PE7/1 : Safety and efficacy of switching to dual therapy (atazanavir/ritonavir + lamivudine) vs. triple therapy (atazanavir/ritonavir + two nucleos(t)ides) in patients on virologically stable antiretroviral therapy: 24-week interim analysis from a randomized clinical trial (SALT study)

14th EUROPEAN AIDS CONFERENCE
OCTOBER 16–19, 2013
BRUSSELS, BELGIUM

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BACKGROUND

Combined antiretroviral therapy (cART) allows indefinite viral control for most HIV-infected patients, with very convenient and well-tolerated dosing schedules. Nevertheless, the problems associated with lifelong cART (adherence, toxicity, convenience, and cost) mean that simplification strategies must be sought. Monotherapy with boosted protease inhibitors (lopinavir, darunavir, and atazanavir) is a valuable alternative, although the non-inferiority of this approach compared with standard cART has not been demonstrated for all scenarios. Dual therapy based on boosted protease inhibitors plus 3TC could help clinicians overcome some of the disadvantages of monotherapy, thus making it a viable alternative for most patients.

METHODS

- **Design:** GESIDA 7011 (SALT study) is a 96-week multicenter, randomized, open-label, phase IV clinical trial that compares ATV/r+3TC with ATV/r+2NUC(t)s (selected at the discretion of the investigator) in HIV-infected patients on a stable 3-drug regimen who switch therapy because of toxicity, intolerance, or simplification. Randomization was stratified by active HCV infection (HCV-RNA+) and switched cART (NNRTI, boosted PI, CCR5 antagonist, or integrase inhibitor). Allocation concealment was ensured by means of a centralized web-based randomization process. **FIGURE 1.**
- **Inclusion criteria:** Age >18 years; treatment switch because of toxicity, intolerance, or simplification; no previous treatment failure; no resistance mutations to the study medications; HIV-RNA <50 copies/mL for ≥6 months; and HBsAg-negative status.
- **Primary objective:** To evaluate in the per protocol population (randomized patients with no major protocol violations) the non-inferior efficacy of maintenance therapy with ATV/r+3TC compared to ATV/r+2NUC(t)s at 48 weeks (non-inferiority margin, –12%).
- **Treatment failure** was defined as 2 consecutive HIV RNA levels >50 copies/mL at week 48, loss to follow-up, or discontinuation/modification of randomized treatment (TLOVR).
- **Safety** assessments included adverse event recording, clinical laboratory tests (hematology, clinical biochemistry, fasting lipids, and urinalysis), physical examination, neuropsychological testing, DEXA (for bone mineral density and fat distribution), vitamin D levels, and anthropometric measurements.

CURRENT ANALYSIS

- **A pre-planned interim analysis** was performed for safety purposes when one-third of the patients reached 24 weeks of follow-up.
- We established the following **stopping rule:** If the 99.95% confidence interval of the difference in efficacy between study arms in the per protocol population indicated inferiority of the ATV/r+3TC arm, the trial was to be interrupted.

RESULTS

- The study population comprised 131 patients. **TABLE 1 & TABLE 2.**
- At week 24 there were no virological failures (confirmed as HIV RNA >50 copies/mL). **FIGURE 2.**
- Treatment efficacy was 87.5% (56/64) for ATV/r+3TC vs. 92.5% (62/67) for ATV/r+2NUC(t)s **FIGURE 3 & TABLE 3.**
- Average change in CD4 count from baseline was +57 cells/µL and –27 cells/µL for ATV/r+3TC and ATV/r+2NUC(t)s, respectively **FIGURE 4.**
- Toxicity leading to interruption of treatment was secondary to grade 3-4 hyperbilirubinemia with/without jaundice.
- Three severe adverse events were recorded. These were not related to study medication.
  - » ATV/r+3TC arm: acute pyelonephritis and traumatic bone fracture (no study treatment interruption for either case).
  - » ATV/r+2NUC(t)s: toxicity due to drugs of abuse (transient study treatment interruption).

CONCLUSIONS:

Dual therapy with ATV/r+3TC seems to be as safe and effective in the short term as switching therapy in virologically stable patients requiring a change in treatment owing to simplification, intolerance, or toxicity.

TABLE 1.
Patient characteristics at baseline

	ATV/r+3TC (n=64)	ATV/r+2NUC(t)s (n=67)	TOTAL (N=131)
Median age (years; IQR)	44 (37-50)	42 (33-47)	43 (35-49)
Female (%)	26.6	22.4	24.4
Autochthonous Spanish (%)	73.4	74.0	74.6
Sub-saharan african	7.8	3.0	5.3
HCV-RNA+ (%)	17.2	17.9	17.6
Active alcohol and/or illicit drug consumption (%)	18.8	19.7	19.2
Previous AIDS-defining illness (%)	31.3	22.4	26.7
Reason for switching (%):			
Intolerance	1.6	1.5	1.5
Toxicity	20.3	13.4	16.8
Simplification	78.1	85.1	81.7
Risk behavior for HIV infection (%)			
MSM	35.9	46.3	41.2
Heterosexual relations	40.6	37.3	38.9
IVDU	18.8	10.4	14.5
Other	4.7	7.0	5.4
Median years of HIV infection (IQR)	4.6 (2.9-8.3)	4.1 (2.4-7.9)	4.5 (2.6-7.9)
Median nadir CD4 cell/µL (IQR)	218 (69-310)	227 (145-334)	226 (95-323)
Median baseline CD4 cell/µL (IQR)	579 (404-702)	578 (425-796)	579 (423-784)
Median months of antiretroviral therapy prior to study entry (IQR)	35.9 (25-48.7)	30.9 (18.8-50)	34.4 (22.3-49.4)
Median months of viral load <50 copies/mL prior to study entry (IQR)	24.5 (16.3-39.8)	27.0 (15-46)	25 (15-43)
Switched treatment including (%):			
NNRTI	32.8	32.8	32.8
Boosted protease inhibitor	62.5	65.7	64.1
TDF	85.9	82.1	84.0
Previous resistance to study drugs (%)	0	0	0

IQR: interquartile range; IVDU: intravenous drug user; MSM: men who have sex with men; NNRTI: non-nucleoside reverse transcriptase inhibitor; TDF: tenofovir disoproxil fumarate.

TABLE 2.
Combined antiretroviral treatment prior to study entry

cART	Treatment arm				Total	
	ATV/r+3TC		ATV/r+2NUC(t)s			
	n	%	n	%	n	%
TDF/FTC + ATV/r	21	32.8	16	23.9	37	28.2
TDF/FTC + LPV/r	10	15.6	12	17.9	22	16.8
TDF/FTC + DRV/r	5	7.8	6	9.0	11	8.4
ABC/3TC + FPV/r	1	1.6	4	6.0	5	3.8
ABC/3TC + ATV/r	1	1.6	3	4.5	4	3.1
TDF/FTC + FPV/r	1	1.6	1	1.5	2	1.5
ABC/3TC + LPV/r	1	1.6	1	1.5	2	1.5
DDI/3TC + SQV/r	0	0.0	1	1.5	1	0.8
TDF/FTC + EFV	14	21.9	15	22.4	29	22.1
ABC/3TC + EFV	5	7.8	3	4.5	8	6.1
TDF/FTC + ETR	1	1.6	3	4.5	4	3.1
ABC/3TC + NVP	1	1.6	0	0.0	1	0.8
TDF/FTC + NVP	0	0.0	1	1.5	1	0.8
TDF/FTC + RAL	3	4.7	1	1.5	4	3.1
Total	64	100.0	67	100.0	131	100.0

TABLE 3.
Discontinued therapy at 24 weeks

	ATV/r + 3TC	ATV/r + 2NUC(t)s
Informed consent withdrawn	6	2
Toxicity	1	3
Virological failure	0	0
Other	1	0
Total	8	5
Blips not leading to treatment interruption*	6	7

* 13 blips corresponding to 12 patients. In one center (7 blips in 6 patients), most of the blips could be attributed to a change in laboratory technique. They were evenly distributed between treatment arms.

FIGURE 1.
Study design

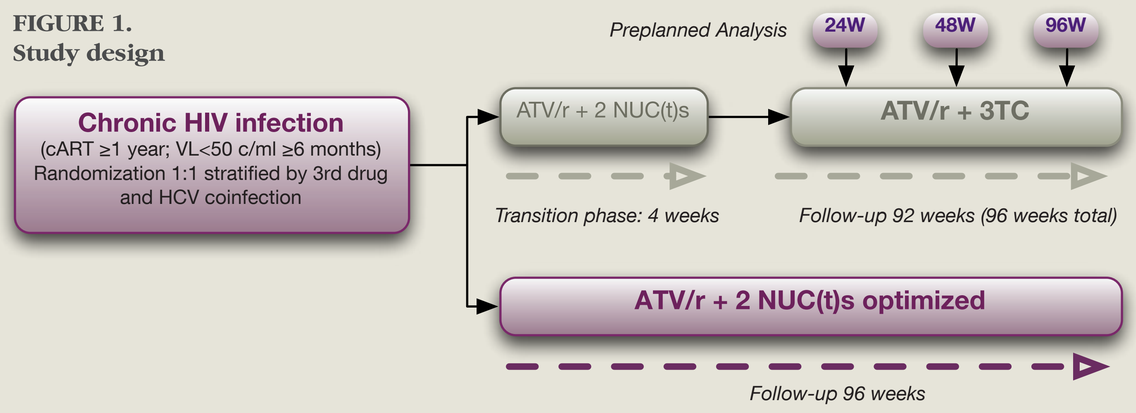
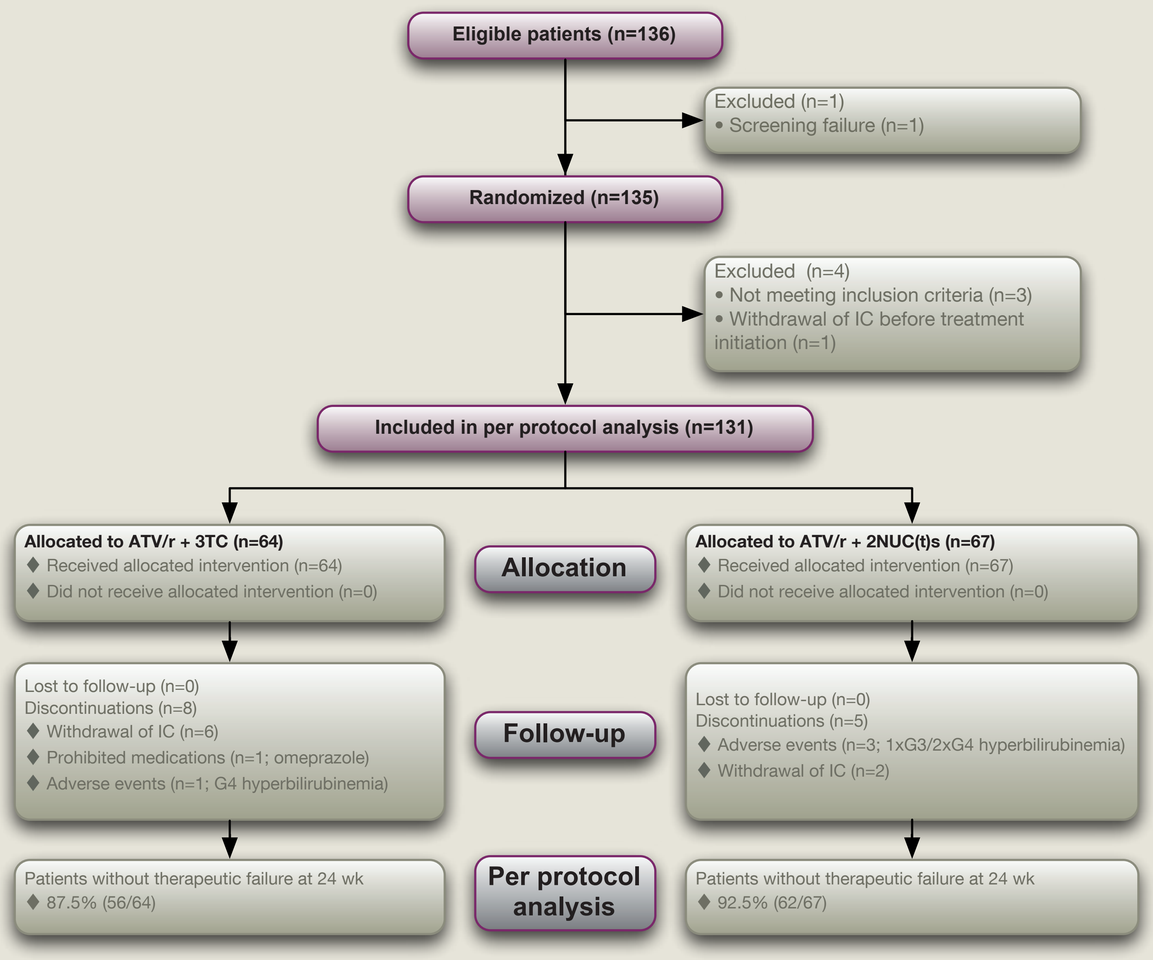
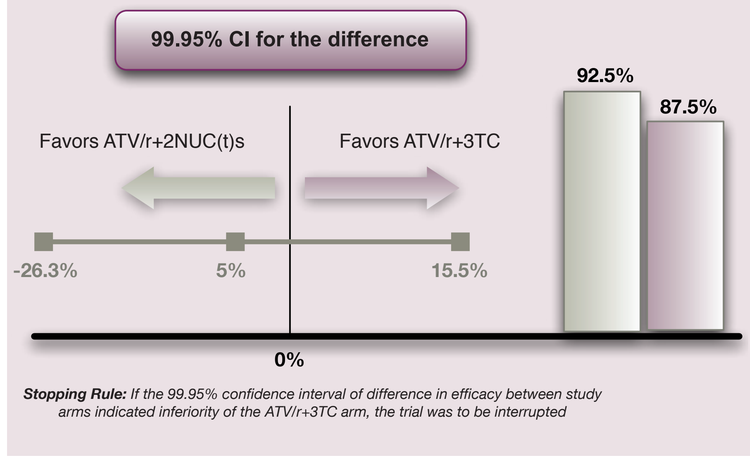


FIGURE 2.
Study flow diagram (Interim analysis at 24 weeks)



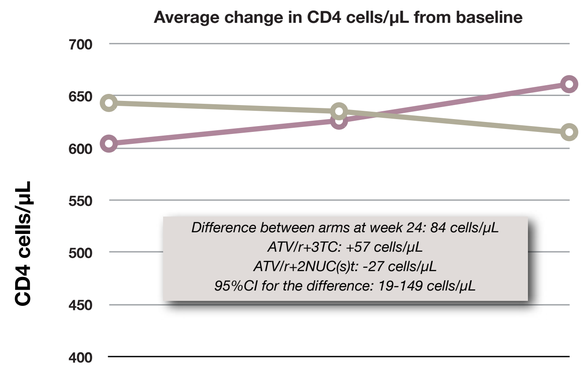
IC: Informed consent

FIGURE 3.
Main analysis



Stopping Rule: *If the 99.95% confidence interval of difference in efficacy between study arms indicated inferiority of the ATV/r+3TC arm, the trial was to be interrupted*

FIGURE 4.
Changes in CD4 cell count from baseline



	Baseline	Week 12	Week 24
ATV/r+2NUC(t)s	643	635	615
ATV/r+3TC	604	626	661

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FUNDACIÓN SEIMC-GESIDA

SALT Ensayo

Ensayo clínico aleatorizado, abierto, de no inferioridad y con seguimiento a 96 semanas, sobre la eficacia de atazanavir/ritonavir+lamivudina como tratamiento de mantenimiento en pacientes con supresión de la carga vírica