Title:

Evaluation of the use of antiretroviral regimens containing Raltegravir for prophylaxis of mother-to-child-transmission of HIV infection in pregnant women presenting with detectable viral load after 28 weeks of gestation: a pilot study

CARLOS BRITES, MD, PhD

UNIVERSIDADE FEDERAL DA BAHIA TEL. 557192329552

EMAIL: crbrites@gmail.com

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1. Background and rationale:

The current available antiretroviral (ARV) agents make possible a successful treatment of virtually all HIV-infected patients, even those heavily experienced subjects, with a history of previous failure to ARV drugs of different classes (1-3). The introduction of new drug classes was determinant to this achievement, since most of viral strains are susceptible for such drugs, allowing treating experienced patients as if they were drug naïve (3). However, some problems are still present, especially for specific populations, like pregnant women and infants. For these groups, most of currently available drugs are not used, because the lack of information on safety, efficacy, and pharmacokinetic/dynamic behavior of ARVs drugs (4-8).

The MTCT is still a problem in certain areas of the world, especially in resource limited settings. It has been demonstrated that the introduction of active ARV therapy for pregnant women, leading to suppression of HIV viremia by the end of pregnancy is a crucial step in the interruption of MTCT (9-11). Pregnant women that reaches a viral load below 1,000 copies of HIV-1 RNA/ml of plasma, by the end of pregnancy, has a decrease in the rates of HIV-1 transmission to less than 2% (10,11). However, some women presents with multi-drug resistant HIV-1 strains, making difficult the choice of an active ARV regimen, since some drugs are not recommended in pregnancy (12,13). On the other hand, in some settings, women often present to their first antenatal care visit late in the pregnancy, posing an additional problem: how to effectively treat these patients to assure they will have an undetectable viral load at the moment of delivering? Depending on the plasma viremia magnitude, and viral susceptibility it can take 6 or more weeks to reduce the viral load to less than the desired 1,000 copies of HIV-1 RNA / ml of plasma. To achieve this goal, it would be necessary the use of a potent, very efficacious ARV regimen that could provide such viral decay in a very short period of time.

In Salvador, Brazil, most of HIV-infected pregnant women are attended in the CEDAP, a referral center for AIDS care. In average, 120 pregnant women are attended at the center every year. An estimated 40% are late-presenters, and have their first medical evaluation with a gestational age higher than 30 weeks. The remaining 60% are already on follow up in the center, or arrive early in the course of pregnancy. However, about 15% of them has some degree of resistance to ARV drugs, and start antenatal care with detectable viral load. Other important point, around 8% of these women are coinfected

by another human retrovirus, the HumanT-cell Lymphotropic Virus type 1 (HTLV-1), which has a life cycle similar to that found in HIV-1, and shares a great similarity between replication enzymes, like reverse transcriptase (RT) and integrase, with HIV-1 (14,16). In vitro studies have demonstrated that most nucleoside reverse transcriptase inhibitors active against HIV-1 are also effective in blocking the HTLV-1 RT activity. Preliminary studies conducted by our group have shown that coinfection with these two agents was associated with a much higher rate of transmission of both viruses (12). The MTCT of at least one of these agents was detected in 63% of 96 coinfected women. Even considering the fact that they probably did not receive any MTCT prophylaxis, the transmission rate was much higher than one could expect. It suggests that coinfection may enhance MTCT for both, HIV-1 and HTLV-1.

Raltegravir (RAL), the first HIV-1 integrase inhibitor, is a potent and safe ARV drug (18). The available evidence suggests that it has no genotoxic potential, and promotes a rapid decline in HIV-1 plasma viremia. In addition, RAL is highly active against viral strains presenting different degrees of resistance to other ARV drugs. Thus, RAL could be an ideal candidate to be used for prevention of MTCT for women with detectable viral load, presenting late in the course of pregnancy. Another attractive point is to consider that, due to the similarity between the integrase enzyme of HIV-1 and HTLV1, RAL could be active against HTLV-1, blocking its replication. If our hypothesis is correct, the use of RAL-containing ARV regimens would reduce the MTCT of both agents.

2. Objectives

Primary:

=>to evaluate the efficacy of RAL containing ARV regimens, compared to a SOC therapy in providing a HIV-1 RNA plasma viral load below 50 copies/ml, at the end of pregnancy, for late-presenters HIV-1-infected women.

Secondary:

=>to evaluate the time to viral suppression in pregnant women using RAL based regimens and comparators;

=>to compare the frequency of adverse events for women using RAL-based ARV regimens and comparators, and for their babies;

=> to evaluate the frequency of MTCT of HIV-1 and HTLV-1 for pregnant women using RAL-based regimens or comparators;

2.1.1 Clinical hypotheses.

- RAL-based ARV regimens are able to suppress HIV viremia in late-presenters pregnant women to undetectable levels at the moment of delivery;
- RAL-based regimens are safe for use in pregnant women, and able to prevent MTCT
- RAL-based regimens are able to prevent MTCT of both, HIV and HTLV, in pregnant, coinfected women

3. *Study design:* This is an exploratory, pilot study to compare the safety and efficacy of RAL-containing ARV regimens and standard of care (SOC - AZT+3TC+LPV/r) therapy for the prophylaxis of HIV-1 and HTLV-1 MTCT, in Bahia, Brazil. Sample size: We intend to enroll pregnant women who accept to participate in the study. We estimate a total of 180 pregnant women will be attended in a 18 months period. From this group, we expect that at least 50 patients will be "late-presenters", and eligible to enter the study. Considering a 8% prevalence of coinfection by HTLV-1, we expect to detect 4-5 coinfected women.

Study procedures- Forty drug-naïve women initiating ARV therapy during "late" (gestational age equal or higher than 28 weeks) pregnancy will be invited to enter the study. They will be randomly assigned to receive a RAL-based ARV regimen (AZT+3TC+RAL), or SOC therapy (AZT+3TC+LPV/r). All HTLV-positive women will be assigned to the RAL arm. Baseline plasma samples will be stored to genotyping for all patients, but the women will be tested only if they present detectable viral load at the end of the trial, for detection of primary resistance mutations. We intend to include 22 patients in each arm of the study. Participation in the study will be offered to all eligible women attending routine medical visits, and they will be included consecutively until we reached the intended number (22 in each arm). Rates of MTCT for both agents will be assessed by molecular detection of HIV-1 and/or HTLV-1 in plasma (HIV-1) and PBMC (both agents) of newborns, after 4 weeks of delivery. After delivering, all women will be referred to their assistant physicians, in order to define if they will continue on ARV therapy or if they interrupt it. The patients enrolled in RAL will switch to SOC treatment if they are recommended to maintain ARV treatment, since the Brazilian Ministry of Health guideline does not recommend RAL as part of initial ARV regimens.

The main study endpoint will be the proportion of patients in each arm with HIV-1 RNA viral load < 50 copies/ml at the end of pregnancy.

Secondary endpoints:

- the time for achieving a VL below 50 copies/ml,
- the rate of MTCT for HIV-1 and / or HTLV-1
- Frequency of adverse events for women receiving RAL or SOC therapy
- Frequency of adverse events for babies born from all mothers included in the study, until completing 6 months of age

Inclusion criteria:

- Pregnant women with confirmed HIV-1 infection (positive Western blot or plasma HIV-1 RNA >1,000 copies/ml)
- Gestational age higher than 28 weeks
- Age equal or higher than 18 years
- HIV-1 plasma viral load ≥ 1,000 copies of HIV-1 RNA/ml
- HTLV serology result
- ARV naïve
- Any CD4 count

Exclusion criteria

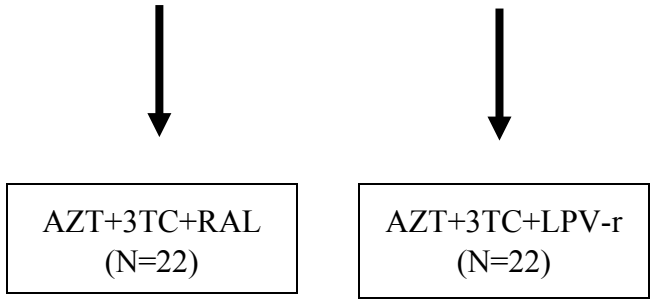
- Previous use of any ARV
- Age lower than 18 years
- Undetectable plasma viral load at screening

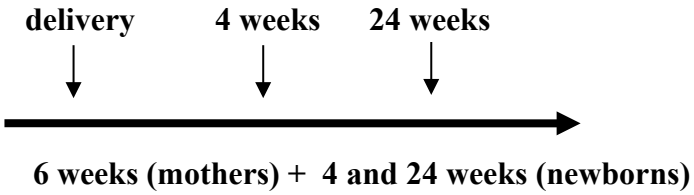
Study Flowchart

-44 pregnant women who meet inclusion criteria:

- Age equal or higher than 18 years

-HIV-1 PVL ≥ 1,000 copies of HIV-





2.5.1. Study timetable

Procedure	**Baseline**	**Week 2**	**Week 4**	**Week 5**	**Week 6**	**Week 4** (newborn)	**Week 24** (newborn)
Informed consent	**X**						
Inclusion / Exclusion criteria	**X**						
Medical History	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse events		**X**	**X**	**X**	**X**		**X**
HIV-1 Viral Load	**X**	**X**	**X**	**X**	**X**	**X**	
CD4/8 count	**X**		**X**		**X**		

Chemistry	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Hematology	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Plasma sample (storage)	**X**						
HIV / HTLV Proviral load						**X**	
HTLV serology	**X**						

2.5.2. Critical evaluations at baseline

Written informed consent (IC) must be obtained from each women before any study initial evaluation procedure be performed. The informed consent must be previously approved by institutional IRB. After signing the IC the women will conclude the initial evaluation to define their eligibility to enter the protocol. Following recruitment, patients will be randomly l assigned to one of the study arms, and will receive a sequential protocol number. Each patient will receive only one allocation number.

2.5.3. Period of initial evaluation

Patients will be randomized as soon as they conclude the initial evaluation. All results of initial evaluation must be available before randomization.

Patients fulfilling the eligibility criteria will be randomized, and will receive a randomization number. The will not be eligible for a new initial evaluation if they were excluded from the study after randomization was completed, for any reason.

2.5.4. Efficacy evaluation

Plasma samples will be collected in each time point, according to the table above, for HIV-1 RNA viral load measurement. The method for VL measurement will be b-DNA or Real-Time PCR, with a limit of detection established in 50 copies/ml, or lower. CD4/8+ cells count will be determined by flow

cytometry.

The primary efficacy parameter will be the HIV-1 RNA VL<50 copies/ml at week 6 (end of pregnancy), using an algorithm missing, switch, discontinuation = Failure (MSDF), according to FDA snapshot algorithm.

Secondary parameters of efficacy will include the following:

- the time for achieving a VL below 50 copies/ml, and
- the rate of MTCT for HIV-1 and / or HTLV-1

2.5.5. Safety evaluations will consist of monitoring and report of all adverse events and serious adverse events for women receiving RAL or SOC therapy, and for their babies, until completing 6 months of age. Safety will be assessed through regular physical examination, and laboratory monitoring of hematology, lipids, glucose, liver enzymes, and creatinine levels. All detected abnormalities in lab results will be reported in CRF.

The laboratory parameters to be tested will be:

-White blood cells count, hemoglobin, platelets

-Fasting glucose, Total Cholesterol, LDL, HDL, and VLDL cholesterol, triglycerides.

- Creatinine, ALT, AST, Alcaline Phosphatase.

2.5.6. Safety parameters

-Incidence and severity of AEs and laboratory abnormalities

- absolute values and changes in results overtime

Proportion of patients interrupting therapy due to AEs

- Changes in baseline physical examination

2.5.7. Toxicity control

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

The safety of Raltegravir in pregnant women was not completely defined, and the investigational product will can be interrupted by the investigator, according to the severity of AE. No reduction on RAL doses will be allowed. All change in the use of RAL must be reported in CRF. In the case of the need of interruption of RAL, the drug will be switched to LPV/r.

Patients presenting a grade 1 or 2 AE will continue to receive RAL, at Investigator discretion. Patients presenting a grade 3 AE can keep using RAL, if the investigator consider the toxicity was not caused by

the drug, but if the AE is considered to be caused by RAL, or if it is classified as grade 4, the drug must be interrupted.

2.5.8. Patients follow up

All patients included in the protocol will be evaluated at baseline, and after 2, 3, 4, 5 and 6 weeks. The newborns will be assessed by a blood collection after 4 weeks, and to a clinical and laboratory evaluation after 24 weeks, to assess any potential AE caused by their mother´s treatment.

Study duration: We intend to recruit the total sample in a 12 months period. Additional 6 months will be spent on newborns evaluation, statistical analysis, and final reviews / reports. Thus, the intended duration of the study will be 18 months.

Sample size justification

This will be an exploratory, pilot study. Power considerations will not apply.

2.7.2 Plan for Statistical Summaries and Analyses

General Considerations

All statistical summaries and analysis will be provided for the intent-to-treat population, defined as all patients who are randomized to treatment. Summaries and analyses of the baseline data and efficacy data will also be provided for the efficacy-evaluable population, defined as patients who meet the inclusion/exclusion criteria, take at least 80% doses of study medication, and complete the Week 6 (or termination) visit.

With the exception of the analysis of the primary efficacy endpoint, percentage of responders for the intent-to-treat population, missing data will not be estimated or carried forward in any statistical analyses.

All comparisons of the treatment groups will be performed using two-sided tests at a 0.05 level of significance (= 0.05). The null hypothesis for all analyses is that there is no difference between the treatment groups.

All summaries, statistical analyses, and individual patient data listings described below will be provided in separate appendices. Separate listings will be provided for each of the treatment groups in the intent-to-treat population as well as for the group of patients not randomized.

Disposition of Patients

Summaries of the number of patients randomized, the number of those completing the study, and the incidence of protocol violations will be provided for each treatment group.

The number (%) of patients with protocol violations that might affect endpoints of the study will be based on review of the database. This assessment will be made prior to determination of treatment assignment for all patients in the database.

Demographic and Disease Characteristics

The statistical analyses described below will be completed for:

the intent-to-treat patient population the efficacy-evaluable population

Demographic Characteristics

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

Table 1: Variables Assessed to Determine Comparability

Variable	Method of Analysis
Gestational Age at randomization	One-way ANOVA/KW
Gestational Age at randomization	One-way ANOVA/KW

Baseline VL	One-way ANOVA/KW
Baseline CD4	One-way ANOVA/KW

Efficacy Endpoints

The statistical analyses described below will be completed for:

the intent-to-treat patient population the efficacy-evaluable population

The primary efficacy endpoint is the number (%) of patients achieving the primary endopoint (HIV-1 RNA Viral Load <50 copies/ml) at the Week 6 (or termination) visit. Patients will be counted as non-responders if they are missing Week 6 (or termination). The Raltegravir treatment group will be compared to SOC group with respect to percentage of responders using a Chi-square test. Two-sided 95% confidence intervals for the percentage of responders will be calculated for each treatment group.

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

Table 2 - Variables Assessed to Evaluate the main endpoints

Frequency of Adverse events (mother and newborns)	Chi-square test
Time to reach VL below 50 copies	One-way ANOVA/KW
% MTCT (HIV, HTLV)	Chi-square test

For each of these variables, the Raltegravir treatment group will be compared to the SOC group.

Safety Endpoints

The summaries and statistical analyses of the safety endpoints will be completed for the intent-to-treat population. The incidence of at least one Grade III or IV adverse event will be the primary safety endpoint of the study. The treatment groups will be compared

with respect to the percentage of patients with at least one Grade III or IV adverse event using a Chi-square test.

Summaries of the number (%) of subjects in each treatment group with at least one adverse event, classified according to preferred term and body system, will also be provided for:

- drug-related adverse events
- serious adverse events

Secondary safety endpoints are the incidence of adverse events classified according to preferred term and body system, clinically significant laboratory test results, and changes in vital signs. The treatment groups will be compared with respect to the percentage of patients with clinically significant laboratory test results at the Week 2, 4, 5, or 6 Visits using Chi-square tests. Summaries of the physical examination data, vital signs (actual value and change from baseline), and laboratory data (actual value and change from baseline) at each visit will be provided.

Power/Sample Size:

Since this is a pilot study, power considerations does not apply.

Specific Drug Supply Requirements The RAL open label supply will be provided by Merck. The additional study drugs (AZT+3TC, LPV/r) will be provided by the Brazilian AIDS Program, since they are part of SOC procedures The drugs must be supplied as its commercial presentation.

Adverse Experience Reporting - The investigator and the site team will be responsible for detection, documentation, and reporting of any events that fulfill the AE definition. AE is defined as any undesired medical event occurring in a patient or individual involved in a clinical investigation protocol, which may be transiently associated to the use a medical product, independently of being considered related or not to the investigational product. A serious adverse event (SAE) is defined as any medical occurrence that results in death, or that be life-threatening, needs or makes hospitalization longer, results in deficiency/disability, be a congenital anomaly/birth defect, all liver injuries grade 3 or higher, caused by drugs

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