Poster # 544

24-Weeks Virologic Efficacy of Fozivudine in ART-Naïve Patients From Africa

Arne Kroidl[1,6], Tessa Lennemann[1/3], Frederic Ello[2,4], Jimson Mgaya[3], Raoul Moh[2,4], Lucas Maganga[3], Serge Eholie[2,4], Pierre-Marie Girard[5], Friedrich von Massow[7], Christine Danel[2], for the FATI study team

1. Division of Infectious Diseases and Tropical Medicine, Medical Center of the University of Munich (LMU), Germany, 2. Programme PAC-CI, CHU Treichville, Abidjan, Côte d'Ivoire ,
3. NIMR-Mbeya Medical Research Center (MMRC), Mbeya, Tanzaniam, 4. Service des Maladies Infectieuses et Tropicales, CHU de Treichville, Abidjan, Côte d'Ivoire
5. Department of Infectious Diseases, University Hospital Saint-Antoine Paris, France, 6. German Center for Infection Research (DZIF), partner site Munich, Germany
7. Institute for Life Sciences and Environment (i-LSE) GmbH, Heidelberg, Germany

Introduction

Zidovudine (ZDV) is widely used and recommended in combined antiretroviral therapy (ART). However, the clinical utility of ZDV is limited by toxicities, particularly those involving the bone marrow which is especially crucial for resource poor settings where anemia is highly prevalent and treatment monitoring is still limited. In addition, the pharmacokinetics of ZDV is characterized by a short elimination half-life which necessitates administration of ZDV every 8 or 12 hours. Mainly due to toxicity and twice daily dosing ZDV has become only an alternative choice for initial/first line treatment by EACS and WHO guidelines and is no longer recommended in the US DHHS guideline.

Fozivudine tidoxil is a thioether lipid-ZDV conjugate (figure 1). Based on the Enhanced Pro Drug (EPD) Technology FZD is bio-activated by two enzymes (NPP1 and NPP3) into the lipid moiety and intracellularly ZVD-monophosphate (ZVD-MP), the latter of which is subsequently phosphorylated to the active metabolite, triphosphorylated ZDV (figure 2). Cells have a large subset of enzymes transferring nutrients from the extra-cellular environment into the cell. Several of these enzymes have their catalytic activity localized on the outside of the cell membrane. Nucleotide pyrophosphatases / phosphodiesterases (NPPs) belong to this group of cellular proteins. NPP 1 and 3 have been identified as the enzymes which cleave liponucleotides to produce a lipid moiety and a nucleoside-mono-phosphate leading to specific enzymatic bio-activation and intracellular supply of the active principle. Both enzymes exist in a wide range of cell types including virus-infected cells but are not present in bone marrow cells.

Figure 1: Fozivudine tidoxil thioether lipid-ZDV conjugate

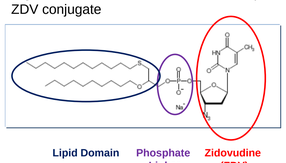
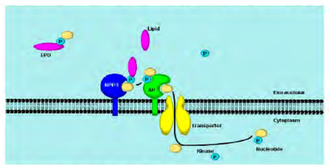


Figure 2: Bio-activation of Liponucleotides



The objectives of Fozivudine are as followed:

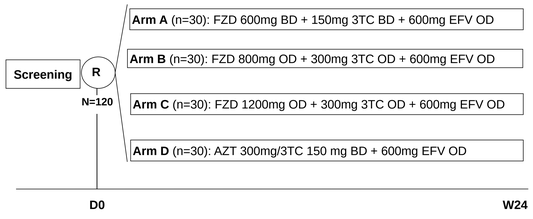
- High potency/efficacy
- Improved safety/tolerability (enhanced therapeutic window, less myelotoxicity than ZDV, „Targeting" by preferential bio-activation, low bio-availability in bone-marrow)
- Substantially longer half-life than ZDV (once daily dosing without dietary restrictions, lower incidence and/or delay of drug resistance due to prolonged pharmacokinetic and high concentration in lymphatic system)
- No or negligible first pass metabolism
- High bio-availability in lymphatic and brain tissues (high blood-brain-barrier penetration)
- No immunosuppressive effect on humoral and cellular immune reactions

Fozivudine (FZD) has been studied in 5 previous single dose escalating or repeated single dose phase I and II studies demonstrating excellent efficacy and tolerability. The objective of the FATI-1 trials was to demonstrate 24-weeks efficacy and tolerability of the FZD as part of a 3-drugs antiretroviral regimen in an African HIV-infected population.

Study Design & Objectives

Open-label, multicentre, prospective, randomized Phase IIa proof of concept and dose evaluating study in ART naïve HIV infected patients from Mbeya/Tanzania and Abidjan/Côte d'Ivoire.

Figure 3: Randomization scheme



FZD was provided in 200mg per tablet plus Lamivudine (3TC) and Efavirenz (EFV) either as a twice daily (Arm A) or once daily regimen (Arms B and C). FZD arms were compared to ZDV/3TC (Combivir) plus EFV (Arm D).

Follow-up visits for virological, immunological, safety and adherence/pill count assessments were performed at weeks 2, 4, 8, 12 and 24.

Pharmacokinetic assessments were performed for plasma, urine and intracellular drugs levels over 12 or 24 hours at baseline and week 4 (data not shown).

The primary endpoint was the proportion of patients with HIV RNA <50 (<400) copies/ml after 24 weeks of treatment.

Secondary endpoints included immunological responses, ART related clinical events and laboratory (especially haematological) toxicity.

Recruitment, Screening, Follow-up & Baseline Characteristics

Figure 4: Recruitment and study flow

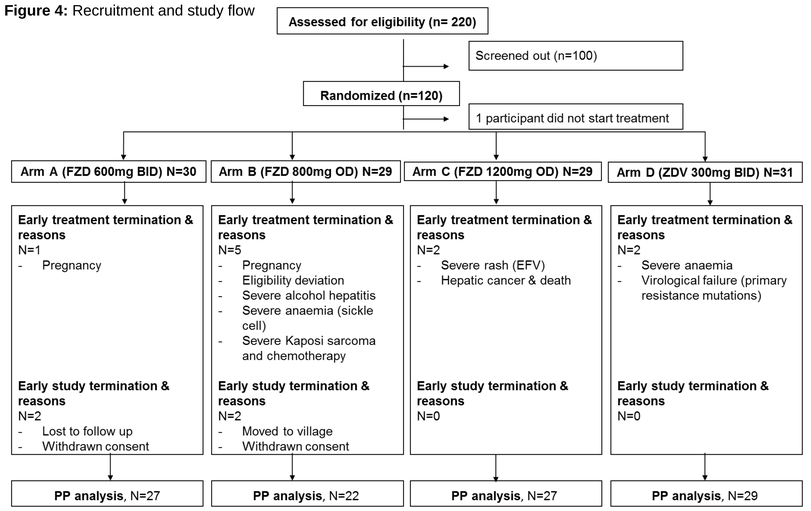


Table 1: Baseline characteristics

Variables		Total N=105	Arm A N=27	Arm B N=22	Arm C N=27	Arm D N=29	P#
Site							
- Abidjan/Côte d'Ivoire	N (%)	59 (49.6)	15 (50)	14 (48.3)	14 (48.3)	16 (51.6)	0.993
- Mbeya/Tanzania	N (%)	60 (50.4)	15 (50)	15 (51.7)	15 (51.7)	15 (48.4)	
Gender							
- Female	N (%)	78 (65.6)	19 (63.3)	19 (65.5)	19 (65.5)	21 (67.7)	0.988
- Male	N (%)	41 (34.4)	11 (36.7)	10 (34.5)	10 (34.5)	10 (32.3)	
Age	Mean (range)	38 (19-67)	36 (23-63)	38 (19-67)	39 (21-61)	39 (23-52)	0.607
CD4 count	Mean (range)	238 (93-715)	244 (97-597)	229 (121-383)	254 (100-431)	227 (93-715)	0.263
HIV-RNA log10	Mean (range)	4.99 (1.76-7.47)	5.00 (1.76-6.36)	5.00 (3.54-7.00)	4.90 (2.72-7.47)	5.07 (2.85-6.52)	0.762
WHO Stage	WHO I	57 (47.9)	13 (43.3)	13 (44.8)	12 (41.4)	19 (61.3)	0.595
	WHO II	24 (20.2)	5 (16.7)	9 (31.0)	6 (20.7)	4 (12.9)	
	WHO III	33 (27.7)	10 (33.3)	7 (24.1)	9 (31.0)	7 (22.6)	
	WHO IV	5 (4.2)	2 (6.7)	0	2 (6.9)	1 (3.2)	
Haemoglobin, g/dl	Mean (range)	12.1 (9.5-16.4)	12.2 (9.8-15.1)	12.0 (9.5-16.4)	12.1 (9.9-16.4)	12.3 (10.0-14.8)	0.702
Neutrophils, cells/ml x 10^3	Mean (range)	1.89 (0.58-6.45)	1.87 (0.89-6.45)	1.64 (0.58-3.33)	2.08 (0.66-4.06)	1.96 (0.85-4.08)	0.327

P-values are based on the Fisher exact test or Krusal Walis rank sum

Results

Table 2 A and B: Proportion of patients with virological suppression <50 or <400 copies/ml after 24 week. A: Per protocol (PP) and B: Intent-to-treat (ITT) SNAPSHOT analysis

A: PP-analysis	Total N=105	Arm A N=27	Arm B N=22	Arm C N=27	Arm D N=29
HIV-RNA <50 c/mL, N (%), [95% CI]	88 (83.8)	24 (88.9) [70.8-97.6]	19 (86.4) [65.1-97.1]	21 (77.8) [57.7-91.4]	24 (82.8) [64.2-94.2]
HIV-RNA <400 c/mL, N (%), [95% CI]	96 (91.4)	25 (92.6) [75.7-99.1]	20 (90.9) [70.8-98.9]	23 (85.2) [66.3-95.8]	28 (96.6) [82.2-99.9]

B: ITT SNAPSHOT analysis	Total (N=119)	Arm A (N=30)	Arm B (N=29)	Arm C (N=29)	Arm D (N=31)
HIV-RNA <50 c/mL, N (%), [95% CI]	88 (74.0)	24 (80.0) [61.4-92.3]	19 (65.5) [45.7-82.0]	21 (72.4) [52.8-87.3]	24 (77.4) [58.9-90.4]
HIV-RNA ≥50 c/mL, N (%), [95% CI]#	22 (18.5)	5 (16.7) [5.6-34.7]	5 (17.2) [5.8-35.8]	6 (22.7) [8.0-39.7]	6 (19.4) [7.5-37.5]
HIV-RNA <400 c/mL, N (%), [95% CI]	96 (80.7)	25 (83.3) [65.3-94.4]	20 (69.0) [49.2-84.7]	23 (79.3) [60.3-92.0]	28 (90.3) [74.2-98.0]
HIV-RNA ≥400 c/mL, N (%), [95% CI] #	14 (11.8)	4 (13.3) [3.8-30.7]	4 (13.8) [3.9-31.7]	4 (13.8) [3.9-31.7]	2 (6.5) [0.8-21.4]
Discontinued study drugs due to AE or Death or pregnancy or eligibility deviation	9 (7.6)	1 (2.2)	5 (17.2)	2 (6.9)	1 (3.2)

defined as (1) last on-treatment HIV-RNA ≤50 (≤400) copies/mL at the Week 24 analysis window, or (2) no on-treatment HIV-1 RNA data at Week 24 analysis window because subjects discontinued study drug prior to window either due to lack of efficacy or due to reasons other than adverse event, death, pregnancy , eligibility deviation and have the last on-treatment visit HIV-1 RNA 50 (≤400) copies/mL.

Results, cont.

Figure 5: Mean HIV-RNA Log10 values by weeks and study arms

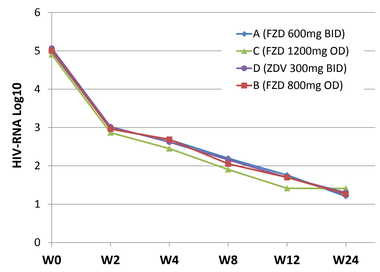


Figure 6: CD4 cells/µl mean increase by weeks and study arms

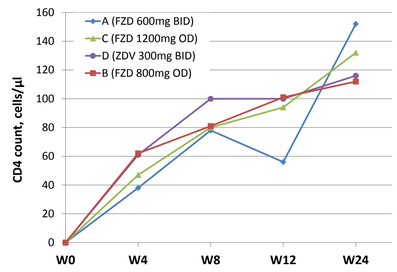


Table 3: Numbers and proportion of patients with treatment related clinical adverse events, commonly observed clinical symptoms and laboratory events related to myelotoxicity.

	Total (N=119)	Arm A (N=30)	Arm B (N=29)	Arm C (N=29)	Arm D (N=31)	P#	FZD (N=88)	ZDV (N=31)	P#
Treatment related clinical events , N (%)									
Any clinical event	48 (40.3)	13 (43.3)	13 (44.8)	13 (44.8)	9 (29.0)	0.523	39 (44.3)	9 (29.0)	0.136
Any Grade 3 or 4 clinical event	11 (9.2)	3 (10.0)	4 (13.8)	2 (6.9)	2 (6.5)	0.750	9 (10.2)	2 (6.5)	0.533
Any serious clinical adverse	5 (4.2)	1 (3.3)	3 (10.3)	0	1 (3.2)	0.249	4 (4.6)	1 (3.2)	0.753
Common treatment related symptoms, N (%)									
Nausea, vomiting	20 (16.8)	7 (23.3)	3 (10.3)	6 (20.7)	4 (12.9)	0.488	16 (18.2)	4 (12.9)	0.499
Dizziness	18 (15.1)	4 (13.3)	5 (17.2)	6 (20.7)	3 (9.7)	0.661	15 (17.1)	3 (9.7)	0.325
Gastro-intestinal disorder (dyspepsia, flatulence, pain)	10 (8.4)	4 (13.3)	1 (3.5)	2 (6.9)	3 (9.7)	0.568	7 (8.0)	3 (9.7)	0.766
Malaise and fatigue	8 (6.7)	1 (3.3)	3 (10.3)	3 (10.3)	1 (3.2)	0.500	7 (8.0)	1 (3.2)	0.366
Headache	7 (5.9)	2 (6.7)	2 (6.9)	3 (10.3)	0	0.381	7 (8.0)	0	-
Rash, urticaria	5 (4.2)	3 (10.0)	1 (3.5)	1 (3.5)	0	0.267	5 (5.7)	0	-
Haematological events, N (%)									
Grade 1 or 2 anaemia	17 (14.3)	2 (6.7)	5 (17.2)	4 (13.8)	6 (19.4)	0.515	11 (12.5)	6 (19.4)	0.348
Grade 3 or 4 anaemia	2 (1.7)	0	1 (3.5)	0	1 (3.2)	0.571	1 (1.1)	1 (3.2)	-
Grade 1 or 2 neutropenia	64 (53.8)	19 (63.3)	14 (48.3)	18 (62.1)	13 (41.9)	0.261	51 (58.0)	13 (41.9)	0.124
Grade 3 or 4 neutropenia	33 (27.7)	5 (16.7)	9 (31.0)	6 (20.7)	13 (41.9)	0.120	20 (22.7)	13 (41.9)	**0.040**

P-values are based on the Fisher exact test

Figure 7: Mean haemoglobin decrease (g/dl) from baseline by weeks and combined FZD vs ZDV

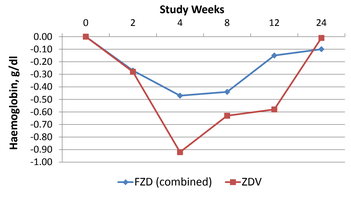
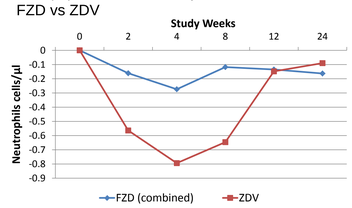


Figure 8: Mean neutrophils decrease (x 10^3 cells/µL) from baseline by weeks and combined FZD vs ZDV



Conclusion

- In this proof of concept study 24 weeks virological treatment efficacy was demonstrated for three investigated doses of Fozivudine as part of a NNRTI based treatment regimen.
- Once daily dosing showed comparable outcome results to twice daily dosing or the ZDV based control group in per protocol analysis. In ITT snapshot analysis Arm B showed a trend towards lower proportion of responders due to high rates of early treatment interruptions.
- Overall, the study regimen was well tolerated, treatment related adverse events and toxicities were as expected in an HIV infected, African populations.
- Despite small samples size a trend for lesser myelotoxicty was demonstrated by mean haemoglobin and neutrophil decrease observed for FZD as compared to the ZDV based regimen.
- Pharmacokinetic analysis is current pending as an additional criterion for dose selection.
- The FATI-1 trial was the first study conducted in Africa investigating a new antiretroviral drug.

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