

Preliminary safety results of co-administration nevirapine (NVP) or efavirenz (EFV), and rifampicin (RMP) in HIV-tuberculosis (TB) co-infected patients in Maputo (Mozambique), ANRS 12146 (CARINEMO)

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Introduction

- In TB-HIV co-infected patients, NVP-based antiretroviral therapy (ART) is the 1st line treatment in most sub-Saharan Africa.
- Co-administration with RMP may result in sub-therapeutic NVP concentrations.
- EFV-based ART is recommended in TB-HIV co-infected patients.
- Problem of access to EFV and teratogen risk in childbearing women.
- Skipping NVP two weeks leading dose in patients under RMP could prevent sub-therapeutic NVP levels but could increase toxicity.
- No large randomised clinical trial evaluated the efficacy and safety of NVP when given in co-administration with RMP.

Objective

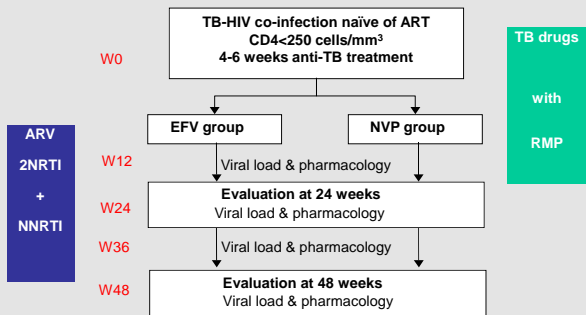
- To assess preliminary overall safety results of the CARINEMO trial between November 2007 and December 2008.

CARINEMO trial

- To compare, in terms of therapeutic efficacy and clinical safety, NVP-based ART to EFV-based ART in HIV-TB co-infected patients with RMP.

Methods

- Open-label, randomized non-inferiority trial in Maputo, Mozambique.



Patients with a Karnofsky score < 60%, ALAT \geq 4N (Hepatitis grade 3 or 4), grade 4 biological result and women with a positive urine test for pregnancy were excluded

Study drugs

- Lamivudine 30mg + stavudine 150mg twice a day +
- EFV 600mg once daily or
- NVP 200mg twice daily **without leading dose**

Safety assessment

- Weekly clinical assessment during first 8 weeks and then monthly
- Bi-weekly alaninotransferase (ALAT) measure during first 8 weeks and then monthly

Treatment Emergent Adverse Event (TEAE) after 1st study drug intake

- TEAE of interest: hepatitis and rash
- Grading: I - mild, II - moderate, III - severe, IV - life threatening
- Use of MEDdra coding

Serious adverse events (SAE)

- Whose progression is fatal (death)
- Immediately life-threatening
- Grade 4 laboratory abnormality
- Results in a clinically significant handicap (temporary or permanent)
- Leads to hospitalization or prolongation of hospitalization
- Results in a congenital abnormality or defect in the offspring

Results

- Until December 2008, 236 patients were randomized.
- Treatment discontinuation in 4.7% (11/236) of patients.
 - Due to death (6)
 - Consent withdrawal (3)
 - Lost of follow-up (1)
 - Other (1)

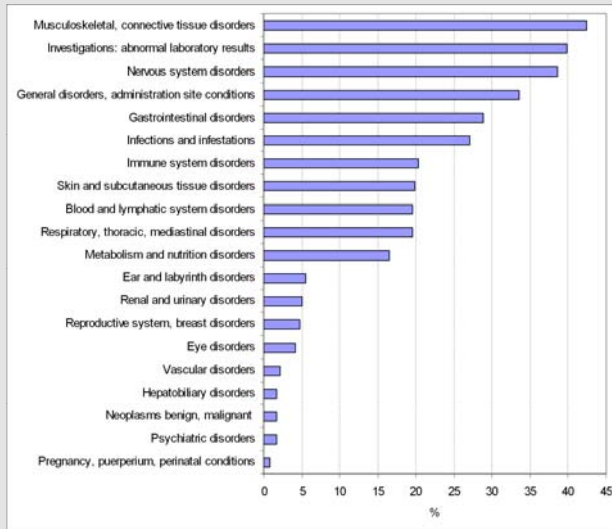
Overall baseline characteristics of randomized patients

	n	%
Sex (% male)	236	60.3
Age, years, median (IQR)	236	34 (28-41)
Baseline weight, Kg, median (IQR)	236	53.0 (47.9-58.9)
Baseline Body Mass Index, Kg/m ² , median (IQR)	236	19.0 (17.6-20.4)
Pulmonary TB, %	236	73.3
Delay for ARV initiation, weeks, median (IQR)	236	4.7 (4.3-5.1)
ALAT, U/l, median (IQR)	228	22.2 (14.0-36.4)
Hemoglobin, g/dL, median (IQR)	231	9.4 (8.5-10.5)
Baseline CD4+ cell count, cells/mm ³ , median (IQR)	230	85.0 (44.0-148.0)
Baseline HIV-1 RNA, log, median(IQR)	198	5.5 (5.1-6.0)
HBsAg reactive, N (%)	128	34 (26.6)

Results

Adverse Events

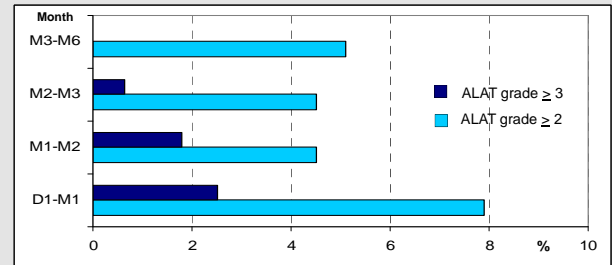
- 204/236, 86.4% of patients presented at least one TEAE.



TEAE of interest

Hepatitis

Percentage of ALAT increase based on the intensity



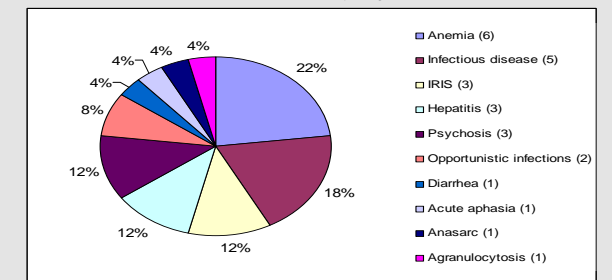
Grade I: 1.25-2.5xUNL, Grade II: >2.5-5.0xUNL, Grade III: > 5.0-10.0xUNL, Grade IV: >10.0xUNL
Five (2.1%) patients permanently interrupted treatment due to hepatitis.

Rash

- Skin related TEAE were reported in 19.9% (47/236) but none were severe
- 4.7% (11/236) patients had an ALAT increase (\geq grade 3) and one skin allergic reaction

SAE

- 26 SAE were declared and in 6 patients resulted in death.
- None of the death was related to use of the study drugs.



Discussion and Conclusion

- There was no serious safety concern in the CARINEMO trial.
- The absence of severe rash, the relatively low number of severe hepatitis and definitive treatment interruptions due to TEAE are reassuring but need to be confirmed with final results expected at the end of 2010.

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