection systems. It houses dedicated servers for file storage, electronic mail, active directory (domain) management, proxy, fire-wall and database management systems. The IT operations are outsourced to GijimaAST, one of the biggest IT companies in South Africa. Daily back-ups are made and off-site backups are done twice a week. Internet connectivity is provided through a link with the University of KZN. A dedicated link provides the connectivity to the Durban laboratory. Locally developed systems include data entry and validation programmes, sample tracking and management, data extraction and intranet-based utility systems.

**Advanced Computer Systems:**

The Africa Centre has a GIS laboratory comprising 4 desktop computers (with enhance graphical facilities) and 1 laptop. Software licences are held for MapInfo, Idrisi and Vertical Mapper GIS packages.

The bioinformatics unit is comprised of 1 desktop computer (with 8 processors and large disk space) and 2 bioinformatics servers with 4 dual core-processors that are professionally maintained at MRC server room in Durban. In addition, the bioinformatics unit has access to a 312 CPUs computer cluster located at the Meraka Institute in Pretoria. Bioinformatics software applications that are installed in the servers include phylogenetic packages such as Phyml, PAUP*, MrBayes, BEAST, Tree-Puzzle, Phylip, PAML and Splits-tree; sequence visualization and alignment programs such as the Genetic Data Environment, Se-Al, ClustalX and Genious; tree visualization software such as FigTree, TreeEdit and Treeview; and a number of software produced in our research group such as the REGA HIV-1 Subtyping Tool, BlastAlign web interface, HIV-1 Sequence Quality Analysis Tool, Micropop and the Phylotype tool. More detailed information on our software development is found in the bioafrica website (http://www.bioafrica.net).

For details of publications, datasets and procedures please access http://www.africacentre.com.
15.5 Appendix 5. Support letter from Department of Health
15.6 Appendix 6. Information and consent forms
15.7 Appendix 7. Follow-up algorithms

15.7.1 Intervention clusters
15.7.2 Control clusters

- Enrolment visit
  - Known HIV infection not on ART
    - Confirm HIV infection
      - CD4-cell count and clinical staging
    - Screen for ART initiation
  - Known HIV infection on ART
    - Review HIV RNA and CD4 cell count
      - Continue existing ART or switch to study drugs
    - Screen for isoniazid & cotrimoxazole
      - Repeat CD4-cell count and staging in 6 months
  - Unknown HIV infection
    - Informed consent for HIV test
      - HIV positive
      - Prevention interventions
        - Repeat HIV test at next visit
      - ART eligible
        - Screen for ART initiation
      - CD4-cell count and clinical staging
      - Not ART eligible
        - Screen for isoniazid & cotrimoxazole
        - Repeat CD4-cell count and staging in 6 months
        - Screen for ART initiation
      - Not ART eligible
        - Screen for isoniazid & cotrimoxazole
        - Repeat CD4-cell count and staging in 6 months
      - HIV negative
      - Not ART eligible
        - Screen for isoniazid & cotrimoxazole
        - Repeat CD4-cell count and staging in 6 months
15.8 Appendix 8. Signatures
15.9 Appendix 9. Insurance certificate
15.10 Appendix 10. UKZN Biomedical Research Ethics Committee approval letter