

# A RANDOMIZED CONTROLLED COMPARISON OF ABACAVIR (ABC) AND STAVUDINE (d4T), COMBINED WITH 3TC/EFV, IN ANTIRETROVIRAL-NAÏVE PATIENTS. FINAL 96-WEEK RESULTS (ABCDE STUDY)

Podzamczar D<sup>\*1</sup>, Ferrer E<sup>1</sup>, Sánchez P<sup>1</sup>, Gatell JM<sup>2</sup>, Crespo M<sup>3</sup>, Lonca M<sup>2</sup>, Sanz J<sup>4</sup>, Niubo J<sup>1</sup>, Veloso S<sup>5</sup>, Llibre JM<sup>6</sup>, Barrufet P<sup>7</sup>, Ribas MA<sup>8</sup>, Merino E<sup>9</sup>, Martínez-Lacasa J<sup>10</sup>, Alonso-Villaverde C<sup>11</sup>, Aranda M<sup>12</sup>, Pulido F<sup>13</sup>, Berenguer J<sup>14</sup>, Delegado A<sup>15</sup>, Pedreira JD<sup>16</sup>, Llerida A<sup>17</sup>, Rubio R<sup>13</sup>, Del Rio L<sup>18</sup> and the ABCDE Study team

Hospitals Universitari de Bellvitge<sup>1</sup>; Clínic<sup>2</sup>; Vall d'Hebron<sup>3</sup>; Príncipe de Asturias<sup>4</sup>; Joan XXIII<sup>5</sup>; Sant Jaume<sup>6</sup>; de Mataró<sup>7</sup>; Son Dureta<sup>8</sup>; General de Alicante<sup>9</sup>; Mutua de Terrassa<sup>10</sup>; Sant Joan de Reus<sup>11</sup>; Comarcal Terrassa<sup>12</sup>; 12 de Octubre<sup>13</sup>; Gregorio Marañón<sup>14</sup>; Sant Pau i Santa Tecla<sup>15</sup>; Juan Canalejo<sup>16</sup>; Sant Llorenç<sup>17</sup>; and CETIR<sup>18</sup>, SPAIN

## BACKGROUND

Mitochondrial toxicity (MT) is an important adverse effect of nucleoside analogues (NA), leading to lipodystrophy and other symptoms such as pancreatitis, peripheral neuropathy and even life-threatening metabolic acidosis in uncommon cases. When this study was designed, most available data regarding NA-related MT came from studies evaluating NA included in protease inhibitor-regimens. Moreover, head-to-head studies comparing stavudine and abacavir-regimens to evaluate their efficacy and tolerability has not been yet published. We present the final 96-week results of the ABCDE study.

## OBJECTIVE

To evaluate lipodystrophy, other toxicities, and efficacy of two HAART PI-sparing regimens containing d4T or ABC plus 3TC/EFV.

## PATIENTS AND METHODS

**Design:** Randomized, multicenter and open-label trial.

**Setting:** Seventeen Spanish University teaching hospitals.

**Patients:** Adult (>18 years) HIV-infected naive patients with HIV-1 RNA >1,500 copies/mL.

**Intervention and follow-up:** Between February 2001 and June 2002, pts were randomized to one of these regimens: lamivudine (3TC) (150 mg bid, or 300 QD since approval) plus efavirenz (EFV) (600 mg daily), plus either 1 stavudine (d4T) (30 or 40 mg bid, according to weight) or 2) abacavir (ABC) (300 mg bid). Clinical evaluation, including assessment of toxicity, adherence, questionnaire on body changes and anthropometry (mid arm, thigh, waist and hip circumferences) and laboratory parameter measurements (blood cells, platelets, ALT, alkaline phosphatase, GGT, albumin, glucose, creatinine, amylase, fasting total cholesterol and triglycerides, HIV-1 RNA, CD4 cells -except in month 1) were performed at baseline, and at weeks 4, 12, and every 12 weeks thereafter. In a subgroup of patients the following studies were performed: determinations of venous lactate (weeks 0, 48 and 96), HDL, LDL, apoprotein A1 and apoprotein B (weeks 0, 48 and 96), PBMC mtDNA/mDNA ratio (at weeks 48 and 96), and DEXA scan evaluation (Gen. Electric-Lunar, Prodigy model, software version V 6.50.069) (weeks 0, 48 and 96). Primary end-point was the presence of lipodystrophy (a moderate to severe subjective lipodystrophic feature apparent for both physicians and patients), secondary end-points were virological, clinical and immunological efficacy, and tolerability. AIDS-defining diseases (ADD) were diagnosed according to standard clinical, microbiological and/or histologic criteria.

**Statistical analysis: Sample size:** It was calculated that 116 patients per arm would be necessary to detect a difference of at least 15%, with a power of 80% and a significance of 0.05, assuming that 20% of patients in the d4T arm would present lipodystrophy and only 5% in the ABC arm, with an estimated loss of 20%. **Toxicity** (including body changes evaluated by observation, anthropometry or DEXA) was evaluated using intent-to-treat analysis. To evaluate **efficacy**, intent-to-treat (switch of (any drug from the initially allocated regimen) = failure) and on-treatment analyses were performed. Proportions of pts with VL < 50 were compared using the chi square test. Changes in CD4 counts, lipids, circumferences and DEXA scans were compared using the U Mann Whitney. Changes in body fat evaluated via physician/patient observation were compared using the Fisher exact test. A two-sided p value <0.05 was considered statistically significant.

## BASILINE CHARACTERISTICS

	d4T/3TC/EFV n=112	ABC/3TC/EFV n=116	p
Age, years (range)	38.9 (21-69)	39.2 (20-75)	0.79
Mean	37.2	37.87	
Median			
Sex (n(%))			0.48
Male	96 (78.7)	86 (74.8)	
Female	26 (21.3)	29 (25.2)	
Race (n(%))			
White	108 (88.5)	107 (93.0)	
Sub-saharian Africa	4 (3.3)	2 (1.7)	
North African	3 (2.5)	0 (0.0)	0.31
Hispanic	7 (5.7)	5 (4.3)	
Asian	0 (0.0)	1 (0.9)	
HIV transmission category (n(%))			
Drug users	34 (27.9)	35 (30.4)	
Homosexuals	22 (27.0)	23 (20.0)	
Menstruals	48 (39.3)	52 (45.2)	0.72
IDU + HBV*	1 (0.8)	1 (0.9)	
Transfusion	1 (0.8)	0 (0.0)	
Unknown	8 (6.3)	8 (7.0)	
Prior AIDS (n(%))	34 (27.9)	21 (18.3)	0.08
CD4 count (cells/mL (range))			
Mean	223 (2-841)	203 (0-832)	0.19
Median	201	175	
HIV-1 RNA (log <sub>10</sub> copies/mL (range))			
Mean	5.21 (3.15-6.9)	5.23 (3.23-6.9)	0.88
Median	4.91	4.95	

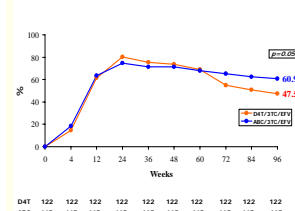
\*IDU = HIV seronegative drug users + Heroin users.  
No significant differences were found in baseline laboratory parameters except for cholesterol: Median 4.31 mmol/L (SD ± 1.09, d4T) VS 4.03 mmol/L (SD ± 0.8, ABC), p<0.05.

## 96-WEEK CHANGES IN BODY FAT OBSERVED BY BOTH PHYSICIAN AND PATIENT\*

	d4T/3TC/EFV n (%)	ABC/3TC/EFV n (%)	p
<b>Fat accumulation</b>			
Abdomen			0.038
Yes	19 (23.5)	9 (10.7)	
No	62 (76.5)	75 (89.3)	
Breasts			1
Yes	2 (2.5)	2 (2.4)	
No	79 (97.5)	82 (97.6)	
Neck			0.24
Yes	2 (2.5)	0 (0)	
No	78 (97.5)	84 (100)	
<b>Fat loss</b>			
Face			<0.001
Yes	21 (25.9)	3 (3.6)	
No	60 (74.1)	80 (96.4)	
Arms			<0.001
Yes	14 (17.1)	1 (1.2)	
No	66 (82.5)	83 (98.8)	
Buttocks			<0.001
Yes	21 (25.9)	2 (2.4)	
No	60 (74.1)	82 (97.6)	
Legs			<0.001
Yes	19 (23.5)	1 (1.2)	
No	62 (76.5)	83 (98.8)	

\*A moderate to severe subjective lipodystrophic feature apparent for both physicians and patients identified in at least one localization was observed in 38.3% vs. 4.8%, p<0.001; in 2 or more localizations in 27.2% vs. 1.2%, p<0.001; in 3 or more localizations in 18.5% vs. 1.2%, p<0.001; in 4 localizations in 1.2% vs. 0.032.

## PROPORTION OF PATIENTS WITH HIV-1 RNA < 50 copies/ml (INTENT-TO-TREAT ANALYSIS)



\* 95% CI 51.3-69.8 \*\* 95% CI 38.4-56.7

## LIPODYSTROPHY: FEATURES OBSERVED BY BOTH PHYSICIAN AND PATIENT CORRELATED WITH 96-WEEK CHANGES IN ANTHROPOMETRIC MEASURES\*

	Changes in circumferences (cm) mean(range)	p
↑ abdomen	Yes 6.80 (-1.2 to 23)	0.005
	No 2.94 (-9.5 to 18.5)	
↓ arm	Yes -0.04 (-4 to 8)	0.020
	No 1.68 (-5 to 2)	
↓ buttock	Yes -1.12 (-12 to 6)	0.022
	No 2.10 (-14 to 19)	
↓ legs	Yes -0.76 (-6 to 6)	0.017
	No 2.26 (-13 to 34.5)	

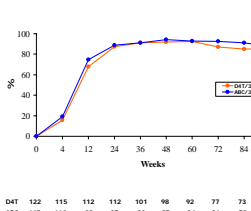
\*By intent-to-treat analysis, in patients with anthropometric data (n=114)

## Changes in body weight according to treatment arm

	d4T	ABC	p
48 weeks	+3.21	+3.13	NS
96 weeks	+2.25	+4.70	0.056

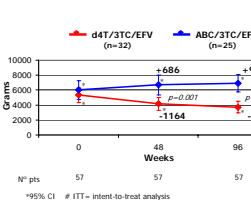
## RESULTS

### PROPORTION OF PATIENTS WITH HIV-1 RNA < 50 copies/ml (ON-TREATMENT ANALYSIS)



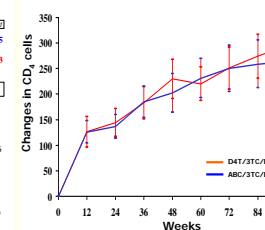
\* 95% CI 51.3-69.8 \*\* 95% CI 38.4-56.7

### CHANGES IN LIMB FAT BY DEXA SCAN, ACCORDING TO TREATMENT ARM (ITT\*)



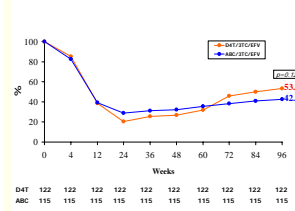
\* 95% CI # ITT = intent-to-treat analysis

### CHANGES (± SE\*) IN CD4 CELLS ACCORDING TO THERAPY



\* SE = standard error

### PROPORTION OF PATIENTS WITH HIV-1 RNA > 50 copies/ml, PROGRESSION TO AIDS\* OR DEATH (INTENT-TO-TREAT)



\* 24 active opportunistic diseases (17 confirmed/7 probable) in 20 pts (15 ABC vs. 5 d4T, p=0.013) after a median period of 28 days (1-315). Only one CD occurred after 6 months of study initiation. Opportunistic diseases observed were: 5 in d4T arm (2 tuberculosis, 2 M. kansasii infections and 1 CMV disseminated infection) and 19 in ABC arm (8 tuberculosis, 3 cryptosporidiosis, 3 disseminated 1 CMV encephalitis, 1 progressive multifocal leukoencephalopathy, 1 Pneumocystis jirovecii pneumonia, 1 Kaposi's sarcoma and 1 gastric lymphoma)

### VENOUS LACTATE AND LIPID VALUES ACCORDING TO TREATMENT ARM

	d4T/3TC/EFV mean (range)	ABC/3TC/EFV mean (range)	p
Lactate (mmol/L)*	0.37 (0.12 to 2.86)**	0.37 (0.9 to 2.23)**	0.95
Total cholest. (mmol/L)	0.89 (4.04 to 3.44)*	1.09 (3.27 to 4.85)*	0.25
Triglycerides (mmol/L)	0.85 (1.49 to 5.7)*	0.28 (5.55 to 6.13)**	0.03
HDL (mmol/L)	0.2 (-0.53 to 1.73)*	0.47 (0.83 to 2.16)*	<0.001
LDL (mmol/L)	0.27 (-0.36 to 2.79)*	0.58 (2.72 to 4.83)*	0.23
TC:HDL	-0.06 (-6.49 to 5.31)	-1.51 (-39.57 to 5.68)	0.005
LDL:HDL	-0.3 (-12.15 to 3.38)	-0.71 (-20.26 to 5.18)	0.142
apoA1 (mmol/L)	0.17 (-0.18 to 1.21)*	0.31 (0.42 to 1.66)*	<0.001
apoB (mmol/L)	0.12 (1.18 to 1.35)*	0.12 (-0.65 to 1.03)*	0.99

Comparing baseline vs. 96-week data in both arms: \* increase p<0.001, \*\* increase p<0.001. Comparing baseline vs. 96 weeks data only in ABC arm: decrease p<0.001, decrease p<0.002.  
# if analyzed by LOCF, data are 0.77 vs. 0.32 (p=0.1), with significant increase comparing baseline vs. 96 wks, only in d4T arm (p<0.001)

## CONCLUSIONS

- After 96 weeks, d4T showed a higher rate of lipodystrophy than ABC, when both were combined with 3TC/EFV.
- ABC was associated with a better lipid profile: lower increase in TG, greater increase in HDL and in apoA1, and a greater reduction in TC:HDL ratio.
- A lower virological response was found in the d4T arm with ITT analysis, related to a higher incidence of drug discontinuation.
- A higher frequency of AIDS-defining diseases were observed in the first six months in ABC arm, possibly related to immune reconstitution?

### \*Other members of the ABCDE Study team are:

Barberá MJ, Santín M, Físcac C, Ruiz I, Fax C, Vila A and Gudíol F<sup>1</sup>; Murillas J<sup>2</sup>; Ribera E, Ocaña I and Falco V<sup>3</sup>; Casas E, Aranz A and de Miguel J<sup>4</sup>; Vidal F<sup>5</sup>; Valero S<sup>6</sup>; Forca L<sup>7</sup>; Salas A<sup>8</sup>; Portilla J, Boix V<sup>9</sup>; González MA and Coll B<sup>11</sup>; Del Molino F and Anoro E<sup>12</sup>; Cepeda C and Torralba M<sup>13</sup>; Cosin J and Ramirez M<sup>14</sup>; Javaloyas M<sup>15</sup>.