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Safety of Fosamprenavir in a Cohort of HIV-1-infected Patients with Co-morbidities

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Abstract. *Background: The hypothesis that fosamprenavir-including highly active antiretroviral therapy (HAART) regimens would be associated with few metabolic and hepatic side-effects was investigated. Patients and Methods: An observational single-arm retrospective study was set up on a cohort of 139 human immunodeficiency virus (HIV)-infected patients, followed up at A.O.R.N. Cotugno Hospital, Naples, Italy, treated with antiretroviral regimens including fosamprenavir, in order to evaluate the safety of these regimens in relationship to hepatic and metabolic side-effects, also considering co-morbidities and other risk factors. Results: Only seven patients met the criteria to reach the primary end-point (grade ≥3 adverse event) and none of them discontinued HAART therapy during the follow-up period. Eighty percent of the patients reached viral load <50 cp/μl at 48 weeks of observation. At the end of follow-up, no patient with fasting serum total cholesterol and/or fasting serum triglycerides above grade 3 was found, while 1 out of 114 (0.88%) cases presented aspartate transaminase and alanine transaminase ≥grade 3 and 1 out of 114 (0.88%) cases had fasting serum glucose ≥grade 3. One out of 137 patients developed a malignant neoplasm (0.73%) and 4 (2.92%) displayed newly diagnosed hypertension. Conclusion: Fosamprenavir-based regimens caused a low number of serious metabolic adverse events during a 48 week follow-up period, with a low incidence of co-morbidities and satisfying results in terms of viro-immulogical response including for patients with already existing co-morbidities requiring other therapies.*

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To date, therapy for human immunodeficiency virus (HIV) infection is characterized by the use of a combination of three drugs, mostly including two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) and a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) (1). This therapy, commonly referred to by the acronym HAART (highly active antiretroviral therapy), has greatly improved the survival of patients with HIV infection. However, in the absence of an eradication treatment for this infection, it is imperative that patients take antiretroviral (ARV) drugs assiduously throughout their life. Therefore the management of long-term toxicity of HAART is currently one of the priorities of the clinician, because patients are now treated for a long period of time and most of the discontinuations are toxicities related. For this reason, many studies on the interruption of antiretroviral treatment have been conducted in order to limit these toxicities. Unfortunately, these studies have led to unsatisfactory results and currently, ARV interruptions are strictly not recommended (1). Hence, the synthesis of new drugs and combinations, with a high efficacy profile and a reduced short and long term side-effects such as metabolic syndrome (2) characterized by fat redistribution, abnormal lipid and glucose profile has been prompted.

The liver is a key organ for the modern management of HIV infection, and it is important to emphasize that HIV and hepatotropic virus (HCV, HBV), sharing the route of transmission (parenteral, sexual), often coexist in the same individual (approximately 35% of HIV-positive people in Western nations are co-infected with HCV), making the therapeutic approach still more complex (3-5).

Furthermore, considering the increased survival of HIV patients, following the introduction of HAART, HCV-related liver disease is emerging as a conditioning factor for the survival of these patients beyond the HIV infection itself (6-9) and in HIV-infected individuals, chronic liver disease progresses to cirrhosis and/or to hepatocellular carcinoma (10-12) faster and more frequently than in the HIV-negative

Table I. *Adverse events classification from DAIDS AE Grading Table (45).*

Fasting Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life threatening
AST	1.25-2.5×	2.6-5.0×	5.1-10.0×	>10.0×
ALT	1.25-2.5×	2.6-5.0×	5.1-10.0×	>10.0×
Cholesterol (mg/dL)	200-239	240-300	>300	N.D
Triglycerides (mg/dL)	N.A.	500-750	751-1,200	>1,200
Glucose (mg/dL)	116-160	161-250	251-500	>500

DAIDS: Division of AIDS; AE: adverse events; AST: aspartate transaminase; ALT: alanine transaminase. Normal range: AST 10-40 U/L; ALT 10-60 U/L; cholesterol 0-200 mg/dL; triglycerides 0-170 mg/dL glucose 50-110 mg/dL.

population. Consistently HIV/HCV co-infected patients have a significantly increased risk of death related to liver disease (13-15). Recent report confirmed that even if the hepatotoxicity varies according to the use of different PIs, co-infection with hepatitis C is a predisposing factor favoring this toxicity (11, 16).

The development of non-HIV-related malignancies, heart and kidney alterations, as well as bone metabolism impairment related to antiretroviral therapy are also a concern (17).

Since liver impairment could result in an excessive exposure to antiretroviral drugs in plasma with a consequent increase in the incidence of side-effects and adverse drug interactions, the management of emerging disorders such as the metabolic syndrome, or cardiovascular diseases or carcinomas is essential for the survival of this kind of patient.

Fosamprenavir, the pro-drug (phosphate ester) of amprenavir, is quickly transformed after oral administration into the active form in the gut epithelium by the action of an acid phosphatase (18, 19) and metabolized in the liver by the CYP3A4 enzyme complex (20).

The incidence of adverse hepatic events in patients receiving fosamprenavir including combinations seems to be low, also in those co-infected with hepatitis virus and in those with significant liver fibrosis (21-44).

The aim of this study was to evaluate the metabolic and hepatic safety of fosamprenavir including HAART regimens in patients affected by co-morbidities.

Patients and Methods

A retrospective survey was conducted on 139 HIV-1 infected patients, followed at the A.O. Cotugno Hospital of Naples, Italy, treated with combination therapies including fosamprenavir, in order to evaluate the impact of these regimens in particular on liver function, metabolic profile and any co-morbidities including AIDS and non-AIDS-related tumors and relating them to individual risk factors such as smoking.

Medical history was collected with particular emphasis on demographic data, co-morbidities, previous antiretroviral therapy and response to treatment in terms of viro-immunological efficacy, separating HAART-naïve from-experienced patients and checking eventual incidence of novel co-morbidities. Follow-up was carried out up to 48 weeks for each patient, with a minimum follow-up of 24 weeks.

The primary end-point of the study was to determine the percentage of subjects experiencing a grade ≥3 adverse event in fasting total serum cholesterol, triglycerides, glucose, aspartate transaminase (AST) and alanine transaminase (ALT), according to the DAIDS (Division of Acquired Immunodeficiency Syndrome – NIH) (45) criteria (Table I), and the percentage of patients who discontinued treatment due to severe adverse events (grade 4).

Secondary end-points were the percentage of patients with AST and ALT grade ≥3 at the end of follow-up, the percentage of patients with fasting total cholesterol, triglycerides and glucose grade ≥3 at the end of the follow-up, the assessment of patients requiring interruption of current therapies for co-morbidities and the proportion of subjects with viral load <50 cp/μl after 24 and 48 weeks of HAART therapy.

Statistical analysis. Continuous variables were reported as mean and standard deviation (SD). Changes of continuous variables during the study were analyzed by linear mixed models, in order to take into account the correlation between repeated measures and missing points for patients not completing the study. The categorical variables, expressed as percentages, were analyzed by exact Chi-square test. The data were analyzed using SAS 9.2 (SAS, Inc., Cary, NC, USA).

Results

One hundred and thirty-seven out of 139 evaluated patients were included in the study (two were excluded because their baseline metabolic parameters already reached levels consistent with the primary objective). Table II describes the general characteristics of the population at baseline. Sex and race were unevenly distributed, with 79.56% males and mostly Caucasians (83.21%). Thirty-eight patients (27.74%) were aged >50 years. The risk for HIV infection in 68.16% of the patients was the use of intravenous drugs. Eighty-three patients (60.58%) were co-infected with HCV, 12 patients (8.96%) were co-infected with HBV. Among other risk factors, cigarette smoking was present in the history of 60% of patients. The follow-up period reached 48 weeks in most cases (114 patients, 83.21%), in the remaining cases data were available up to 24 weeks. Fifty-two patients (37.96%) were HAART-naïve,

Table II. *General population features at baseline.*

Variable	n	%	Median (range)
Age (years)	137		45.07 (24-68)
>50	38	27.74	
<50	99	72.26	
Gender			
M	109	79.56	
F	28	20.44	
Race			
Caucasian	114	83.21	
Black	23	16.79	
Risk			
Homosexual	15	11.36	
Heterosexual	26	19.70	
Intravenous drug	90	68.16	
Blood transfusion	1	0.76	
$CD4^+$ (cell/μl)			304.72 (8-1054)
HCV			
Neg	54	39.42	
Pos	83	60.58	
HBV			
Neg	122	91.04	
Pos	12	8.96	
Smoking			
No	50	40.00	
Yes	75	60.00	
NRTI Backbone			
ABC+3TC	21	15.33	
TDF+3TC	11	8.03	
TDF+FTC	73	53.29	
AZT+3TC	7	5.10	
Other	25	18.25	
HAART Exposure			
Experienced	85	62.04	
Naive	52	37.96	
Hypertension*			
No t_0	107	80.45	
Yes t_0	26	19.54	
CHD			
No t_0	132	96.35	
Yes t_0	5	3.65	
Cancer			
No t_0	127	9.71	
Yes t_0	10	7.29	

NRTI: Nucleoside/nucleotide reverse transcriptase inhibitors; ABC: abacavir; 3TC: lamivudine; TDF: tenofovir disoproxil fumarate; FTC: emtricitabine; AZT: zidovudine or azidothymidine; HAART: highly active antiretroviral therapy; CHD: coronary heart disease; t_0: baseline; *missing data for 4 patients.

among the remaining 85 experienced patients (62.04%), 27 had baseline HIV-RNA level <50 cp/μl. The backbone therapy most frequently associated with fosamprenavir was emtricitabine (FTC) plus tenofovir disoproxil fumarate (TDF) (53.29%).

Seven patients (5.11%, 95% CI 0.0208-0.10249) had a grade ≥3 adverse event during treatment (Table III). No patient discontinued therapy due to adverse events. There

Table III. *Patients with grade > adverse event (the primary end-point; reported in gray).*

Patient	1	2	3	4	5	6	7
AST t_0	184	24	32	61	88	95	130
AST t_{12}	329	20	33	4	102	-	-
AST t_{24}	74	19	76	4	90	329	209
AST t_{48}	56	17	49	47	120	58	675
ALT t_0	137	20	41	58	79	114	101
ALT t_{12}	163	13	22	49	103	-	-
ALT t_{24}	75	8	93	41	96	438	152
ALT t_{48}	49	15	89	57	133	35	477
GLY t_0	80	148	90	122	91	68	77
GLY t_{12}	74	234	79	123	110	-	-
GLY t_{24}	67	142	80	189	87	74	94
GLY t_{48}	69	226	88	356	96	87	68
CHOL t_0	109	139	236	149	255	99	172
CHOL t_{12}	154	188	307	180	340	-	-
CHOL t_{24}	144	223	250	168	270	112	209
CHOL t_{48}	155	123	265	-	274	152	211
TRYG t_0	123	88	309	418	91	70	118
TRYG t_{12}	181	771	356	333	116	-	-
TRYG t_{24}	134	855	254	239	99	66	81
TRYG t_{48}	145	549	402	263	69	69	104

AST: Aspartate transaminase; ALT: alanine transaminase; GLY: blood glucose; CHOL: total serum cholesterol; TRYG: blood triglycerides; t_0: baseline; t_{12}: 12 weeks; t_{24}: 24 weeks; t_{48}: 48 weeks.

was no statistically significant correlation between the adverse events and age or backbone therapy or difference between HAART-naïve and -experienced patients.

At the end of follow-up (t_e: 48 weeks), 1/114 patients (0.88%) had an elevation of AST and ALT ≥grade 3, no patient showed elevation of total cholesterol or trglycerides ≥grade 3, 1/114 patients (0.88%) showed elevation of blood glucose level ≥grade 3. During the follow-up, 1/137 patients (0.73%) developed a malignancy and in 4 patients (2.92%) new-onset of systemic hypertension occurred, while none presented significant newly diagnosed heart disease such as coronary heart disease or myocardal infarction. All therapies administered for co-morbidities were well tolerated and did not need any discontinuation during the follow-up period. None of the 137 patients discontinued ARV treatment during the follow-up. A total of 95/125 patients (76%) reached HIV viral load <50 cp/μl at 24 weeks of observation and 96/120 patients (80%) had HIV RNA <50 cp/μl at the end of follow-up (Table V), with an average increase of $CD4^+$ cells count of about 210 cells (Table IV).

Changes in blood levels of AST and ALT, cholesterol, triglycerides and glucose and the onset of co-morbidities (hypertension and cancer) showed no statistically significant differences between HAART-naïve and -experienced groups of patients. In addition, there was no statistically significant difference on further separating these populations in subgroups according to age (>50 years).

Table IV. *Evolution of co-morbidities during the 48-week follow-up*

Variable	n	Median	S.D.	Range	%
Chol t_0	130	157.96	40.34	50.00-264.00	
Chol t_e	110	181.46	44.02	70.00-274.00	
Trygl t_0	129	140.72	81.60	30.00-418.00	
Trygl t_e	112	161.13	116.68	39.00-687.00	
Glyc t_0	133	91.38	17.56	59.00-174.00	
Glyc t_e	114	95.73	30.41	56.00-356.00	
CD4+ t_0		304.72	193.28	8-1054	
CD4+ t_e		515.20	323.50	22-1128	
Hypertension t_0*	26				19.54
Hypertension t_e	30				22.56
CHD** t_0	5				3.65
CHD** t_e	5				3.65
Cancer t_0	10				7.29
Cancer t_e	11				8.03

t_0: Baseline; te: end of follow-up; CHOL: total serum cholesterol; TRYG: blood triglycerides; GLY: blood glucose; $CD4^+$: cluster of differentiation 4-positive T-helper cells; CHD: coronary heart disesase; *missing data for 4 patients.

Table V. *HIV-RNA trend (n, %) during the follow-up.*

HAART	T_0	T_{24} <50 cp/uL	Missing data	T_{48} <50 cp/μL	Missing data
Naïve	52	31 (63.26%)	3	34 (73.91%)	6
Experienced >50 cp/uL	58	42 (79.24%)	5	42 (84.00%)	8
Experienced <50 cp/uL	27	22 (95.65%)	4	20 (83.33%)	3
Total	137	95 (76.00%)	12	96 (80.00%)	17

HAART: Highly active antiretroviral therapy; T_0: baseline; T_{24}: 6 weeks; T_{48}: 48 weeks.

It must be emphasized that the statistical analysis revealed some interesting correlations between metabolic parameters and some bio-pathological conditions. The HIV/HCV co-infection was significantly related to increased levels of AST and ALT (respectively, p=0.0040 and p=0.00779) and displayed a negative correlation with the cholesterol serum levels (p<0.001). Females were significantly less susceptible to the increase of triglyceridemia and glycemia (p=0.0005; p=0.0164), while age >50 years was associated with increased blood glucose levels (p=0.0332).

Discussion

In this retrospective study, few (5.11% of cases) relevant metabolic toxicities were found with the regimens containing fosamprenavir, with satisfactory viro-immunological recovery: 95/125 patients (76%) reached HIV viral load <50 cp/μl at 24 weeks and 96/120 patients (80%) had HIV-RNA <50 cp/μl at the end of follow-up, with an average $CD4^+$ cell count increase of about 210 cells. During the follow-up, co-morbidities were found in only 2.92% (hypertension) and 0.73% (malignancies) of the patients. None of the patients required interruption of HAART or therapies for prior existing or concurrent co-morbidities. These data were also confirmed in the subset of older patients (age>50 years) and independently of the backbone therapy used. The study population included a high percentage of patients co-infected with HCV (60.58%) and HIV/HCV was shown to correlate with increased AST and ALT and inversely with the levels of cholesterol, while age>50 years was associated with serum hyperglycemia consistently with a well-known general population trend.

Virtually all antiretroviral drugs that are adopted in Western nations can have toxicities, but some of them are able to cause specific alterations more frequently than others (*e.g.* renal impairment during treatment with tenofovir, facial lipoatrophy in patients treated with thymidine NRTIs *etc.*). Reviewing the evolution of HAART over the past decade, some indications are evident. In particular, with the advent of next-generation NRTIs (emtricitabine, tenofovir and abacavir), the observation of liver toxicity associated with NRTI has been significantly reduced from moderate or severe reactions observed with zidovudine, stavudine and didanosine in percentages ranging from 7% to 16% (46), to occasional observations of asymptomatic or mild to moderate liver toxicity (mostly increase in AST and ALT) (47). Among the NNRTI, nevirapine has been associated with liver toxicity more frequently than efavirenz, with incidence rates of symptomatic events around 5% (48, 49) and with particular regard to women of black race and women with $CD4^+$ cell counts >250 cells/μl (50). The frequency of liver toxicity with protease inhibitors is reported from 1% to 9.5% of cases with elevated AST and ALT levels, hyperbilirubinemia (especially with atazanavir) and also liver failure. Ritonavir is considered, especially if used at full dosage, the most hepatotoxic protease inhibitor (51-53), although cases of serious and sometimes fatal evolution have been reported using tipranavir in patients with HCV coinfection (54, 55).

The administration of fosamprenavir with ritonavir significantly increases plasma levels of amprenavir and the dosage of 700 mg of fosamprenavir together with ritonavir 100 mg twice daily, is recommended and approved in EU countries. Several studies have in fact demonstrated the effectiveness of this regimen in both naïve and experienced patients, with a rather peculiar resistance profile, characterized by a reduced cross-resistance with other PIs (22-25). It is interesting also to underline that the plasma exposure of ritonavir, when given with fosamprenavir is lower than that achieved in combination with other PIs such

as lopinavir and saquinavir (26-42). In patients with varying degrees of hepatic impairment, plasma levels of amprenavir vary considerably in relation to the degree of impairment. Compared with patients with preserved liver function, plasma levels (AUC) of this drug appear to be steadily increased, from double to over four times, according to moderate or severe hepatic impairment. A linear correlation between the AUC and the score obtained by the Child-Pugh classification was demonstrated (43, 44).

Thus, the availability of a drug such as fosamprenavir, with a good efficacy in terms of suppression of viral load and immune recovery, with the possibility of modulation of empirical therapeutic doses in combination with various therapeutic backbones, is certainly a useful tool for the management of patients with HIV infection with significant co-morbidities.

In conclusion, for HIV-positive patients with co-morbidities, HAART regimens containing fosamprenavir are safe and able to maintain adequate viro-immunological control without interfering with the management of co-pathologies, with relatively low incidence of relevant adverse events.

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