LBPE18: Switching to dual therapy (atazanavir/ritonavir+lamivudine) vs. standard triple therapy (atazanavir/ritonavir+two nucleos(t)ides) is safe and effective in patients on virologically stable antiretroviral therapy: 48-week primary endpoint results from a randomized clinical trial (SALT study)

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BACKGROUND

The problems associated with lifelong cART (adherence, toxicity, convenience, and cost) mean that simplification strategies must be sought. Monotherapy with boosted protease inhibitors 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.
- **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) whether maintenance therapy with ATV/r+3TC is non-inferior 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, physical examination, neuropsychological testing, DEXA (for bone mineral density and fat distribution), vitamin D levels, and anthropometric measurements.

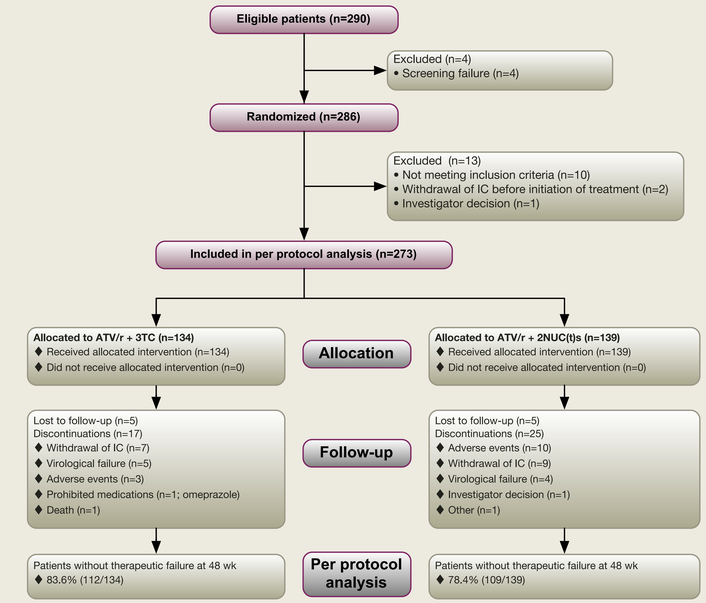
RESULTS

- The **study population** comprised 286 patients (Table 1,Table 2, and Figure 1).
- **Treatment efficacy** was 83.6% for ATV/r+3TC vs. 78.4% for ATV/r+2NUC(t)s (Figure-2 and Table-3). Non inferiority was demonstrated and the results were consistent across the sensitivity analysis (Table-4).
- At week 48 there were 9 **virological failures** (confirmed as HIV RNA >50 copies/mL): 5 in the ATV/r+3TC arm vs. 4 in the ATV/r+2NUC(t)s arm. Six could not be amplified because of low viral load, and only 1 patient (ATV/r+2NUC(T)s arm) developed resistance mutations (M184V). No NRTI or PI resistance mutations were documented in the ATV/r+3TC arm.
- Average **change in CD4** count from baseline was +9.9 cells/µL for ATV/r+3TC and –9.2 cells/µL for ATV/r+2NUC(t)s (difference 19.1 cells/µL; 95% CI, –39.7 to 77.9).
- 154 patients (54.8%; evenly distributed between the study groups) presented grade III-IV **toxicity**.The proportion of grade III-IV AE was similar in both arms (Table-5).
- There were 13 (4.6%) **severe adverse events** (Table-6).These were not related to the study medication.
- Changes in **renal function, bone density,** and **fat** gain/distribution between groups were similar
- Changes in **lipid** values were related to previous TDF and/or PI use: percentage change in triglycerides was related to previous use of PI/r (–5.7%) vs. non-PI use (+7.1%) (p=0.041), percentage change in total cholesterol was associated with previous use of TDF (+1.6%) vs. no TDF (–5.6%) (p=0.015), and absolute change in the atherogenic index was related to previous use of PI/r (–0.2) vs. no PI (+0.03) (p=0.037).
- Changes in **neurocognitive** function (global deficit score; 5 domains) was not significantly different between the study arms: –0.26 (95% CI, –0.4 to –0.07) ATV/r+3TC vs. –0.082 (95% CI, –0.2 to +0.07) ATV/r+2NUC(t)s.

CONCLUSIONS:

Switching to ATV/r+3TC is effective, safe, and non-inferior to ATV+2NRTIs in virologically suppressed HIV+ patients who need to switch cART because of toxicity, intolerance, or simplification.

FIGURE 1.
Study flow diagram (primary endpoint analysis [48 weeks])



IC: Informed consent

TABLE 1.
Patient characteristics at baseline

	ATV/r+3TC (n=143)	ATV/r+2NUC(t)s (n=143)	TOTAL (N=286)
Median age (years; IQR)	45 (38-52)	42 (36-48)	43 (38-50)
Female (%)	31.0	22.5	26.8
Autochthonous Spanish (%)	79.6	80.3	79.9
Sub-Saharan African	5.6	2.1	3.9
HIV-1 B subtype	88.5	82.5	85.4
HCV-RNA+ (%)	20.3	20.3	20.3
Previous AIDS-defining illness (%)	26.8	26.3	26.5
Reason for switching (%):			
Intolerance	2.8	4.3	3.5
Toxicity	22.7	14.2	18.4
Simplification	74.5	81.5	78.1
Risk behavior for HIV infection (%)			
MSM	36.0	42.8	39.4
Heterosexual relations	37.4	32.6	35.0
IVDU	23.0	17.4	20.2
Other	3.6	7.2	5.4
BMI (kg/m²; IQR)	25 (22-28)	24.8 (23-28)	24.9 (22.8-28)
Known duration of HIV infection (years; IQR)	6.4 (3.4-11.4)	5.6 (2.7-11.1)	5.9 (3.2-11.3)
Median nadir CD4 cell/µL (IQR)	204 (90-309)	222 (139-323)	212 (108-318)
Median baseline CD4 cell/µL (IQR)	579 (397-770)	617 (441-801)	583 (417-784)
Median months of antiretroviral therapy prior to study entry (IQR)	45 (26-62)	41 (22-63)	43 (24-62)
Median months of viral load <50 copies/mL prior to study entry (IQR)	27 (16-49)	28 (15-58)	28 (15-51)
Switched treatment including (%):			
NNRTI	31.5	30.1	30.8
Boosted protease inhibitor	61.5	64.3	62.9
TDF	81.1	78.3	79.7
Previous resistance to study drugs (%)	0	0	0

BMI: body mass index; 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	52	38.2	38	27.5	90	32.8
TDF/FTC + LPV/r	14	10.3	20	14.5	34	12.4
TDF/FTC + DRV/r	8	5.9	13	9.4	21	7.7
ABC/3TC + FPV/r	2	1.5	4	2.9	6	2.2
ABC/3TC + ATV/r	8	5.9	10	7.2	18	6.6
TDF/FTC + FPV/r	2	1.5	1	0.7	3	1.1
ABC/3TC + LPV/r	1	0.7	2	1.4	3	1.1
ZDV/3TC + LPV/r	0	0	3	2.2	3	1.1
TDF/FTC + SQV/r	1	0.7	0	0	1	0.4
DDI/3TC + SQV/r	0	0.0	1	0.7	1	0.4
TDF/FTC + EFV	30	22.1	31	22.5	61	22.3
ABC/3TC + EFV	8	5.9	5	3.6	13	4.7
TDF/FTC + ETR	2	1.5	4	2.9	6	2.2
ABC/3TC + NVP	1	0.7	0	0.0	1	0.4
TDF/FTC + NVP	3	2.2	3	2.2	6	2.2
TDF/FTC + RAL	4	2.9	2	1.4	6	2.2
ABC/3TC + MVC	0	0	1	0.7	1	0.4
Total	136	100.0	138	100.0	274	100.0

Information on previous cART was not available for 12 patients.

TABLE 3.
Treatment efficacy at 48 weeks (TLOVR; PP population; n=273)

	ATV/r + 3TC	ATV/r + 2NUC(t)s
HIV-RNA <50 copies/mL; n (%)*	112 (83.6)	109 (78.4)
HIV-RNA >50 copies/mL	5 (4.5)	4 (3.6)
Withdrawal of informed consent	7 (5.3)	9 (6.5)
Discontinuation because of adverse events	3 (2.2)	10 (7.2)
Loss to follow-up	5 (3.0)	5 (2.9)
Death	1 (0.7)	0 (0.0)
Other	1 (0.7)	2 (1.4)
TOTAL	134 (100)	139 (100)
Patients with blips not leading to interruption of cART	19 (14.2)	23 (16.5)

*All variables are expressed as absolute number and percentage; n (%)

TABLE 4.
HIV RNA <50 copies/mL (%) at week 48, for the per protocol (PP) and intent-to-treat (ITT) populations.

	ATV/r+3TC (%)	ATV/r + 2NUC(t)s	Difference (95% CI)
HIV-RNA <50 copies/mL (PP; TLOVR)	83.6	78.4	5.2 (–4.8 to 15.2)
HIV-RNA <50 copies/mL (ITT; TLOVR)	78.3	76.2	2.1 (–8.3 to 12.5)
HIV-RNA <50 copies/mL (PP; SNAPSHOT)	82.1	77.7	4.4 (–5.5 to 14.6)
HIV-RNA <50 copies/mL (ITT; SNAPSHOT)	76.9	75.5	1.4 (–9.2 to 12.0)

FIGURE 2.
Main analysis (primary endpoint at 48 weeks)

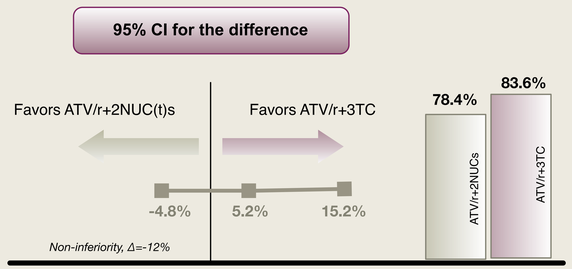


TABLE 5.
Safety summary

	ATVr+3TC n=140	ATV/r + 2NUC(t)s n=141
Toxicity-related discontinuations		
Discontinuations due to any AEs; n(%)*	3 (2.2)	10 (7.2)
HBR and/or ocular icterus	2	3
Renal toxicity	0	2
Increased LFT results	1	1
Nephrolithiasis	0	1
Osteoporosis	0	1
Hypersensitivity reaction to abacavir	0	1
Hypophosphatemia	0	1
Grade III-IV AEs occurring in at least 1% of patients in either group		
Any AEs	76 (54.3)	78 (51.1)
HBR	69 (49.3)	72 (51.8)
Jaundice	0 (0.0)	2 (1.4)
Increased LFT results	2 (1.4)	2 (1.4)
Hyperlipidemia**	4 (2.8)	2 (1.4)
Thrombocytopenia	2 (1.4)	1 (0.7)

*All variables are expressed as absolute number and percentage; n (%);AEs: adverse events; HBR: hyperbilirubinemia: LFT: liver function tests

** Hypertriglyceridemia (n=5) and hypercholesterolemia (n=1)

TABLE 6.
Severe adverse events

Treatment arm	Adverse event	Severity	Treatment interruption
ATV/r+2NUC(t)s	Toxicity due to drugs of abuse	Grade 3	No
ATV/r+3TC	Avascular hip necrosis	Grade 2	No
ATV/r+2NUC(t)s	Acute myocardial ischemia	Grade 3	No
ATV/r+2NUC(t)s	Vulvar abscess	Grade 1	No
ATV/r+2NUC(t)s	Cerebral toxoplasmosis	Grade 4	No
ATV/r+3TC	Acute pyelonephritis	Grade 3	No
ATV/r+2NUC(t)s	Acute tracheobronchitis and respiratory failure	Grade 4	No
ATV/r+2NUC(t)s	Increased transaminase levels	Grade 3	Yes
ATV/r+2NUC(t)s	Cholelithiasis	Grade 3	No
ATV/r+3TC	Alcoholic hepatitis	Grade 4	No
ATV/r+2NUC(t)s	Acute renal failure	Grade 4	Yes
ATV/r+3TC	Thrombopenia	Grade 4	No
ATV/r+3TC	Thrombopenia	Grade 3	No
ATV/r+3TC	Traumatic bone fracture	Grade 3	No

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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