

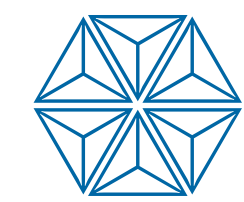
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EFFECTS OF SWITCHING TO RITONAVIR-BOOSTED ATAZANAVIR (ATV) ON HIV-INFECTED PATIENTS RECEIVING ANTIRETROVIRAL THERAPY WITH HYPERLIPIDEMIA

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INTRODUCTION

- Hyperlipidemia may be relatively prevalent among treated HIV-infected patients, particularly with the use of protease inhibitors. Hyperlipidemia is also a leading factor responsible of the increased risk for coronary heart disease associated with the exposure to antiretroviral therapy.
- Replacing the protease inhibitor component with drugs from another antiretroviral class (generally a non-PI containing regimen such as NNRTI or NRTI) has usually shown an improvement of lipid parameters, though at an increased risk for clinically significant adverse effects associated with replacing drugs and for virological failure.
- Switching from nelfinavir to unboosted atazanavir in patients without prior virological failure to protease inhibitors has been associated with an improvement of lipid parameters without an increased risk for clinically significant adverse effects associated with atazanavir and for virological failure.
- Atazanavir boosted with ritonavir (ATV/RTV) has shown a favorable lipid profile and a durable virological response compared to twice-daily lopinavir/ritonavir (LPV/RTV) in patients with prior virological failure.
- This substudy was designed to assess the impact on lipid parameters of switching to an antiretroviral regimen containing boosted ATV in HIV-infected patients with dyslipidemia.

ABSTRACT

**Background:** ATV even when boosted with RTV has favourable lipids (TC, LDL-C and TG) compared to twice-daily lopinavir/ritonavir (LPV/r) which result in significantly less usage of lipid lowering therapy. However, a single ATV study describing lipid improvement in hyperlipidemia patients has not been reported.

**Methods:** Treated HIV-infected patients with hyperlipidemia defined by at least one of the following: fasting triglycerides (TG) >500 mg/dL, total cholesterol (TC) >200 mg/dL, or LDL-cholesterol (LDL) >130 mg/dL for at least the previous three months were offered to receive antiretroviral therapy containing ritonavir-boosted ATV as part of BMS Early Access Program (EAP). Clinical and fasting laboratory data were collected at baseline, 1, 3 and 6 months. Pre-entry stable lipid-lowering therapies could be maintained but new prescriptions or dose modifications were not allowed during the study.

**Results:** At the time of this analysis, of 162 (77% men) patients recruited in 35 centers, 41 (25%) completed at least 6 months of follow-up. Median (IQR) age was 40 (4) years. At baseline, 45% had <500 copies HIV-1 RNA/mL. The drugs most frequently discontinued on starting ritonavir-boosted ATV were LPV/r (34%) and other boosted protease inhibitors (14%). The drugs most frequently administered with ritonavir-boosted ATV were tenofovir (56%), didanosine (44%) and lamivudine

METHODS

The BMS ATV EAP is a multinational prospective trial for HIV treatment-experienced patients who switch to ATV-based therapy due to treatment failure (not only immunovirological failure but also for toxicity, adherence or hyperlipidemia issues). Spain enrolled 1621 patients from November 2002 to September 2004. Nested subanalysis were proposed and carried out in Spanish centers being 880 patients evaluated. For this specific analysis, only patients receiving boosted ATV and showing hyperlipidemia at baseline defined by at least one of the following criteria were selected:

- fasting triglycerides (TG) >500 mg/dL,
- total cholesterol (TC) >200 mg/dL,
- or LDL-cholesterol (LDL) >130 mg/dL

Clinical and fasting laboratory data were collected at baseline, 1, 3, 6, 9 and 12 months as long as the patient remained on therapy. Data management and statistical analysis were performed using SAS software (ver 8.3). To assess significance in changes observed over time, McNemar or binomial test were used. To evaluate changes in proportions from baseline, Rank-signed Wilcoxon test were performed. Finally to study potential association between baseline parameters and outcome of specific variables, the Chi-square test or ANOVA were applied.

(26%). Only 7 patients (4.3%) discontinued ritonavir-boosted ATV during the follow-up, one (0.6%) due to jaundice. At month six, 58% had <500 copies HIV-1 RNA/mL. Median (IQR) baseline values of TG, TC, LDL and HDL were 289 (411), 225 (48), 138 (44), and 39 (15) mg/dL. Median lipid changes from baseline to month 6 were: -18% in TG (P<0.0001), -12% in TC (P<0.0001), -10% in LDL (P<0.0001) and -3% in HDL (P>0.05). The proportions of patients with: TG >500 mg/dL decreased from 33% to 10% (P<0.0001), TC >200 mg/dL from 90% to 51% (P<0.0001), and LDL >130 mg/dL from 65% to 36% (P<0.0001).

**Conclusions:** Switching to antiretroviral therapy containing ritonavir-boosted ATV in HIV-infected patients with persistent hyperlipidemia was associated with significant improvements in plasma lipids without an increased risk of virological failure.

CONCLUSION

- Switching to antiretroviral therapy containing ritonavir-boosted ATV in this cohort of HIV-infected patients with persistent hyperlipidemia was associated with significant improvements in plasma lipids without an increased risk of virological failure and generally well tolerated.
- These data may constitute the rationale to assess the hypolipemic benefit of switching to ritonavir-boosted ATV in further randomized studies.

RESULTS

- Out of 593 patients included receiving ATV/RTV, 255 met entry criteria and were prospectively followed for a cumulative follow-up of 1383 patient-months. Fifty six percent of patients completed at least 6 months of treatment.
- Baseline characteristics are shown at Table-1.
- Most patients came from a previous PI regimen (mainly LPV/RTV) and drugs more frequently coadministered with ATV/RTV were TDF, DDI and 3TC (Table-2).
- Forty percent of patients had multiple (>2) major risk factors or coronary heart disease (CHD) or equivalent (Table-3). These numbers could be infraestimated since information about family history of early CV events was not collected.
- Evolution of absolute values of TG, TC, LDL, Non-HDL, HDL, percentage of change from baseline and proportion of subjects with lipids above clinically significant levels are shown in Graph-1 to Graph-5, respectively.
- Baseline demographic, HIV infection, and laboratory factors were analyzed to establish any potential association with successful lipid outcome defined as TC<200, LDL<130 or TG<500 at month 6 but none of them was significantly associated.
- TC/HDL ratio, decreased from 5.7 at baseline to 4.9 at month 12 (p=0.006). Moreover, the proportion of patients at higher risk (>6.4) also dropped from 33% to 18% (p>0.05).
- There was also a significant reduction in the proportion of patients using concomitant lipid-lowering therapy. Almost one third of those who were receiving this kind of drugs at baseline stopped them during the follow up.(Graph 6).

**TABLE-1**  
**BASELINE CHARACTERISTICS** N=255

Age (median, years)	41
Males (%)	77.5
CDC stage (% category C)	40.7
Hep B/C coinfection (%)	47.3
HIV RNA (median, log10 copies/mL)	4.4
HIV RNA (% below 500 cp/mL)	53.4
CD4 count (median, cells/mm <sup>3</sup> )	380
Lipodystrophy (%)	65.2
Active enolism (%)	6.7
Fasting triglycerides (TG) >500 mg/dL (%)	29
Total cholesterol (TC) >200 mg/dL (%)	93
LDL-cholesterol (LDL) >130 mg/dL (%)	64

**TABLE-3**  
**CARDIOVASCULAR RISK FACTORS** N=255

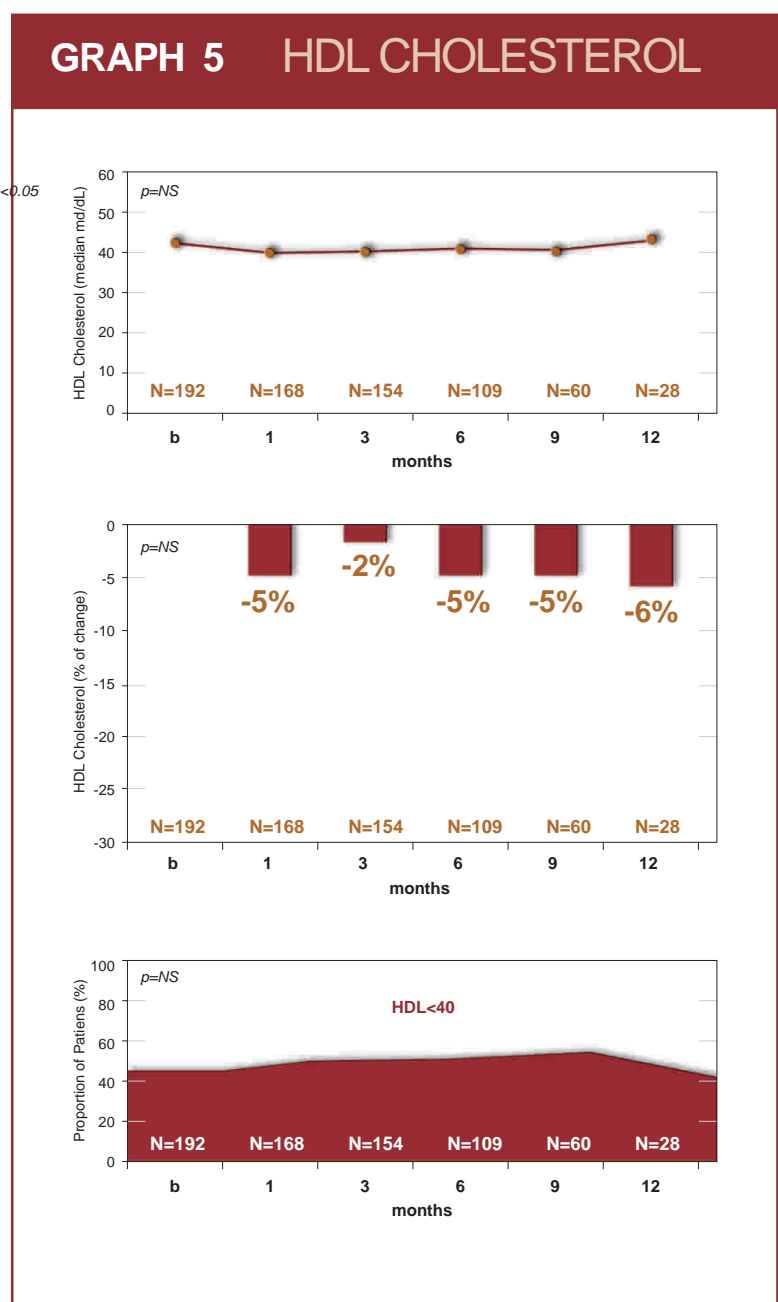
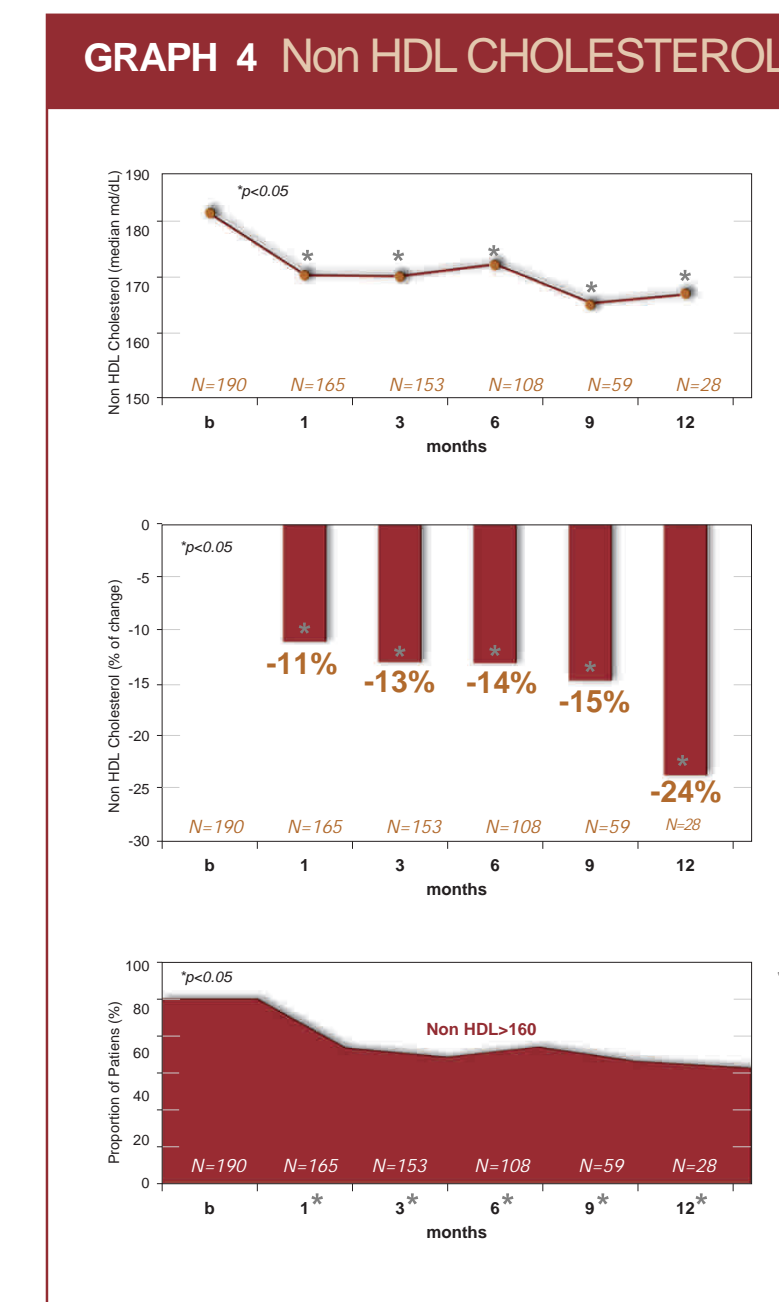
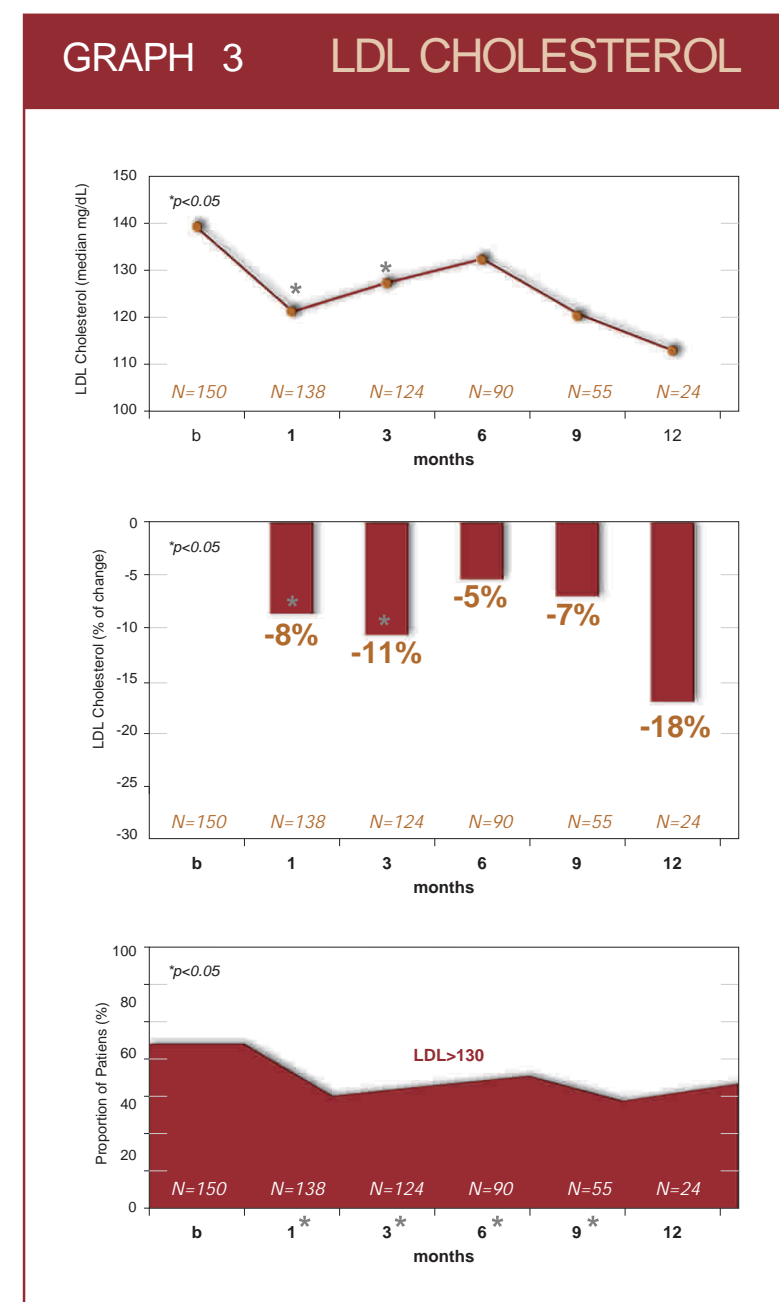
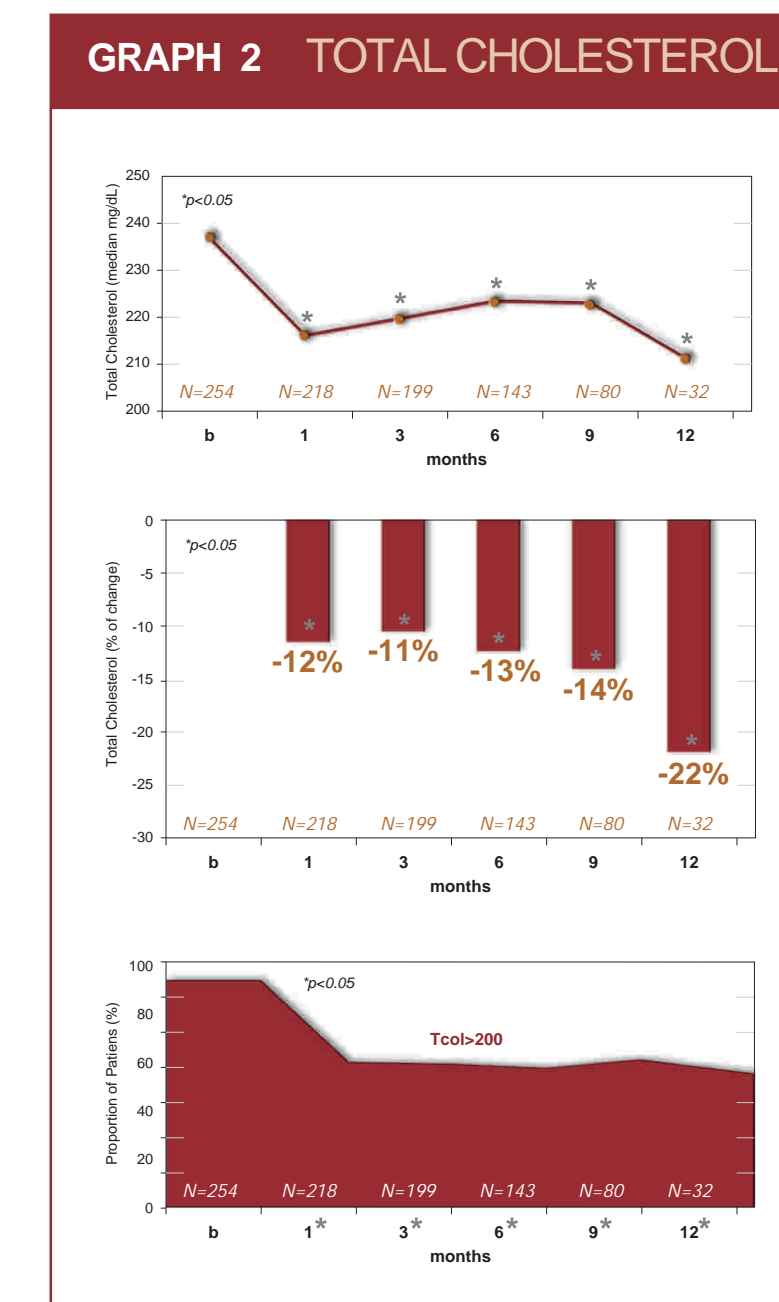
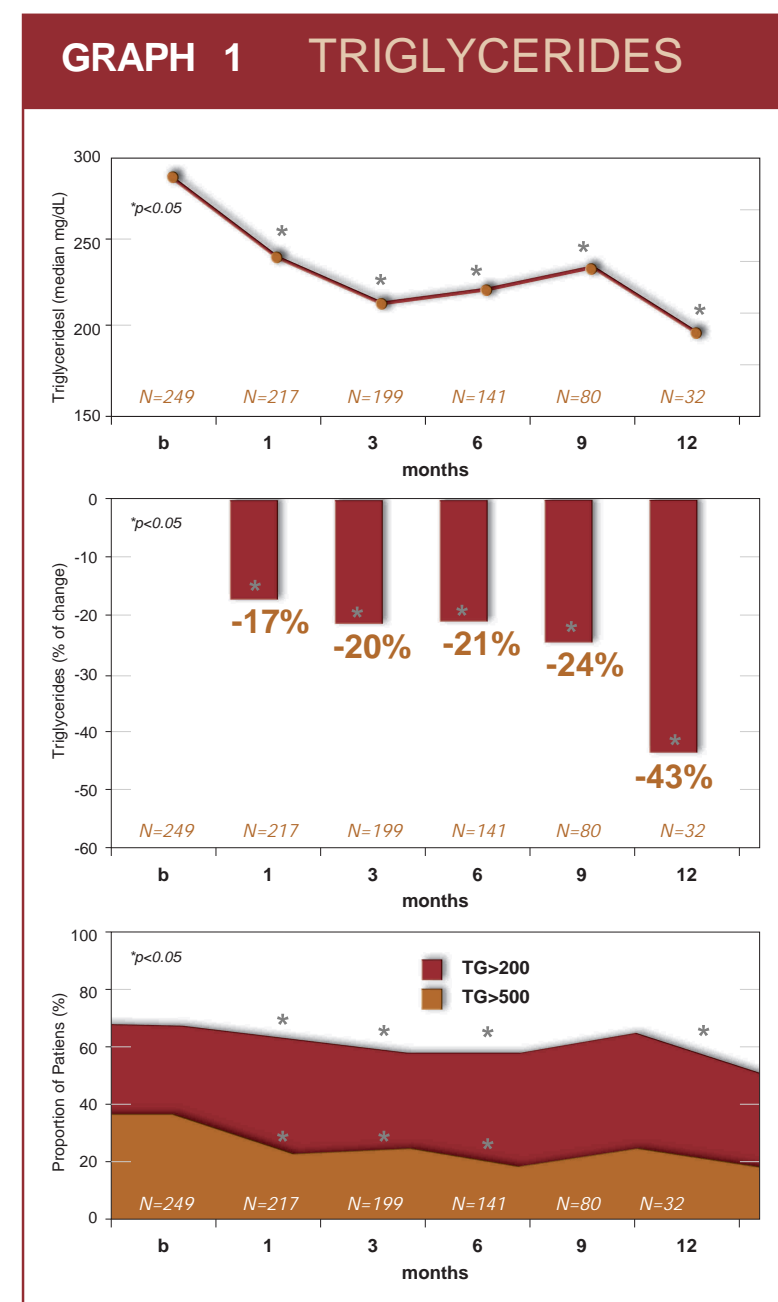
Smoking (%)	43.2
HTA (%)	5.3
Age (males 45, females 55 years) (%)	29.9
HDL <40 (%)	42.7
Cardiovascular event familiar history (%)	NA
Diabetes Mellitus (%)	7.9
Previous cardiovascular event (%)	3.6
0-1 risk factors (%)	59.2
2 risk factors (%)	32.2
Previous CV event/DM (%)	8.6

**TABLE-2**  
**TREATMENT HISTORY %** N=255

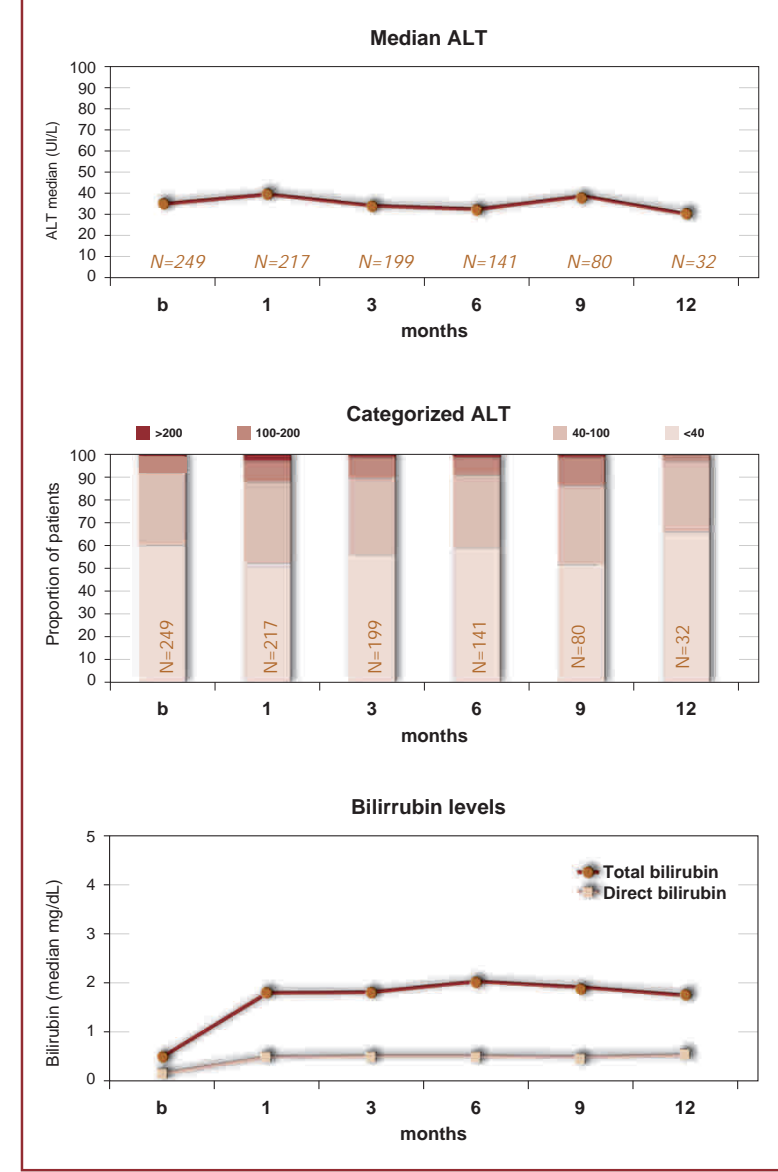
<b>Prior ARV use</b>	
NRTIs	97
NNRTIs	74.1
PIs	90.6
<b>Preceding Therapy</b>	
Only NRTIs	5.6
NNRTI-based	70.2
PI-based	43.2
- LPV/RTV	8.2
- NFV	8.2
- APV or APV/RTV	8.2
- SQV/RTV	6.3
- IDV or IDV/RTV	4.3
<b>Drugs used with ATV/RTV</b>	
TDF	67.5
DDI	48.2
3TC	34.9
ABC	16.9
d4T	14.9
EFV	11
Other PI	5.5

**TABLE-4**  
**REASONS FOR DISCONTINUATION** N=255

Adverse Event, n (%)	8 (3.1)
Jaundice/Scleral icterus, n (%)	3 (1.2)
Death, n (%)	3 (1.2)
Virological Failure, n (%)	4 (1.6)
Other Reasons, n (%)	14 (5.5)
Total Discontinuations, n (%)	29 (11.4)

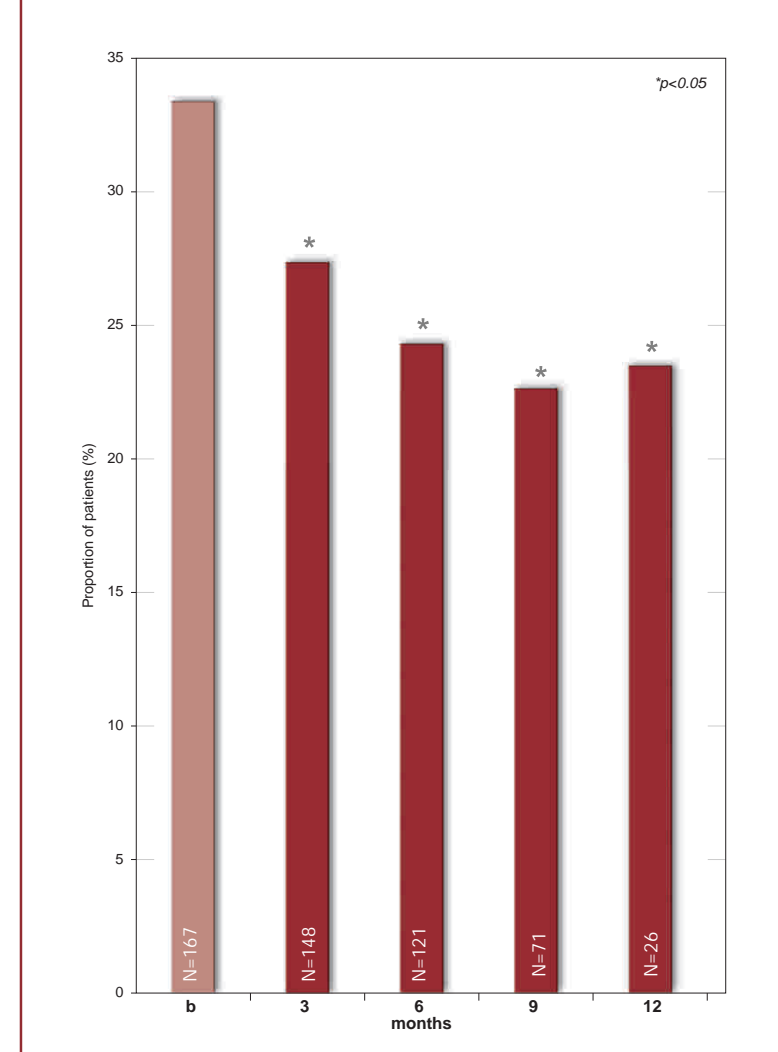


**GRAPH 7 LABORATORY (ALT & BIL)**



- Jaundice was diagnosed in 14 (5.5%) patients but only 3 (1.2%) discontinued therapy.
- ALT values over 200 IU/L (Graph-7) were rarely observed during follow-up and only one patient discontinued due to elevated transaminases, despite half patients were HIV-hepatitis B/C coinfectied.

**GRAPH 6 LIPID-LOWERING THERAPY USAGE**



**Safety assesment**

- Therapy was generally well tolerated. Only 8 (3.1%) of patients discontinued due to ATV-related adverse events. Total discontinuations and reasons for discontinuation are shown at Table-4. The three deaths observed were HIV-related and no therapy-related.