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Impact of a Dolutegravir-based regimen on early mortality in participants with AIDS: a pilot study.

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Content

1. Goals

1.1. Primary

- To assess early (all-cause) mortality rates within the first year of treatment in participants symptomatic with AIDS who started antiretroviral therapy with regimens based on Dolutegravir (DTG) or Efavirenz (EFV).

1.2. secondary

- Evaluate the proportion of participants with suppression of plasma viremia (CV less than 50 copies/ml), at different times of the study;
- Compare CD4+ gain over time for both groups;
- Compare the frequency of adverse events in participants using regimens with DTG and EFV.

2. Clinical Hypotheses

- DTG-based regimens are most effective in rapidly recovering CD4+ cells within the first year of therapy;
- DTG-based antiretroviral regimens are able to promote more rapid suppression of HIV plasma viremia than EFV;
- The group of participants treated with DTG-based regimens will have a lower rate of early mortality than those treated with the comparator drug.

3. Background and Justification

Currently available antiretroviral agents (ARVs) have made it possible to successfully treat virtually all HIV-infected participants, but some problems related to early mortality are still a matter of concern, especially in countries with limited resources (1,2). There are several reports showing that these participants have a significantly higher risk of death during the first few months of treatment compared to results observed in developed countries (3-11). One of the consistently detected risks for early mortality across these reports is low baseline CD4+ counts, although it does not appear to be the only reason for such an outcome. Other factors associated with higher mortality rates for participants starting antiretroviral therapy (ART) are anemia, low body weight, and ongoing opportunistic infections (12,13). Mortality rates for participants starting

antiretroviral therapy are quite variable, ranging from 1.8%, as demonstrated by a study carried out in Baltimore/USA, to values as high as 54%, in some areas of the African continent (3- 13).

A recent study comparing mortality rates between low-income and high-income countries in participants with AIDS starting ARV therapy demonstrated that the risk ratio for early death was 4.3 times higher (95% CI: 1.6 - 11 .8), in poorer countries, but dropped to 1.5 after seven months of therapy (6). Furthermore, another report comparing mortality rates among participants with AIDS in Brazil and the USA showed that individuals with CD4+ cell counts below 50 cells/mm³ had a 4.8 times greater risk of death after starting ART and the proportion of early deaths in the first three months was significantly higher for Brazilian participants compared to Americans (14).

In Brazil and other developing countries, there is still a large proportion of participants with AIDS who are diagnosed with AIDS, or who only seek health care for HIV infection in the final course of the illness. While a median first CD4+ cell count below 200 is a frequent finding for most countries in the world, it is expected to be even lower for participants living in resource-limited countries, making the problem of early mortality an issue. important concern.

Dolutegravir (DTG), an HIV-1 integrase inhibitor, is a potent and safe antiretroviral drug (14). Available evidence suggests that drugs in this class promote a more rapid reduction in HIV-1 plasma viremia, and a greater increase in CD4+ cell count, compared to EFV (15,16).

We propose to compare the impact of DTG versus EFV on early mortality rates in critically ill participants starting antiretroviral therapy (CD4+ <50 cells/mm³).

4. Study Design

This is a pilot, open-label study to prospectively assess the rate of early all-cause mortality in participants initiating ART with DTG-based regimens. Retrospectively, the medical records of participants who used EFV in the years 2014-2016 will be reviewed for comparison purposes.

5. Local

The study will be conducted by FBaI - Fundação Bahiana de Infectologia (Bahia) - Investigator: Dr. Carlos Brites, and will include 4 additional sites in different Brazilian cities (Manaus, Natal, Florianópolis, and Porto Alegre)

6. Sample size

The total number of participants included in each study arm will be 92. The calculation of this sample size is detailed in the SAMPLE SIZE section.

6.1. Primary outcome

- The primary study endpoint will be the all-cause mortality rate in the first year of therapy for critically ill participants starting ART.

6.2. Secondary Outcomes

- The proportion of patients who achieved a Viral Load (CV) below 50 copies/ml at weeks 4, 8, 12, 24 and 48;
- Gain of CD4+ cells after 24 and 48 weeks
- Frequency of adverse events in participants receiving DTG or EFV therapy.

7. Inclusion criteria

7.1. Retrospective Group

- Participants with confirmed HIV-1 infection (Western Blot positive or HIV-1 RNA > >1,000 copies/ml);
- Having used EFV as initial therapy in the years 2013-2016;
- Baseline CD4+ cell count equal to or less than 50 cells/mm³;
- Age equal to or greater than 18 years;
- Plasma viral load immediately prior to initiation of therapy ≥ 1000 HIV-1 RNA copies/ml.

7.2. Prospective Group

- Participants with confirmed HIV-1 infection (Western Blot positive or HIV-1 RNA ≥ 1000 copies/ml);
- Not having previously used any ARV (treatment-naïve participants);
- Baseline CD4+ cell count equal to or less than 50 cells/mm³;
- Age equal to or greater than 18 years;

- Plasma viral load ≥ 1,000 HIV-1 RNA copies/ml in the last 30 days.
- The participant or his/her legal representative is willing and able to understand and provide signed and dated free and informed consent prior to any study procedure.

8. Exclusion Criteria

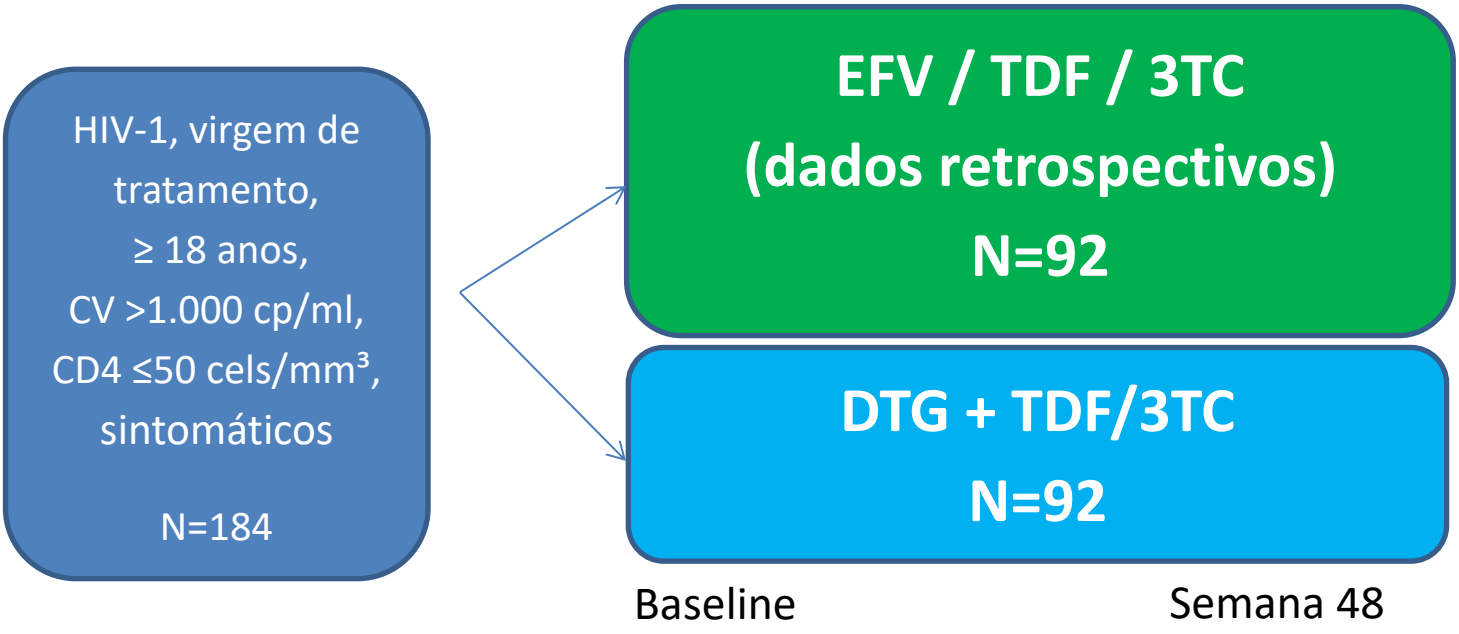
8.1. Retrospective Group

- Asymptomatic individuals (at the beginning of ART).

8.2. Prospective Group

- Undetectable plasma viral load at screening;
- CD4+ cell count > 50 cells/mm³;
- Age less than 18 years old;
- Asymptomatic individuals.

9. Study Flowchart



10. Study Procedures

10.1. Retrospective Group

Procedures	*Basal	Without 24	Without 48
TCLE	Not applicable		
Inclusion and Exclusion Criteria	X		
Medical History	X		
Adverse events	During the 48 weeks		
CV HIV-1	X	X	X
CD4+ / CD8 count	X	X	X
Biochemistry	X	X	X
Hematology	X	X	X

NOTE: A window of -30/+30 days for each visit will be acceptable for collecting this data.

*In the baseline visit, results of laboratory tests up to 90 days before screening will be accepted.

10.2. Prospective Group

Procedures	Basal	Without 4	Without 8	Without 16	Without 24	Without 48
TCLE	X					
Inclusion and Exclusion Criteria	X					
Medical History	X					
Adverse events		X	X	X	X	X
CV HIV-1	X	X	X	X	X	X
CD4+ / CD8 count	X	X	X	X	X	X
Biochemistry	X	X	X	X	X	X
Hematology	X	X	X	X	X	X
Plasma Sample (Storage)	X					
Vitamin D3	X				X	X

NOTE: A window of -30/+30 days for each visit will be acceptable for collecting this data.

10.3. Basal Critical Ratings

The Informed Consent Form (TCLE) must be obtained from each potentially eligible individual (or their legal representative) by the study center staff before any study procedure . The TCLE must have been approved by the Research Ethics Committee (CEP). Upon signing up, participants will complete initial assessments to determine their eligibility. Each participant selected for evaluation of inclusion in the study will be assigned an allocation number, given sequentially in chronological order of inclusion.

10.4. Initial Evaluation Period

Participants who meet the eligibility criteria will be included after signing the TCLE.

10.5. Efficacy Assessment

Plasma samples will be collected at each evaluation point, according to table 10.2. The method used to measure VC will be real-time PCR, with a detection limit set at 40 copies/ml. The CD4+ / CD8 cell count will be determined by flow cytometry.

- Primary Efficacy Parameters
  - The all-cause mortality rate in the first year of therapy using an absence, switch, discontinuation = failure (MSDF) algorithm, as per the FDA algorithm.
- Secondary Efficacy Parameters
  - Proportion of patients achieving VC < 50 copies/ml at 4, 8, 12, 24 and 48 weeks;
  - CD4+ T cells gained at each assessment point;
  - Frequency of adverse events in participants receiving DTG or EFV therapy.

Safety assessments will consist of monitoring and reporting of all adverse events and serious adverse events in participants receiving DTG. Safety will be assessed through regular physical examination, and laboratory monitoring of hematology, lipids, glucose, liver enzymes and creatinine levels . All abnormalities detected in laboratory results and clinical changes will be reported in the Clinical File (CRF).

The laboratory parameters to be tested will be:

- Complete blood count;

- Fasting Glucose, Total Cholesterol and Fractions, Triglycerides, Vitamin D3 (25-OH), Creatinine, TGO/TGP and Alkaline Phosphatase.

10.6. Security Parameters

- Incidence and severity of adverse effects and laboratory abnormalities;
- Absolute values and changes in results throughout the study;
- Proportion of participants discontinuing therapy due to adverse events;
- Changes in the initial physical examination.

10.7. Toxicity Control

The occurrence of an Adverse Event (AE) during the study period will be evaluated by the investigator and classified according to the Division of AIDS (DAIDS) toxicity scales.

The safety of Dolutegravir as initial therapy in critically ill participants has not been fully defined and the investigational product may be discontinued by the investigator according to the severity of the AE. No reduction of DTG doses will be allowed. Any change in the use of DTG must be recorded in the CRF. In case there is a need to interrupt the DTG, the drug will be replaced by a PI/r.

Participants who experience a grade 1 or 2 AE will continue to receive DTG at the Investigator's discretion. Subjects who experience a Grade 3 AE may continue to use DTG if the investigator is of the opinion that the toxicity was not caused by the drug, but if the AE is found to be caused by the DTG, or if it is classified as a Grade 4, the drug should be interrupted.

10.8. Follow-up of Participants

All participants included in the protocol in the Prospective Group will be evaluated at baseline and after 4, 8, 16, 24, 36 and 48 weeks.

11. Study Duration

We estimate to recruit 92 participants over a period of 10 months. Considering the need for follow-up to 48 weeks, the total duration of the study will be 22 months. An additional two months will be spent on data analysis and manuscript preparation, giving us a total of 24 months to complete the study. The retrospective study should be

completed within the same time period. The selection of patients will be carried out considering eligible participants, consecutively, until the predicted N is reached.

12. Statistical Analysis and Justification of the Sample Size

12.1. Sample Size Justification

Mortality rates are quite variable, depending on region, specific study, and population.

Most studies from African countries have shown that mortality in the first 3 months of ART for participants with CD4+ cells under the threshold of 50 cells/mm³ is generally greater than 30%, and may reach 52% in some reports.

On the other hand, in developed countries, most deaths in such a population usually occur after 7 months of therapy and the mortality rate is just as low (1.8% for the first year of treatment).

We estimated that early mortality for participants included in the EFV arm would be similar to the rates detected in African countries (around 30%). We hypothesize that participants using DTG-based regimens would benefit from faster recovery of CD4+ cell count and that they behave like those individuals starting antiretroviral therapy in developed countries (mortality rate around 2%).

Considering a lower limit of 2% (DTG arm) and an upper limit of 25% (EFV arm), a 95% CI and 80% power to detect differences between groups, it would be necessary to treat a total of 84 participants (42 on each arm). Adding 10% for dropouts, this would result in a total of 92 subjects (46 in each arm).

With the recent changes in treatment recommendations, all 92 participants will receive DTG. Participants who used EFV will be retrospectively evaluated, through the review of medical records, in an identical number (92 participants).

This will be an exploratory pilot study.

12.2. Statistical Analysis Plan

12.3. General considerations

intent-to-treat population , defined as all participants who are randomized to treatment. With the exception of the Primary Efficacy Endpoint Analysis, percentage responders to

the intention-to-treat population, missing data will not be estimated or carried forward in any statistical analyses.

All comparisons of treatment groups will be performed using two-tailed tests at a significance level of 0.05 ($p< 0.05$). The null hypothesis for all analyzes is that there is no difference between treatment groups.

All summaries, statistical analyzes and individual participant registration data described below will be provided in separate attachments. Separate listings will be provided for each of the treatment groups in the intent-to-treat population.

12.4. Disposition of Participants

Summaries of the number of patients randomized, number completing the study, and incidence of protocol violations will be provided for each treatment group. The number (%) of participants with protocol violations that may affect the study objectives will be based on database analysis. This assessment will be made prior to determining the treatment allocation for all participants in the database.

12.5. Demographic Characteristics and Disease

The statistical analyzes described below will be completed for:

- The participating intent-to-treat population;
- The evaluable population of efficacy.

Demographic Characteristics

The table below identifies the demographic and disease characteristics used to determine the comparability of treatment groups and the methods used to analyze them.

Table 1 - Variables analyzed to determine comparability

Variable	Analysis method
Baseline age	One-way ANOVA/KW
baseline CV	One-way ANOVA/KW
basal CD4+	One-way

	ANOVA/KW

The primary efficacy endpoint is the number (%) of participants who met the primary endpoint (HIV-1 RNA Viral Load <50 copies/ml) at the week 48 visit (or discontinuation). Participants will be counted as non-responders if they do not show up by Week 48 (or termination).

The DTG treatment group will be compared to the EFV group with respect to the percentage of responders using a chi-square test. Two-tailed 95% confidence intervals for the percentage of responders will be calculated for each treatment group.

The following table identifies secondary efficacy endpoints and the methods used to analyze them.

Table 2 - Variables analyzed at the main points of analysis

Variable	Analysis method
Frequency of Adverse Events	Chi-square test
Proportion of participants achieving CV <50 copies/ml at each analysis point	Chi-square test
proportion of deaths	Chi-square test
CD4+ count at each analysis point	One-way ANOVA/KW

12.6. security endpoints

Summaries and statistical analyzes of safety endpoints will be completed for the intention-to-treat population. The incidence of at least one grade III or IV event will be the primary safety endpoint of the study. Treatment groups will be compared with respect to the percentage of participants with at least one grade III or IV adverse event using a Chi-square test.

12.7. Serious Adverse Events

Secondary safety endpoints are the incidence of adverse events categorized according to preferred term and body system, clinically significant laboratory test results, and changes in vital signs. Treatment groups will be compared with respect to the percentage of participants with clinically significant laboratory test results at Week 4, 8, 16, 24, 36, or 48 visits using Chi-square.

Summaries of physical examination data, vital signs (actual value and change from baseline), and laboratory data (actual value and change from baseline) will be provided at each visit.

12.8. Report of Adverse Experiences

The investigator and the site team will be responsible for documenting, detecting and reporting events that meet the definition of Adverse Event is defined as any unwanted medical event occurring in a participant or individual involved in a clinical investigation protocol, which may be transiently associated with the use of a medical product, regardless of whether or not it is considered to be related to the investigational product. A serious adverse event (SAE) is defined as any medical occurrence, resulting in death, or life-threatening, requiring hospitalization, resulting in impairment/disability, being a congenital anomaly, or all liver injuries grade 3 or higher , caused by drugs.

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14. Plan for Publication

We intend to have enough data to guarantee a scientific publication 3 months after the end of the protocol. We plan to have 2-4 abstracts submitted to international scientific meetings by the end of the research project. Finally, we think that at least 2 scientific papers will be published with the results of the project.