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STATISTICAL ANALYSIS PLAN		*2*	*22/11/2017*

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ANRS 12 290 STATIS Trial

Systematic empirical vs. Test-guided Anti-tuberculosis Treatment Impact in Severely immunosuppressed HIV-infected adults initiating antiretroviral therapy with CD4 cell counts <100/mm3: the STATIS randomized controlled trial

Clinical trial registration number : NCT02057796

This statistical analysis plan (SAP) contains a technical description of the principal features stated in the protocol and details the procedures for executing the statistical analysis (ICH: E9: Statistical principles for clinical trials).

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1. SUMMARY OF THE TRIAL PROTOCOL

1.1 OBJECTIVES

1.1.1 Primary objective

The primary objective of the trial is to compare the 24-week risk of death or occurrence of invasive bacterial infection between two experimental strategies in HIV-1 infected adults who start ART with a CD4 count <100/mm^3: continuous extensive TB testing *versus* systematic empirical TB treatment started 2 weeks before ART initiation.

1.1.2 Secondary objective

To compare between the two strategies, over a period of 24 and 48 weeks:

- Mortality;
- Occurrence of invasive bacterial infection;
- Occurrence of AIDS-defining morbidity;
- Occurrence of severe HIV-non-AIDS morbidity;
- Occurrence of TB;
- Occurrence of TB-associated IRIS;
- Occurrence of non TB-associated IRIS;
- Occurrence of grade 3 or 4 adverse events;
- Adherence to ART;
- Probability of being lost to follow-up;
- Immunological and virological efficacy of ART;
- Care consumption (hospital stays, visits, tests, investigations, drugs), costs and cost-effectiveness;
- Risk of resistance to TB drugs.

To assess in each trial arm:

- Adherence to TB drugs during TB treatment.

1.2 DESIGN

This is a multicountry, two-arm, unblinded randomized controlled superiority trial. The trial will be held in four countries: Cambodia, Côte d'Ivoire, Uganda, and Vietnam.

1.3 TREATMENT

At inclusion, participants will be randomized 1:1 in two strategies of TB testing and treatment: extensive TB screening, or systematic empirical TB treatment.

Extensive TB screening (arm 1):

- TB screening point-of-care tests (Xpert MTB/RIF, urine LAM) and chest X-ray will be used extensively at randomisation (in all patients) and during follow-up (in patients with signs or symptoms suggestive of TB);
- Only patients who meet standardized criteria for TB at inclusion or during follow-up will receive a standard TB treatment (2ERHZ/4RH);
- ART (TDF-XTC or AZT-3TC + efavirenz) will be started immediately after randomization in patients not put on TB treatment, and 2 weeks after initiation of TB treatment in others.

Systematic empirical TB treatment (arm 2):

- TB screening point-of-care tests will not be used;
- All patients will start a 6-month standard TB treatment (2ERHZ/4RH) at randomization;
- ART (TDF-XTC or AZT-3TC + efavirenz) will be started 2 weeks after TB treatment initiation.

Both strategies will apply to the first 24 weeks in the trial (intervention period).

From week-24 to week-48, the choice of TB tests and the prescription of TB treatment will be left upon the decision of the investigator in both trial arms.

1.4 CALENDAR

- First inclusion: September 2014 ;
- Inclusion time: 30 months ;
- Time of follow-up for each participant: 48 weeks ;
- Last visit for the last patient: April 2018.

1.5 ELIGIBILITY CRITERIA

1.5.1 Inclusion criteria

- Age ≥18 years;
- HIV-1 infection as documented at any time prior to trial entry, as per national testing procedures;
- CD4 <100 cells/mm^3 ;
- No history of antiretroviral drug use, except transient ART for PMTCT;
- Able to correctly understand the trial and to sign the informed consent.

1.5.2 Non-inclusion criteria

- HIV-2 co-infection;
- Contra-indication to efavirenz;
- AST or ALT >5 times the upper limit of normal;
- Creatinine clearance <50 ml/min;
- Overt evidence that TB treatment should be started immediately;
- History of TB treatment in the past 5 years;
- Ongoing TB chemoprophylaxis (isoniazid preventive therapy);
- Any condition that would lead to differ ART initiation (e.g. acute condition requiring investigations and/or treatment prior to ART initiation);
- Current pregnancy or breastfeeding.

1.6 SAMPLE SIZE

We hypothesize that the probability of death or invasive bacterial infections within the first 6 months of ART in patients with CD4 counts <100/mm^3 who initiate ART and do not receive systematic TB treatment is 14% (arm 1).
We hope to demonstrate a 40% reduction in this probability in patients receiving a systematic TB treatment (arm 2), compared to patients who do not (arm 1). According to the sample size calculation formula and the log-rank test for comparing survival between two groups (NQuery software), and using α-value of 5% and 1-β power of 80%, we need to include 502 x 2 = 1004 patients.
Assuming a 4.5% loss of follow-up rate, we will need 46 additional patients, leading to a total of 1050 patients, i.e. 525 in each arm.

1.7 RANDOMIZATION

Eligible subjects will be randomized in a 1:1 ratio for a total of 525 patients per trial arm, using a computer generated random list. The randomization list will be pre-established by an independent statistician and be kept secret from the investigators.
Randomization will be blocked and stratified by CD4 count (0-50; 51-99/mm3) and by country. The number of participants per stratum will not be capped.
The investigators will have 24/24h private access to the online randomization system, which will allow them to check out the eligibility criteria, confirm the decision to randomize, and sequentially allocate a trial arm and a corresponding unique subject identification number to the patient.
Once a participant identification number has been assigned, the patient will be considered to be randomized in the trial.

1.8 ENDPOINTS

1.8.1 Primary endpoint

The primary endpoint is the composite of (i) 24-week all-cause mortality and (ii) 24-week incidence of invasive bacterial infections

1.8.2 Secondary endpoints

The following secondary endpoints will be measured at 24 and 48 weeks:

- Components of the composite primary endpoint (all-cause mortality; incidence of invasive bacterial infections);
- Incidence of confirmed/probable/possible TB;
- Incidence of AIDS-defining diseases other than TB;
- Incidence of serious HIV-non-AIDS morbidity;
- Incidence of TB-associated IRIS ;
- Incidence of non TB-associated IRIS;
- Incidence of grade 3 or 4 adverse events;
- Incidence of loss to follow-up;
- Incidence of loss to follow-up or death;
- CD4 cell count evolution;
- Percentage of patients with undetectable HIV-1 viral load;
- Number of days spent in hospital;
- Number of attended scheduled trial visits;
- Number of unscheduled trial visits;
- Number of investigations/tests done, overall and by type of tests;
- Number of days of treatment other than TB treatment and ART, by type of drugs;
- Costs of care ;
- Percentage of patients with a *M. tuberculosis* strain resistant to first-line anti-TB drugs;
- Time to ART initiation
- Antiretroviral medication possession ratio, defined as the number of daily doses of ARV drugs actually provided divided by the total number of follow-up days since treatment initiation;
- TB medication possession ratio, defined as the number of daily doses of TB drugs actually provided divided by the total number of follow-up days since treatment initiation.

2. RULES, DEFINITIONS AND METHODS

2.1 STRATEGY OF ANALYSIS

When comparing endpoints and determining interactions, we will perform two-sided tests and use a type I error α-value of 5%.

For the analyses, we will use two timelines: W24 (concerning the period between W0 and W24) and W48 (concerning the period between W0 and W48).

Prior to the analysis, we will:

- Describe baseline and follow-up characteristics overall, by arm and by country.
- Compare baseline characteristics between arms.

A description by continent, center and baseline CD4 count strata, and a comparison between countries, continents, centers or baseline CD4 count strata may be required by the investigators whenever they are deemed useful to understand the results.

The primary analysis will be an intention-to-treat. It will be performed on available data.

The primary analysis will compare the probability of death or incident invasive bacterial infections at W24 between trial arms in intention-to-treat. It will be adjusted for:

- The two randomization stratification variables (country and baseline CD4 count)
- And any other baseline characteristic that would be found statistically different between arms despite randomization.

These adjustments may require appropriate models, depending on the distribution and type of variables.

Secondary analyses will include:

- Secondary analyses of the primary endpoint at W24 and W48
- Analyses of secondary endpoints at W24 and W48.

2.2 PATIENTS INCLUDED IN THE ANALYSIS

Statis protocol:

All randomized patients should be included in the analysis, including patients who died, were lost to follow-up, or withdrew from the trial.
The scientific committee may decide to exclude a patient from the analysis if the trial coordination center recommends it using documentation. The scientific committee decision to exclude a patient must be taken while blinded to the patient's trial arm and his/her outcomes since inclusion. A patient may be excluded from the analysis if he/she meets one of the following criteria:

- Did not initiate the trial arm to which s/he was randomized (as long as s/he did not know to which group s/he was randomized);
- Withdrew consent;
- Was wrongfully included with respect to major eligibility criteria.

Patients excluded from the analysis, as per the decision of the Statis Scientific Advisory Board (September 18th 2017)

- For violation of eligibility criteria, the SAB decided :
    - **to exclude** the patients with past history of ART from the analysis,
    - **not to exclude** patients with HIV 1+2 dual infection from the analysis.
- For consented withdrawal, the SAB decided :
    - **not to exclude** patients who withdrew consent from the analysis.
    - **censor the data** of patients who withdrew consent :
        - at the date of their last contact with study team for patients not known to be dead after their last contact with study team.
        - at the date of death for patients known to be dead after their last contact with study team.

2.3 FOLLOW-UP TIME, LOSS TO FOLLOW-UP

Follow-up time for a given participant: time between W0 and the date of censoring.

Last visit = last scheduled or unscheduled visit of the participant at the study clinic or at hospital (ie: last time the participant was seen alive at the study clinic or at hospital).

Last contact with study team (LCST) = date of the last direct or indirect information that the participant was alive.

Vital status: information that a participant is alive or dead at a given date.

- **Indirect information** on vital status: the information that the participant was alive or death was obtained through relatives (visited at home, talked to on the phone, etc.)
- **Direct information** on vital status: the team had a contact with the participant inside or outside the hospital or the study clinic (visited at home, talked to on the phone, etc.).

*Decision of the Statis SAB (*September 18th 2017):

- Indirect information of death is considered valid

Loss to follow-up (Statis protocol, par. 9.8.2):

> *« A patient who does not show up for a given scheduled visit will be considered lost-to-follow-up when his/her last contact with the trial team (either at the clinic, via telephone, or at home) was recorded prior to the date of his/her last scheduled visit to the clinic as per the trial protocol »*

Decision of the Statis SAB (September 18th 2017):

- A participant who did not show up for the last scheduled visit but whose vital status is documented through direct or indirect information will not be considered as lost to follow-up if: (i) s/he is dead; or (ii) the date of his/her last contact with study team is ≥ the date of his/her last scheduled protocol visit.

Consent withdrawal: written evidence that a participant voluntarily decided not to participate in the trial anymore before the date of his/her last scheduled protocol visit.

Discontinuation of the trial strategy: patients who have discontinued ART either permanently or during a significant period of time, or who have not received full anti-TB treatment.

2.4 DATE OF CENSORING

2.4.1 For intention to treat analysis

W24 analysis:

In the following paragraph:

W24 = theoretical date of W24 visit, as scheduled in the protocol

DOS = date of censoring

For the primary outcome (death or invasive bacterial infection):

- If the patient is known to be dead and:
    - Date of death < W24+7days: **DOS=date of death**
    - Date of death > W24+7days: **DOS=W24**
- If the patient is not known to be dead and:
    - Date of « last contact with study team » (LCST) < W24 : **DOS=LCST**
    - Date of LCST ≥ W24 : **DOS=W24**

For the components of the primary outcome:

« Death »: DOS will be the same as for the primary outcome.

« Invasive bacterial infections alone »:

- If date of Last visit at the study center < W24: **DOS=date of last visit at the study center.**
- If date of Last visit at the study center ≥ W24: **DOS=W24**.

W48 analysis:

In the following paragraph:

W48 = theoretical date of W48 visit.

For the primary outcome (death or invasive bacterial infection):

- If the patient is known to be dead and:
    - Date of death < W48+7days: **DOS=date of death**
    - Date of death > W48+7days: **DOS=W48**
- If the patient is not known to be dead and:
    - Date of LCST < W48 : **DOS=LCST**
    - Date of LCST ≥ W48 : **DOS=W48**

For the components of the primary outcome:

« Death »: DOS will be the same as for the primary outcome.

« Invasive bacterial infections alone »:

- If date of Last visit at the study center < W48: **DOS=date of last visit at the study center.**
- If date of Last visit at the study center ≥ W48: **DOS=W48**.

2.4.2 For on-treatment analysis

For on-treatment analysis, follow-up will be censored when the trial strategy is discontinued either permanently or during a significant period of time.

Table 1. Protocol requirement and censoring date for on-treatment analysis

Arm	Tuberculosis status	Protocol requirement	Treatment status	Censoring date
Arm1	No TB during follow-up	Start ART at baseline to W48	never started ART	Baseline
			started ART	Last contact prior to first prolonged ART discontinuation
	TB documented at baseline	Start ART at W2 to W48	never started ART	W2
	TB documented after baseline	Start ART at baseline to W48		Baseline
	TB documented at baseline or during follow-up		started ART	Last contact prior to first prolonged ART discontinuation
		Start 6 months anti-TB from TB documentation	never started anti-TB	Date of TB documentation
Arm 2		Start ART at W2 to W48	never started ART	W2
			started ART	Last contact prior to first prolonged ART discontinuation
		Start 6 months anti-TB from baseline	never started anti-TB	Baseline
			started anti-TB	TB treatment early discontinuation

2.5 STATISTICAL METHODS

2.5.1 Data description

When describing data, convenient graphical representations will be made whenever possible.

The number and proportion of missing data will be showed for each variable.

Qualitative variables

Qualitative variables will be described in terms of numbers and percentage per category. Confidence intervals will be estimated when appropriate.

Quantitative variables

Quantitative variables will be described in terms of absolute frequency, mean, standard deviation, median, range and interquartile range. Data may be transformed and normalized whenever necessary.

Time-to-event outcome

For each time-to-event outcome, we will estimate:

- The probability of occurrence over time (with 95% confidence interval) using the Kaplan-Meir method
- The rate per 100 person-years, by dividing the number of first episode of the event by the cumulative time at risk. The time at risk will start at randomization. It will end at the date of the first episode of the event for participants who underwent at least one episode and at the date of censoring (see section 2.4 and 2.4.2) for other participants.

2.5.2 Comparison between arms

Baseline and follow-up characteristics

For qualitative variables, we will use the χ^2, the χ^2 corrected or the Fisher's exact test when appropriate.

For quantitative variables, we will use the Student's t test or the Kruskal Wallis test, depending on the distribution of the variable.

For time-to-event variables, we will use the log-rank test

Primary analysis, and secondary analysis of time-dependent secondary outcomes

We will use multivariate Cox proportional-hazards models to compare the occurrence of the primary outcome and of all time-dependent secondary outcomes (including the primary outcome components) between arms.

The main explanatory variable will be the trial arms. Hazard ratios will be adjusted for the two randomization stratification variables (country and baseline CD4 count strata), and for any other baseline characteristics that will be found statistically different between arms despite randomization.

Prior to the analysis, we will examine the assumption of the proportional hazards, and will look for interaction between adjustment variables.

Other secondary analyses

For the analysis of the relationship between a binary dependent variable and qualitative or quantitative independent variables, we will use logistic regression models.

For the analysis of the relationship between quantitative dependent variable and qualitative or quantitative independent variables, we will use linear regression models.

For the analysis of repeated data, we will use mixed effects models.

For these models, independant variables will be included in multivariate analysis if they are significantly associated to the dependent variable with a level of significance p=0.25 in univariate analysis, or if they have been previously shown to be associated to the dependent variable in the literature. Two models will be derived: a model including all independant variables (“initial model”), and a model resulting from a stepwise descending procedure (“final model”).

2.6 MISSING DATA

Incomplete calendar date:

- If the day is missing, we will use “15” (middle of the month). The consistency of an imputed day will be verified before the date is used for calculation of time to events.
- If the month or year are missing, the entire date will be considered as missing.

There will be no imputation for all other missing data.

2.7 MISCELLANEOUS

The time between 2 dates will be calculated as follows:

- in days = (Date 2 – Date 1)
- in weeks = (Date 2 – Date 1)/7
- in months = (Date 2 – Date 1)/30.4375
- in years= (Date 2 – Date 1)/365.25

If Date 2 = Date 1, the time between the two dates will be = 1

For all other variables, the difference between a given value at time T and a value at time T’ will be :

Delta = value at T’ – value at T

2.8 SOFTWARE

We will use SAS® software versions 9.2 and higher (SAS Institute Inc., Cary, NC) to prepare files, and conduct statistical analyses.

3. FLOW DIAGRAM

A flow diagram (“study profile”) will be made according to the CONSORT rules

4. ANALYSIS

4.1 PRE-INCLUSION

- Number of pre-included patients
- Number of non-included patients and percentage of non-included among pre-included
    - Reasons for non-inclusion (qualitative, *as per* CRF)

4.2 INCLUSION

- Number of included participants
- Inclusion completion curve over time

4.3 RESPECT OF ELIGIBILITY CRITERIA

- Number (%) of included participants who did not fulfil 100% of eligibility criteria, overall
- Number (%) of included participants who did not fulfil eligibility criteria, by criteria
- Number (%) of eligibility criteria violation that were not formally authorizated by the investigators

4.4 INCLUSION IN THE ANALYSIS

- Number and percentage of included participants who are excluded from the analysis
    - Reasons of exclusion from the analysis (qualitative)

The rest of the document concerns patients included in the analysis
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4.5 CHARACTERISTICS AT BASELINE (W0)

Demographic:

- Age (quantitative variable)
- Age in class: <25, [25;35[, [35;45[,≥45 (qualitative)
- Sex: Male/Female (qualitative)

History (other than TB):

- Ongoing OI Prophylaxis
    - Primary (qualitative, *as per* CRF)
    - Secondary (qualitative, *as per* CRF)
- Hepatitis B previous status availability: yes/no
    - If yes, positive/negative
- Hepatitis C previous status availability: yes/no
    - If yes, positive/negative
- For women, contraceptive methods: yes/no
    - If yes, type of contraception (qualitative, *as per* CRF)
- Alcohol consumption:
    - In routine how often do they drink alcool (qualitative, *as per* CRF)
    - In the last month, number of days when they had 6 drinks or more?
- Illicit drug consumption:
    - Ever used drug: yes/no
        - If yes, still using drugs ? : yes/no
            - If yes: Route of administration (qualitative, *as per* CRF)
            - If yes: drug(s) currently taken (qualitative, *as per* CRF)
- Time (in months) between HIV diagnosis and W0
- Diabetes: yes/no
- Peripheral neuropathy: yes/no
- Symptomatic chronic liver disease: yes/no

TB and TB testing

- At least one chest X-ray within last 6 months (qualitative, *as per* CRF)
- At least sputum smear within last 6 months (qualitative, *as per* CRF)
- Past history of active tuberculosis (all >5 years) (qualitative, *as per* CRF)
- Past history of isoniazid preventive therapy (qualitative, *as per* CRF)
- TB symptoms at W0, cough: yes/no
- TB symptoms at W0, fever: yes/no
- TB symptoms at W0, weight loss: yes/no
- TB symptoms at W0, sweats: yes/no
- TB symptoms at W0, number: 0, 1, 2, 3, 4
- Xray of the chest at W0:
    - Number of patients with Xray performed/no performed
        - If performed : number of Xrays normal/abnormal
            - If abnormal: signs (qualitative, *as per* CRF)
            - If abnormal: number of patients with at least one sign other than cardiomegaly or calcification
- Arm 1:
    - Xpert MTB/RIF on sputum at W0: yes/no
        - If yes : result (qualitative, *as per* CRF)
    - LAM on urine at W0: yes/no (qualitative variable)
        - If yes : result (qualitative, *as per* CRF)
    - AFB examination and/or culture at W0: yes/no (qualitative variable)
        - If yes : number (%) AFB positive
        - If yes : number (%) culture positive
        - If yes : number (%) with AFB or culture positive

Clinical examination

- Other symptoms, Chest pain: yes/no
- Other symptoms, Hemoptoic expectoration: yes/no
- Other symptoms, Dyspnea: yes/no
- Other symptoms, Crackles: yes/no
- Other symptoms, Wheezing: yes/no
- Other symptoms, Ronchus: yes/no
- Other symptoms, Reduced breath sounds: yes/no
- Other symptoms, Dullness on percussion: yes/no
- Other symptoms, Abdominal pain: yes/no
- Other symptoms, Jaundice: yes/no
- Other symptoms, Dullness on percussion: yes/no
- Other symptoms, Hepatomegaly: yes/no
- Other symptoms, Splenomegaly: yes/no
- Other symptoms, Distended abdomen: yes/no
- Other symptoms, Distended abdomen: yes/no
- Other symptoms, Poly-lymphadenopathy: yes/no
- Other symptoms, Mono-lymphadenopathy: yes/no
- Other symptoms, Poly-lymphadenopathy or Mono-lymphadenopathy: yes/no
- Height (m)
- Weight (kg)
- Body temperature (°C)
- BMI (kg/m^2)
- BMI in class: <18.5, [18.5;20.5[, [20.5;22.5[, ≥22.5
- Systolic and Diastolic Blood Pressure (mmHg)
    - Number (%) with HTA (TAS ≥150 or TAD ≥ 90)
- Karnofski (%)
- Karnofski in class: <80%, ≥80% (qualitative variable)
- WHO clinical stage (1,2,3,4).

Biological characteristics

- Haemoglobin (g/dl)
- Haemoglobin in class : DAIDS grades 0, 1, 2, 3, 4
- Neutrophils (/mm^3)
- Neutrophils in class : DAIDS grades 0, 1, 2, 3, 4
- Platelets (x10^3/mm^3)
- Platelets in class : DAIDS grades 0, 1, 2, 3, 4
- Creatinine (mg/ml)
- Creatinine clearance (ml/min)
- Creatinine clearance in class : <50, ≥50
- Transaminases (AST) (UI/l)
- Transaminases(AST) in class : ≤50,]50-100],]100-200],]200-400], ≥400
- Transaminases (ALT) (UI/l)
- Transaminases (ALT) in class : ≤50,]50-100],]100-200],]200-400], ≥400
- Transaminases (highest AST/ALT value) (UI/l)
- Transaminases (highest AST/ALTvalue) in class : ≤50,]50-100],]100-200],]200-400], ≥400
- CD4 cell count (/mm^3)
- CD4 cell count in class : <50, ≥50
- HIV-1 RNA (copies/ml)
- HIV-1 RNA (log_{10} copies/ml)
- HIV-1 RNA (log_{10} copies/ml) in class: <5, ≥5
- HBs Ag: Positive/Negative
- HCV Ab: Positive/Negative

4.6 FOLLOW-UP

- Number (and %) of protocol visits attended/ scheduled, overall and by visit
- Follow-up time per participant (months) (definition in section 2.3)
- Cumulated follow-up time (patient-years) (sum of the follow-up per participant, definition in section 2.3)
- Number (and %) of patient who withdrew from trial follow-up (definition in section 2.3)
- Number (and %) of patient who discontinued the trial strategy (definition in section 2.3)
- Number (and %) of patients with the following status at W24 and W48:
  - Alive and in active follow-up
  - Death
  - Others :
    - Withdrawal of care, no consent withdrawal and no lost to follow-up (visit missing)
    - Lost to follow-up, no consent withdrawal (definition in section 2.3)
    - Withdrawal consent (definition in section 2.3)

4.7 PRIMARY ENPOINT

4.7.1 Description

Components of the primary endpoint

Death

- Number (%) of death, overall (quantitative variable)
- KM curve, probability of death
- Rate of mortality per 100 person-years

Invasive bacterial diseases

- Number (%) of prevalent episodes of invasive bacterial diseases, overall and :
- Number (%) of incident episodes of invasive bacterial diseases, overall and :
  - By specific diagnosis
  - By documentation (confirmed/probable)
  - By clinically significant pathogen isolated

  - By groups of body fluid in which the pathogen was isolated (3 groups: pathogen isolated in at least 1 blood culture/pathogen isolated only in other fluid(s)/no pathogen isolated)
  - By tests found to be contributive (table “invasive bacterial diseases” of CRF “event validation”: put number of episodes in each cell)
  - By hospitalization (yes/no)
  - By specific diagnosis and by documentation
  - By specific diagnosis and by pathogen
  - By specific diagnosis and by body fluid
  - By specific diagnosis and by hospitalization
- Number (%) of first incident episodes of invasive bacterial diseases, overall
- Type of (%) of first incident episodes invasive bacterial diseases, number (%)
- KM curve, probability of first incident episode of invasive bacterial diseases
- Rate of first incident episode of invasive bacterial diseases per 100 person-years

Combined primary endpoint

- Number (%) of patients with incident invasive bacterial diseases or death, overall (quantitative variable)
- KM probability of overall first incident invasive bacterial diseases or death
- Rate of first episode of incident invasive bacterial diseases or death per 100 person-years

4.7.2 Primary analysis

We will use a Cox proportional hazards model to compare the probability of death or incident invasive bacterial infections at W24 between trial arms in intention-to-treat.

The main explanatory variable will be the effect of the randomization arm. The model will be adjusted for:

- the two randomization stratification variables (country and baseline CD4 count)
- and any other baseline characteristic that would be found statistically different between arms despite randomization.

We will verify the proportional hazard assumption. If the proportional hazard assumption is not satisfied for the variable “arm”, we will present time-dependant results by periods of time. If the proportional hazard assumption is not satisfied for another variable, we will do a proportional hazard model stratified on this variable.

We will also check for interaction between adjustment variables. If there is an interaction between these variables, we will present the stratified data for the variables concerned.

4.7.3 Secondary analyses of the primary endpoint

- **Analysis of the components of the primary endpoint:** same method as primary analysis *but* the endpoint will be “death alone” in one model, and “incident invasive bacterial diseases alone” in a separate model.

The following analyses will then be run using successively “death or incident invasive bacterial diseases”, “death alone”, or “incident invasive bacterial diseases alone” as endpoint.

- **On-treatment analysis** (« per protocol analysis »): same method as primary analysis *but* the follow-up of patients who did not 100% follow the trial strategy for TB diagnosis and treatment will be censored at the time when they stopped respecting the trial strategy.
- **Long term effect:** same method as primary analysis *but* the timepoint will be W48 instead of W24
- **Sensitivity analyses** (to test the robustness of the main result) :
  - “Missing=failure” analysis: same method as primary analysis *but* loss to follow-up will be considered as a failure
  - Residual and unmeasured confounding effect: to take into account the potential confounding effects of key variables that have been shown to be associated with death in low resource settings in the HIV literature, we will run a sensitivity analysis adjusting on these variables even if they are statistically different between arms. These variables are: sex, baseline WHO clinical stage, baseline BMI,

baseline haemoglobin, and first line ART regimen (TDF-regimen versus ZDV-regimen): same method as primary analysis *but* these variables will be included in the model.

- **Explanatory analyses (to assess the role of key factors) :**
  - Effect of cotrimoxazole prophylaxis: same method as primary analysis *but* cotrimoxazole will be included in the model as a time-dependant variable.
  - Effect of the context: same method as primary analysis *but* adjusting on the continent (Africa/Asia) instead of adjusting on the country.
  - Heterogeneity between countries: if the effect of the country is found to significant in the model used in primary analysis:
    - In secondary analysis, we will stratify the variable "country" in the model
    - Another secondary analysis will be done separately by continent and by country

4.8 SECONDARY ENDPOINTS

4.8.1 TB and TB drugs

TB occurrence and documentation

- Number (%) of validated TB episodes, overall and :
  - By type ("only pulmonary" *vs.* disseminated)
    - When disseminated: by specific locations
  - By anteriority (prevalent/incident)
  - By documentation (confirmed/probable/possible)
  - By DAIDS grade of seriousness (1,2,3,4)
  - By hospitalization (yes/no)
  - By "mycobacteriological tests found to be positive" (3 groups: At least 1 Xpert positive/Only other mycobacteriological test(s) positive/no test positive)
  - By tests found to be contributive (table "TB Location" of the CRF "event validation": ": put number of episodes in each cell)

  Tables 2 x2 :

  - By type and by documentation
  - By type and by "mycobacteriological tests found to be positive"
- Number (%) of first episodes of incident TB, overall
- Type of (%) of first episodes incident TB, number (%)
- KM curve, probability of first episode of incident TB
- Rate of first episode of incident TB per 100 person-years
- Number (%) of first episodes of incident or prevalent TB, overall
- Type of (%) of first episodes of incident or prevalent TB, number (%)
- KM curve, probability of first episode of incident or prevalent TB
- Rate of first episode of incident or prevalent TB per 100 person-years

TB curative treatment and outcomes of validated prevalent or incident TB episodes

- Number (%) of TB curative treatment received for validated prevalent or incident TB episodes (quantitative variable), overall and
  - By type of treatment received : 2ERHZ/4RH, others
    - Detail "others",
      - Detail reasons for other treatments (qualitative, *as per* CRF)
  - By treatment outcome (qualitative, *as per* CRF)
- Medication possession ratio of TB drugs
- Medication possession ratio of TB drugs in class: [0-50%] /]50-80%] /]80-95%] / >95%
- Overall number of TB drug permanent discontinuation during TB curative treatment
  - Reason for TB drugs discontinuations (qualitative).
- Number (%) of patients who permanently discontinued at least one TB drug.

TB empiric treatment in Arm 2

- Number (%) of patients who received TB empiric treatment in Arm 2
    - Number (%) of patients who completed the 6-month TB empiric treatment in Arm 2
        - Reason for empiric treatment permanent discontinuation (qualitative).
    - Medication possession ratio of TB empiric treatment in Arm 2 (quantitative variable).
    - Medication possession ratio of TB empiric treatment in Arm 2 in class: [0-50%] /]50-80%] /]80-95%] / >95%
    - Overall number of TB drug permanent discontinuation during TB empiric treatment in Arm 2
        - Reason for TB drugs discontinuations (qualitative).
    - Number (%) of patients who permanently discontinued at least one TB drug during TB empiric treatment in Arm 2.

4.8.2 Morbidity (including TB)

- Number (%) of prevalent events, any grade, overall, and
    - By group of diagnosis
    - By diagnosis
    - By classification (AIDS defining, HIV-non AIDS defining, Non HIV)
    - By DAIDS seriousness (grade 1, grade 2, grade 3, grade 4)
    - By hospitalisation (yes/no)
    - By cause of death (no/probable/possible)
- Number (%) of incident morbidity events, any grade, overall, and
    - By group of diagnosis
    - By diagnosis
    - By classification (AIDS defining, HIV-non AIDS defining, Non HIV)
    - By DAIDS seriousness (grade 1, grade 2, grade 3, grade 4)
    - By hospitalisation (yes/no)
    - By cause of death (no/probable/possible)

  Tables 2 x2 : incident morbidity events:

    - By group of diagnosis and classification
    - By group of diagnosis and seriousness
    - By group of diagnosis and hospitalisation
    - By group of diagnosis and cause of death

- Number (%) of first episodes of grade 3-4 incident morbidity events (quantitative variable)
- KM probability of first episode of grade 3-4 incident morbidity events
- Rate of first episode of grade 3-4 incident morbidity events
- Number (%) of first episodes of AIDS defining incident morbidity events (quantitative variable)
- KM probability of first episode of AIDS defining incident morbidity events
- Rate of first episode of AIDS defining incident morbidity events

4.8.3 Drug toxicity

- Number (%) of drug-toxicity related (*as per* CRF event validation) prevalent events, overall
- Number (%) of drug-toxicity related (*as per* CRF event validation) incident events, overall and:
    - By diagnosis
    - By groups of diagnosis (renal, neurological, cutaneo-mucous, haematological, others)
    - By drug in cause
    - By group of drugs in cause (antiTB, ART, cotrimoxazole, others)
    - By DAIDS seriousness (grade 1, grade 2, grade 3, grade 4)
    - By hospitalisation (yes/no)
    - By imputation (at least one drug considered as “probably in cause”/Only drug(s) “possibily” in cause)
    - By group drug discontinuation/interruption (discontinuation, interruption, no discontinuation/interruption)
    - By cause of death=no/probable/possible

Tables 2 x2: incident events related to drug toxicity

- By group of drugs in cause and by groups of diagnosis
- By group of drugs in cause and by seriousness
- By group of drugs in cause and by imputation
- By group of drugs and cause of death=no/probable/possible

- Number (%) of first episodes of incident drug toxicity-related grade 3-4 events
- KM probability of first episode of incident drug toxicity-related grade 3-4
- Rate of first episode of incident drug toxicity-related grade 3-4

4.8.4 IRIS

- Number (%) of events validated as IRIS (*as per* CRF event validation), overall and:
  - By type (Unmasking/paradoxical)
  - By diagnosis associated (TB, crytococcosis, etc.)
  - By prevalent/incident characteristic of the diagnosis associated
  - By IRIS severity (Mild/moderate/severe/life-threatening)
  - By IRIS certainty (possible/probable)
  - By hospitalization (yes/no)

  Tables 2 x 2 :

  - By diagnosis associated and type
  - By diagnosis associated and certainty
  - By diagnosis associated and severity

- Number (%) of first episodes of IRIS, any grade
- KM probability of first episode of IRIS, any grade
- Rate of first episode of IRIS, any grade
- Distribution of time between W0 and first episodes of IRIS, any grade
- Number (%) of first episodes of severe or life-threatening IRIS
- KM probability of first episode of severe or life-threatening IRIS
- Rate of first episode of severe or life-threatening IRIS
- Distribution of time between W0 and first episodes of severe or life-threatening

4.8.5 Loss to follow-up

- Number (%) of patients lost to follow-up, overall and by:
  - Sex
  - Age class
  - Baseline Haemoglobin class
  - Baseline BMI class
  - Baseline Viral load class
  - First-line ART regimen class
- KM probability of loss to follow-up
- Rate of loss to follow-up

4.8.6 Antiretroviral treatment (ART)

Regimen

- Number (%) of patients who ever started ART and never started ART
  - Time between W0 and ART initiation (days)
  - Time between W0 and ART initiation: W0 /]W0-W2] /]W2-W4] / >W4
  - Groups of First-line ART regimen (qualitative).
  - Number (%) of patients who ever permanently discontinued at least one ARV drug
    - Reason for at least one ARV drugs discontinuation (quantitative)
    - Time (days) between ART initiation and first ARV drug permanent discontinuation, in days
  - Number (%) of patients who ever switched to 2nd line ART
    - Time (months) between ARV initiation and switch to 2nd line AR

        - Groups of Second-line ART regimen (qualitative).
    - Medication possession ratio of ART
    - Medication possession ratio of ART in class: [0-50%] /]50-80%] /]80-95%] / >95%

4.8.7 CD4 evolution

- CD4 cell count (/mm^3) distribution at week 24 and at week 48
- Delta of CD4 cell count (/mm^3) between baseline and week 24 or week 48
- Number (%) of patients with CD4 cell count in each CD4 strata (<25, 25-50, 50–100,100-200,200-350 and >350/mm^3) at week 24 and at week 48 (qualitative variable)
- Cumulative time (months) spent in each CD4 count stratum (<50, 50–100,100-200,200-350 and >350/mm^3) (censoring at date of last visit).

4.8.8 Viral load evolution

For calculations that use the viral load as a quantitative variable, HIV-RNA measures below the lower limit of detection of the technique of measurement will be replaced by the value of the lower limit of detection.

- Number (%) of patients with undetectable/detectable Viral load at week 24 and at week 48
- Number (%) of patients with undetectable Viral load load OR a $\geq$2 $\log_{10}$ decrease since W0 in Viral load at week 24 and at week 48
- Distribution of time (months) to first undetectable viral load
- KM probability of reaching first undetectable viral load
- Number (%) patients with Viral load (copies/ml) in each Viral load strata (<50, 50-400, 400-1000,1000-10000, 10000-100000 and >100000) at week 24 and at week 48 (qualitative variable)
- Cumulative time (months) spent with undetectable/detectable Viral load (undetectable/detectable)

4.8.9 Visits and tests

- Overall Number of visits, scheduled and unscheduled
- Overall Number of Hospitalisation
- Number (%) of patients with at least one hospitalisation

Imaging tests

- Overall Number of “Imaging tests” performed, overall and by category (as per CRF other tests)
- Number (%) of patients with at least one of each category of Imaging tests
- Number of Imaging tests per patient in each category of Imaging tests

Microbiology tests

- Overall Number of “Microbiology tests” performed, overall and by category (as per CRF other tests)
- Number (%) of patients with at least one of each category of Microbiology tests
- Number of Microbiology tests per patient in each category of Microbiology tests

Hematology/Biochemistry tests

- Overall Number of “Hematology/Biochemistry” tests performed, overall and by category (as per CRF other tests)
- Number of Hematology/Biochemistry per patient in each category of Hematology/Biochemistry tests

LAM

- Overall Number of Urine LAM performed;
    - Number (%) of patients with at least one Urine LAM

- Number of Urine LAM per patient

Xpert

- Overall Number of Xpert performed, overall
  - Number (%) of patients with at least one Xpert
  - Number of Xpert per patient
- Overall Number of Xpert performed, by specimen
  - Number (%) of patients with at least one Xpert in each specimen
  - Number of Xpert per patient and per specimen

4.8.10 Cotrimoxazole (CTX)

- Number (%) of patients who ever started cotrimoxazole.
  - Time (days) between W0 and cotrimoxazole initiation
  - Time between W0 and cotrimoxazole initiation : W0 /]W0-W2] /]W2-W4] / >W4
  - Medication possession ratio of CTX
  - Medication possession ratio of CTX in class: [0-50%] /]50-80%] /]80-95%] / >95% (qualitative variable)
  - Number (%) of patients who permanently discontinued CTX
    - Reasons for CTX permanent discontinuation (qualitative)
- Cumulative time (person-years) spent “off” and “on” CTX