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Hematological Benefit of Switching From Regimens Combining Protease Inhibitors and Zidovudine plus Lamivudine to Once-daily Emtricitabine, Didanosine and Efavirenz. A Sub-study of the ANRS 099 ALIZE Trial

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Introduction

- Anemia is a relatively common manifestation of HIV infection and AIDS and is an independent risk factor for decreased survival among HIV-infected patients (Berhane K et al, J AIDS, 2004, 37:1245-52)
- HAART therapy is associated with resolution of anemia, but several nucleoside analogues used for the treatment of HIV-infection are myelosuppressive and may contribute to the incidence and the severity of anemia (Moyle G et al, Clinical Therapeutics, 2004, 26:92-97)
- Anemia and neutropenia associated with HIV-infection and antiretroviral therapy may impact the quality of life of patients, and are well known treatment limiting side-effect of drugs such as zidovudine (ZDV)
- It is unclear however if patients tolerating long-term therapy with ZDV-including regimens will benefit from a switch to non-ZDV-including HAART

Objectives

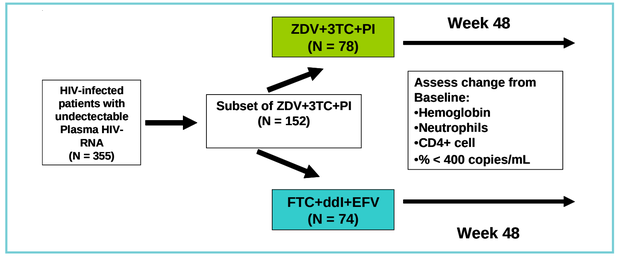
- To assess the hematological benefit of switching from an ZDV+3TC+ PIs containing regimen to a once-daily FTC+ddI+EFV regimen in long term virologically suppressed HIV-infected patients

Methods

- ANRS-099 was a randomized, open label, 48-week switch study in 355 patients on a stable PI-containing HAART regimen with plasma HIV RNA levels <400 copies/mL in the previous 6 months. Patients were randomized to continue the PI regimen or switch to the entirely once-daily regimen of FTC+ddI+EFV (Figure 1)
- A subset of enrolled patients (n = 152) who were taking ZDV+3TC as a component of their stable PI HAART regimen at entry were identified. Amongst those patients, 74 patients were randomized to once-daily FTC+ddI+EFV, and the remainder were randomized to continue their ZDV+3TC+PI regimen.
- Change from baseline in CD4+ cell count, hemoglobin and neutrophils were compared between randomized treatment arms at Week 48 in this population and compared using a two sample t-test
- Week 48 plasma HIV-1 RNA comparisons were made using differences in binomial proportions (% < 400 copies/mL) between treatment groups with p-values from the associated normal distribution

Methods (cont'd)

Figure 1. ANRS-099 Study Design



Results

Table 1. Baseline Characteristics

Demographic/Characteristics	ZDV + 3TC + PI (n = 78)	FTC + ddI + EFV (n = 74)	Total (n = 152)
Gender: n (%)			
Male	67 (86)	62 (84)	129 (85)
Female	11 (14)	12 (16)	23 (15)
Mean Age (years) (SD)	45 (11.6)	45 (10.3)	45 (11.0)
Median [range] HIV-1 RNA (log copies/mL)	1.54 [1.3 - 3.86]	1.65 [1.20 – 2.94]	1.60 [1.20 - 3.86]
Mean CD4+ (cells/mm^3)	575	545	561
Median [range] Prior ART (years)	3.4 [0.6 - 8.7]	3.2 [0.7 - 11.6]	3.3 [0.6 – 11.6]
Median [range] Prior ZDV+3TC (years)	3.3 [0.6 - 8.7]	3.1 [0.7 - 11.6]	3.2 [0.6 - 11.6]

- In this ZDV+3TC+PI subset population, the median duration of HAART was 3.3 years at study entry. The prior median duration of ZDV+3TC was 3.2 years.
- A significant improvement in hemoglobin and neutrophil count was observed in patients switching to the entirely once-daily regimen of FTC+ddI+EFV while maintaining virologic control and immunologic response
- Change from baseline results for hemoglobin, neutrophils, CD4+ T-lymphocytes and plasma HIV-1 RNA are shown in Table 2

Results (cont'd)

Table 2. Change from Baseline in Hemoglobin and Neutrophils at Week 48 by Treatment Group

Lab Parameter	Analysis Variable	ZDV + 3TC + PI (n = 78)	FTC + ddI + EFV (n = 74)	difference	p-value
Hemoglobin (g/dL)	Baseline Mean ± SD	14.0 ± 1.4	13.8 ± 1.3	0.2	0.45
	W48 Change from Baseline	**-0.4**	**+0.7**	**1.1**	**<0.01**
Neutrophils (x10^9/L)	Baseline Mean± SD	3083 ± 1253	2825 ± 1355	258	0.23
	W48 Change from Baseline	**+82**	**+607**	**525**	**<0.03**
CD4+ (cells/mm3)	Baseline Mean± SD	483 ± 322	463 ± 309	20	0.69
	W48 Change from Baseline	+9	+34	25	0.27
Plasma HIV-1 RNA	W48 <400 c/mL (%)	90%	95%	5%	0.26

Figure 2. Mean Change from Baseline in Hemoglobin by Treatment Group and by Week

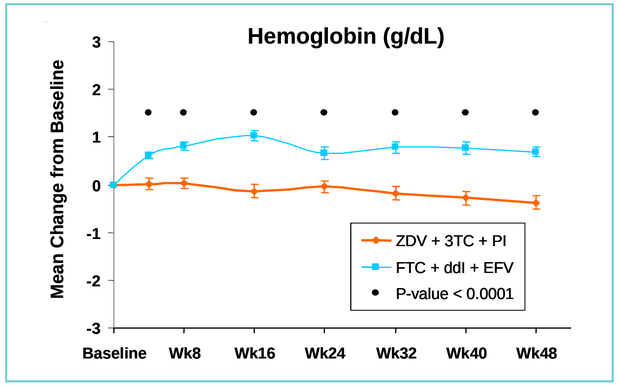
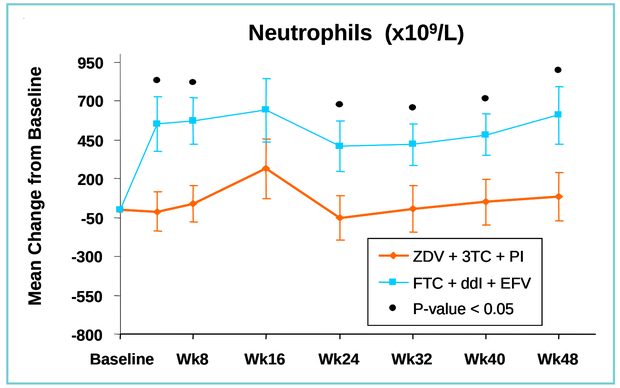


Figure 3. Mean Change from Baseline in Neutrophils by Treatment Group and by Week



Conclusions

- **Even in patients who received and tolerated ZDV+3TC+PI for approximately 3 years, a statistically significant improvement in hemoglobin levels and neutrophils percent was observed at Week 4 continuing through Week 48 after switching to the entirely once-daily regimen of FTC+ddI+EFV**
- **Virologic and immunologic responses were maintained after the switch**
- **An FTC+ddI+EFV regimen can be substituted for a ZDV+3TC+PI regimen in order to reverse bone marrow toxicity while maintaining antiviral and immunological efficacy**