Triglycerides/HDL Ratio And Its Impact On Risk Of Diabetes Mellitus Development During Antiretroviral Therapy

Short running title: Triglycerides/HDL Ratio and Diabetes' risk

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Key words: HIV, diabetes, Triglycerides, HDL, dyslipidemia

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SYNOPSIS

Objectives

Our primary aim was to study Diabetes Mellitus (DM) arising during combination Antiretroviral Therapy (cART), and to attempt to identify associations between these cases, and triglycerides (TRG) and triglycerides to high-density lipoprotein cholesterol ratio (TRG/HDL). Our secondary aim was to analyze the association between DM development and Hepatic fibrosis.

Methods

A retrospective cohort study. Patients from the ICONA Foundation study initiating first-line cART between 1997 and 2013 were selected and observed until new-onset DM or most recent clinical follow-up. The predictive value of TRG and TRG/HDL ratio levels on DM was evaluated using multivariable Poisson regression models.

Results

3,546 patients [males 73.7%, median age 38-yrs; median BMI 23.1; Hepatitis C antibody positive 22.1%] were included. Of these, 80 developed DM over 13,911 PYFU, corresponding to 5.7 cases per 1,000 patient-years of follow-up (95% CI4.6-7.1). At Multivariable analysis, latest TRG/HDL, when high, was associated with significant increases in DM risk (rate ratio [RR] 1.63; 95% CI 1.32-2.01 per 10 points higher), while current TRG, in contrast, was associated with new-onset DM only at crude analysis. Advanced liver fibrosis (defined as FIB-4 index >3.25) was also shown to be an independent risk factor for DM (RR 2.91; 95% CI 1.10-7.72).

Conclusions

High TRG/HDL ratio predicted risk of new-onset DM, independently of other traditional risk factors. Furthermore, our findings suggest that advanced hepatic fibrosis, estimated using FIB-4 score, could provide an additional predictor for DM.

INTRODUCTION

Combination Antiretroviral Therapy (cART) has dramatically reduced morbidity and mortality in HIV-infected patients, prolonging their life expectancy.[1] At the same time, ageing and related co-morbidities represent serious challenges in this population. The incidence of co-morbidities associated with ageing appears to be much higher, and to occur earlier, in HIV-infected individuals with respect to their HIV-uninfected counterparts.[2]

Increased risk of diabetes mellitus (DM) in HIV–infected subjects is a matter of debate. Whilst an association between HIV infection and heightened risk of diabetes has been demonstrated in some studies, [3-5] other researches have failed to support such findings.[6-8]

Dyslipidemia is a common feature among HIV-infected patients, particularly during cART. According to the American Diabetes Association, all overweight patients whose high density lipoproteins-cholesterol (HDL-c) are less than 35 mg/dl (0.9 mmol/l) and whose triglycerides (TRG) are higher than 250 mg/dl (2.8 mmol/l) should undergo testing for diabetes.[9] Moreover, ratio between TRG and HDL-c levels (TRG/HDL) has been cited as a marker of insulin resistance, which is the most important risk factor for developing DM.[10-12]

Although high TRG and low HDL-c are frequently found in HIV-infected patients on cART,[13] they are not always associated with obesity. This is because HIV-infected patients often have lower body mass indexes (BMI) compared to the general population.[14] In addition, the relationship between HDL-c and TRG plasma levels has been postulated to be different in patients with HIV-related, with respect to non-HIV-related dyslipidemia.[15] Finally, cART introduction heavily alters the lipid profile within the HIV-infected population.[16]

Hence, the predictive roles of TRG, HDL-c and TRG/HDL in development of DM are not well estabilished in HIV-infected patients, since it is unclear whether abnormalities in these levels are associated with DM, or are merely side effects of cART which have little impact on DM onset. This question merits further evaluation.

Our primary aim was to verify the association between TRG and TRG/HDL ratio and Diabetes' onset. Our secondary objective was to evaluate associations between DM and liver fibrosis during cART, given the known association between Insulin Resistance and non-alcoholic fatty liver disease (NAFLD).[17,18]

METHODS

The Icona Foundation Study is a cohort of HIV-infected patients, which superseded the original Italian Cohort of Antiretroviral-Naive Patients study, (detailed description of this cohort elsewhere),[19] recruiting HIV-positive naïve patients. CD4+ cell counts and viral load are measured at least every 6 months, as are other laboratory parameters, as well as clinical and therapeutical data.

Ethics

All patients signed consent forms to participate in the Icona Foundation Study, in accordance with the ethical standards of the committee on human experimentation and the Helsinki Declaration (1983 revision).

Patients enrolled in the ICONA Foundation cohort were included in the present analysis if:

- they had begun cART while naïve to antiretrovirals, from 1st January 1997 or later;
- they had at least 1 TRG and HDL-cholesterol fasting value before baseline, which was defined as cART initiation;
- they had a baseline fasting blood glucose <=126 mg/dl (7 mmol/l);
- they were never exposed to anti-diabetic or lipid lowering drugs before baseline;
- they had no diagnosis of DM prior cART initiation;

DM was defined as two consecutive blood glucose values of >126 mg/dl (7 mmol/l), clinical diagnosis of DM, or start of anti-diabetes treatment. Incidence rate of DM was calculated as number of observed cases of DM subsequent to cART initiation divided by person years of follow-up (PYFU). Follow-up period began at commencement of cART and lasted until onset of DM, death or lost to follow up, whichever occurred first.

Univariable and multivariable Poisson regression models were fitted, to assess factors associated with post-cART DM development. Crude risk ratios (RR) were estimated for the following:

- fixed covariates: gender, mode of HIV infection, nationality, years of infection, nadir CD4 cell/mmc,
- covariates at cART start: age, CDC stage, CD4 and log10 HIV-RNA, HCV and HBV co-infection, total cholesterol and triglycerides, TRG/HDL,
- time-dependent covariates that could change value over the course of the observation period and which included all consecutive values of each single variable during the follow-up and which were called follow-up (FU) variables in the text: BMI, total cholesterol, triglycerides, TRG/HDL, type of antiretroviral regimen, type of backbone combination and type of third drug in the regimen, alcohol use and FIB4.

.Patients were pooled according to TRG values at baseline and during follow up:

- ≤ 180 mg/dl (normal TRG)
- 181 mg/dl <TRG <300 mg/dl (mild hypertriglyceridemia)
- TRG >300 mg/dl (moderate/severe hypertriglyceridemia)

Liver fibrosis was evaluated using Fibrosis-4 (FIB-4) score, calculated as:

(Age x AST) / (Platelets x (sqr (ALT))

and divided up into 3 categories, as follows: [20,21]

- FIB4 value>3.25 as a proxy for advanced fibrosis;
- FIB4 value between 1.45 and 3.25 for which fibrosis status is considered to be undetermined;
- FIB4 value<1.45 considered to be absence of advanced fibrosis.

Two different multivariable Poisson regression models were fitted, including all factors associated with p-values of < 0.2 at univariable analysis. An initial model included time-updated values of TRG/HDL, expressed as follow-up FU-TRG/HDL (model A); a second model included time-updated values of TRG, expressed as follow-up FU-TRG (model B).

RESULTS

Of the 3,546 patients included in our analysis, 80 developed DM over 13,911 PYFU, representing an incidence rate of 5.7 per 1,000 PYFU (95%CI4.6-7.1). Most patients were males (73.7%), and their median age was 38 years (IQR 33-45). Median BMI at baseline was 23.1 (IQR 21.1-25.2), and 22.1% of patients tested positive for hepatitis C virus antibodies (HCV-Ab). At baseline most patients (82.6%) had normal triglyceride levels, normal HDL (73% of sample) and median TRG/HDL ratio was 2.8 (IQR 1.8-4.5). Complete patients' characteristics are depicted in Table 1.

During follow-up, 28562 TRG/HDL values were calculated. FU-TRG/HDL ratios affected DM incidence rate: 1.8/1,000 PYFU (95%CI 0.8-4.0) for subjects with ratios lower than first quartile (TRG/HDL ratio 0-1.69), 3.9/1,000 PYFU (95%CI 2.2-6.8) for ratios between first and second quartile (TRG/HDL ratio 1.7-2.69), 5.6/1,000 PYFU (95%CI 3.5-9.0) for ratios between second and third quartile (TRG/HDL ratio 2.7-4.5) and 9.8/1,000 PYFU (95%CI 6.8-14.0) for ratios above third quartile (TRG/HDL ratio>4.5) (figure 1).

FU-FIB-4 score was also associated with increased DM incidence: 3.7/1,000 PYFU (95%CI 2.7-5.0) for subjects with FIB-4 scores of <1.5, 11.4/1,000 PYFU (95%CI 7.5-17.4) for scores between 1.5 and 3.25 and 16.8/1,000 PYFU (95%CI 8.4-33.6) for FIB-4 of >3.25.

At univariable analysis, abnormal values (181-300 mg/dl and >300 mg/dl) of basal TRG as well as time-updated values (FU-TRG) were significantly associated with higher risk of Diabetes' onset, compared to normal values (≤180 mg/dl). Patients with mild (TRG between 181-300) and moderate/severe hypertriglyceridemia (TRG>300) at baseline had RR=4.16 (95%CI 2.62-6.62, p<0.001) and RR=2.78 (95%CI 1.18-6.52, p=0.019) respectively, versus patients with normal values.

Similarly, patients with FU-TRG in the mild and moderate/severe groups were at higher risk of DM, RR=1.83 (95%CI 1.07-3.13, p<0.05) and RR=3.55 (95%CI 2.01-6.28, p<0.001) respectively, compared to subjects with normal values.

Additionally, higher TRG/HDL ratio values, both at baseline and during follow-up, were associated with higher risk of new Diabetes' diagnosis, with RR= 1.16 per 10 points higher (95%CI 1.06-1.27, p= 0.001) and RR= 1.18 (95%CI 1.10-1.26 , p<0.001) respectively.

At univariable analysis, the following risk factors were found to be associated with higher risk of DM: higher age, male gender, nadir CD4<200 cells/mm^3, CDC C stage versus stage A/B, HCV-Ab positive

versus negative, baseline cholesterol between 200 and 240 mg/dL versus normal value ≤200, FU-BMI between 25 and 29.9 and FU-BMI≥30 versus FU-BMI<25, Use of stavudine plus lamivudine in current regimen versus tenofovir plus emtricitabine, Indinavir / IDV-ritonavir use in current regimen versus efavirenz, FU-FIB-4 score (FIB-4) between 1.5 and 3.25 or >3.25 versus. <1.5. (full results in Table 2)

Multivariable analysis (model A and model B) is shown in table 2. The two models differed by the way FU TRG was modeled: model A included FU-TRG/HDL ratio, while model B included FU-TRG. In model A higher FU TRG/HDL ratio was associated with higher risk of DM, independently of all factors included and of FU FIB-4 value. Other factors independently associated with higher risk of diabetes' onset were: older age (per 10 year older, RR 1.44; 95%CI 1.06-1.95), p<0.05), FU-BMI>30 (4.92; 95%CI 2.42-10.00 versus BMI<25, p<0.001), use of stavudine+lamivudine in FU-regimens (6.31; 95%CI 1.95-20.40 versus tenofovir +emtricitabine, p<0.01), use of atazanavir/ritonavir (3.23; 95%CI 1.30-7.98 versus efavirenz, p<0.05), higher FU-TRG/HDL ratios (per 10 points higher 1.63; 95%CI 1.32-2.01, p<0.001), basaline cholesterol between 201-239 mg/dl (2.49; 95%CI 1.30-4.78 versus <=200, p<0.05), and FU- FIB-4>3.25 (2.91: 95%CI 1.10-7.72 versus<1.5, p<0.05).

Additionally, advanced liver fibrosis (defined as FIB-4 index >3.25) was independently associated with higher risk of DM, particularly in model A, with only marginal association evident in model B (Table 2). Of note, this association was much stronger among patients without HCV co-infection (RR 5.28; 95%CI 1.25-22.27) than in those with positive HCV-Ab (RR 1.91; 95%CI 0.61-6.0 p-value for interaction=0.02). In a multivariate model excluding FIB-4, HCV-Ab positivity was independently associated with DM development, confirming a strong interaction between FIB-4 and HCV (data not shown).

We also explored the risk of diabetes when high values of TRG/HDL and FIB-4 were coexisting and we found that in patients with a TRG/HDL ≥4.5 (III quartile) and a FIB-4 >3.25 the RR of diabetes was 4.03 versus those with TRG/HDL<4.5 and FIB-4<1.5 (95%CI 0.86-19.03; p=0.08) confirming a cumulative effect of the two different markers even if this does not reach a statistical significance. The interaction test between TRG/HDL and FIB-4 score was not significant (p=0.33)..

213

DISCUSSION

Our primary goal was to evaluate the incidence and determinants of diabetes in a large cohort of previously antiretroviral treatment-naive patients initiating cART in Italy. In this cohort, incidence of new-onset diabetes was as high as 5.7 per 1,000 PYFU, not significantly higher than the incidence reported for uninfected subjects in Italy.[22,23] Comparing our data with those obtained from other large cohorts of HIV-infected subjects, we found that our findings were very similar to incidences found in the DAD[8] and Swiss HIV cohorts,[6] but lower than the one reported from the ANRS study.[5] The discrepancy between our findings and those of the French study may be attributable to several factors. There were significant age disparities between the two populations: nearly 70% of patients in the French study were over 40 years of age, while median age in our population was 38 years. Also, in our analysis only 37% had started cART before 2005, while the French cohort included patients initiating cART between 1997 and 1999. Such differences in calendar year of inclusion could be an important variable, translating into into exposure to different antiretrovirals regimes. For example, in the French study, new-onset diabetes peak in 1999-2000 and subsequent marked decrease is likely to be related to exposure to first-generation antiretrovirals.

In our study, we did not have a control group of HIV-negative subjects; however, the incidence of diabetes we observed in this large cohort of HIV-infected patients was similar to the incidence reported in a sample of HIV-negative subjects of the same age in northern Italy (5.7 vs. 5.8 per 1,000 PYFU).[22] Studies conducted in the U.S.A. produced conflicting results when comparing HIV-infected patients with HIV-uninfected controls. In the Multicenter AIDS cohort study (MACS), Brown TT et al.[4] reported a significantly higher incidence of diabetes in HIV-infected males on cART compared to HIV-negative males. In contrast, the incidence of diabetes in HIV-infected women in the Women's Interagency Study, undertaken by Tien et al.[7] was significantly lower than that of the MACS study, with no observable differences seen between HIV-infected and HIV-uninfected women. It should be noted, however, that, each of these studies used a different definition for diabetes; only Tien's study,[7] as ours, used the American Diabetes' Association guidelines criteria for definition of DM.

Aiming to define independent predictors of new-onset diabetes, we have found that TRG levels and TRG/HDL ratios in our cohort are predictive of subsequent diabetes in patients initiating cART. This is consistent with data obtained in general population for overweight individuals,[24]since high prevalence of insulin resistance in subjects with BMI>25 usually determines increases in TRG levels, and a proportional decrease in HDL.[25] Importantly, in our study, more than half of patients had a

normal BMI, allowing us to confirm the usefulness of TRG/HDL ratio in predicting diabetes, even in non-overweight HIV-infected patients.

One explanation for the association between TRG/HDL ratio and development of diabetes in HIV-infected patients could be that dyslipidemia and/or insulin resistance are involved in the pathogenesis of type 2 diabetes, paralleling data obtained in the general population.[23,26] Indeed, several reports have suggested that dyslipidemia, in particular high TRG and low HDL levels, play a role in the development of diabetes in HIV negative patients.[27-29] Lipotoxicity, inflammation and endoplasmic reticulum stress are the three pathogenetic mechanisms which have been postulated to explain this association [30-32] and maintaining healthy HDL-c levels has recently been proposed as a means of preventing diabetes [33].

In HIV+ positive patients, the relation between HIV replication, chronic subclinical inflammation and use of cART may enhance the link between dyslipidemia and diabetes, and thus needs to be investigated. Vu et al.[15] recently demonstrated that the inverse correlation between TRG and HDL-c found in general population is not present in the HIV population. In determining these results, the authors took into account CD4 count and detectable viral load, both of which are possible factors affecting the correlation between HDL-c and TRG. Moreover, the authors showed that HIV patients possess a unique cholesteryl ester transfer protein (CETP) mass, as well as specific activity. With these factors in mind, our study may prove to be a useful tool in confirming an association - already well-defined in general population - that merits further investigation in HIV infected patients on cART, due to the unique characteristics of this population.

The introduction of ART determines an increase in all the lipid profile setting values, comparable to, or much higher than, those observed prior to HIV-infection.[16] The role of ART in the development of dyslipidemia is therefore of great significance. For these reasons, and because of the low BMI seen in the majority of HIV+ patients with or without lipoatrophy,[14] our finding that TRG/HDL ratio is predictive of DM, independently of BMI, is of great significance, and justifies screening for diabetes in HIV-infected patients with high TRG and TRG/HDL ratio.

Another important concern highlighted by our findings is the optimal cut-off for TRG/HDL ratio in HIV-infected patients. A significant cut-off of TRG/HDL has been proposed in general population (>3), which has been demonstrated to be effective in overweight subjects.[24] In our study we found a significantly higher incidence of new-onset diabetes for patients in the third quartile for TRG/HDL ratio, corresponding to a ratio-value of >4.5 with a sensitivity of 45.3% and a specificity of 75%.

Considering a cut-off =3.5 sensitivity was higher (62.5%) and specificity was reduced (64.1%) (data not shown). Therefore, we could argue that a cut-off of 4.5 should be used for the HIV population, especially in patients with a normal BMI.

The relation between type of cART, dyslipidemia and incidence of diabetes is a major issue for the management of HIV-patients. We found a strong association between new-onset of DM and exposure to ART, especially with stavudine and indinavir use, consistent with the proven ability of these drugs to induce insulin resistance.[5,6] The association we found with atazanavir is difficult to explain. It did not change even after correcting for atazanavir in first regimen or as a switch. It may reflect the PI-class effect, and the wide use of Atazanavir in recent years, especially among patients with metabolic complications.

Our study also explored the predictive value of a liver fibrosis marker (FIB-4) in detecting patients at risk of DM. In general population, advanced liver fibrosis (defined as FIB-4 index >3.25) has been associated with diabetes, due to the high prevalence of non-alcoholic fatty liver disease (NAFLD) in diabetic patients and drug-induced steatosis.[17,18] FIB 4 has therefore been proposed as an indirect marker correlating with progressive metabolic alterations.

In our cohort, a value of FIB-4 >3.25 was significantly associated with new-onset DM in HCV-Ab negative subjects; furthermore a strong interaction was found between FIB-4 and HCV, as expected. Hepatic fibrosis could be a marker of increased risk of diabetes both for metabolic steatosis and for viral steatosis due to HCV. The association between HCV and diabetes is well described in literature. [34,35] Together with TRG/HDL ratio, FIB-4 >3.25 could therefore prove to be a useful tool for identifying patients with hepatic damage caused both by metabolic and HCV-induced steatosis.

Our study presents some limitations. We did not collect waist circumference that could allow us to evaluate the prevalence of metabolic syndrome in our cohort. Waist circumference is a valid marker of diabetes'risk and could add important informations at our results. On the other hand we focused our attention on a surrogate marker of insulin Resistance (TRG/HDL ratio) that is considered the driving force of metabolic syndrome components. Another limit was the lack of data regarding to HCV-RNA positivity in patients with HCV-Ab positivity that should have provided the exact prevalence of HCV-related damage. However we did not consider HCV role in our conclusions because of this limit. Our analysis is on an observational study and can't provide the strength to define a real causality between the risk factors and development of diabetes, especially regarding to the associations with ART regimens

In conclusion, in studying a cohort of HIV-infected patients previously naïve to antiretroviral treatment, we found that incidence of diabetes was more frequent in subjects with lipid abnormalities, with or without high BMI. TRG/HDL ratio proved to be an independent predictor of diabetes and thus a simple and useful marker to identify patients with insulin resistance who are at subsequent risk of diabetes, in order to enact early prevention strategies. High triglycerides levels observed during cART are likely to be not only a consequence of therapy, but an effective marker of insulin resistance, even in presence of normal BMI. Moreover, measurement of liver fibrosis by FIB-4 could be of use as a supplemental DM surrogate marker.

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Transparency declarations section

None to declare

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Legend to Figure 1:

FU (follow-up), TRG (Triglycerides), FIB-4 (Fibrosis-4 score), HDL (High Density Lipoproteins Cholesterol), PYFU (Person years of follow-up).

Table 1 Study population characteristics N=3546	
Male gender, n (%)	2612 (73.7%)
Age, years, median (IQR)	38 (33-45)
Mode of HIV transmission	
Heterosexual contact	1513 (42.7%)
MSM	1224 (34.5%)
IVDU	598 (16.9%)
Other/unknown	211 (6.0%)
Italian nationality, n(%)	3045 (85.9%)
Duration of HIV infection, years, median (IQR)	1.5 (0.2-5.6)
CDC stage C, n(%)	355 (10.0%)
Nadir CD4 cells/mm^3, median (IQR)	270 (170-361)
<200 cells/mmc, n(%)	1051 (29.6%)
Baseline CD4 cells/mm^3, median (IQR)	286 (181-384)
Baseline log_{10} HIV-RNA copies/ml, median (IQR)	4.8 (4.2-5.2)
HCV positivity, n(%)	766 (22.1%)
HBV positivity, n(%)	159 (4.5%)
Baseline BMI, n(%)	
<25 kg/cm^2	1875 (52.9%)
25-29.99 kg/cm^2	588 (16.6%)
>=30 kg/cm^2	131 (3.7%)
Unknown	952 (26.8%)
Baseline total cholesterol, n(%)	
<200 mg/dl	2943 (83.0%)
201-239 mg/dl	423 (11.9%)
>=240 mg/dl	104 (2.9%)
Unknown	76 (2.1%)
Baseline HDL cholesterol <35 mg/dl, n(%)	957 (27.0%)
Baseline triglycerydes, n(%)	
<=180 mg/dl	2929 (82.6%)
181-300 mg/dl	489 (13.8%)
>300 mg/dl	128 (3.6%)
Baseline triglycerides/HDL cholesterol ratio, median (IQR)	2.79 (IQR 1.76-4.53)
Baseline FIB4 score, median (IQR)	0.87 (0.62-1.28)
First ARV regimen	
NRTIs+NNRTI	1486 (41.9%)
NRTIs+PI/r	1467 (41.4%)
NRTIs+PI	329 (9.3%)
Only NRTIs	137 (3.9%)
Other	127 (3.6%)
Years of cART start	
1997-2001	602 (17.0%)
2002-2005	754 (21.3%)
2006-2009	758 (21.4%)
2010-2014	1432 (40.4%)

467

Legend to the table: IQR (Interquartile range), MSM (Men having sex with men), IVDU Intravenous Drug Users), CDC (Centers for Disease Control and Prevention), HCV (Hepatitis C Virus Antibodies), HBV (Hepatitis B Virus Antibodies), BMI (Body Mass Index), HDL (High Density Lipoproteins Cholesterol), NRTI (nucleoside reverse transcriptase inhibitors), NNRTI (non- nucleoside reverse transcriptase inhibitors), PI (Protease Inhibitors), FU (follow-up), FIB-4 (Fibrosis-4 score).

474 Table 2 Univariate and Multivariate models

	Univariable			Multivariable - Model A			Multivariable - Model B		
	RR	95% CI	P	ARR	95% CI	P	ARR	95% CI	P
Male gender vs female	2.42	1.31-4.47	0.005	2.09	0.91-4.79	0.083	1.71	0.85-3.46	0.136
Age (per 10 yrs older)	1.89	1.55-2.30	<0.001	1.44	1.06-1.95	0.019	1.64	1.26-2.13	0.000
Italian vs not Italian	2.00	0.73-5.47	0.176	1.10	0.29-4.26	0.887	0.69	0.24-1.99	0.488
Nadir cd4 <=200 cells/mmc	2.06	1.31-3.21	0.002	1.16	0.87-1.54	0.320	1.14	0.89-1.47	0.304
CDC stage C vs A/B	2.23	1.32-3.77	0.003	1.18	0.54-2.59	0.676	1.40	0.73-2.70	0.315
HIV-RNA al basale, log_{10} copies/mL (per 1 log higher)	1.22	0.92-1.63	0.173	1.09	0.79-1.52	0.599	1.10	0.82-1.48	0.527
HCV-Ab positive vs negative	1.62	1.01-2.60	0.047	1.70	0.88-3.25	0.112	1.90	1.07-3.36	0.028
Baseline cholesterol, mg/dL									
<=200	1.00			1.00			1.00		
201-239	1.98	1.15-3.41	0.014	2.49	1.30-4.78	0.006	1.82	0.99-3.35	0.054
>=240	1.01	0.25-4.15	0.988	0.80	0.11-5.98	0.832	1.09	0.26-4.58	0.909
FU-TRG/HDL (per 10 points higher)	1.18	1.10-1.26	<0.001	1.63	1.32-2.01	<0.001			
FU-TRG, mg/dL									
<180	1.00						1.00		
180-300	1.83	1.07-3.13	0.027				1.67	0.93-2.98	0.086
>=300	3.55	2.01-6.28	<0.001				2.35	1.19-4.66	0.014
FU-BMI									
<25 kg/cm^2	1.00			1.00			1.00		
25-29.99 kg/cm^2	2.36	1.38-4.02	0.002	1.64	0.87-3.10	0.126	1.99	1.13-3.51	0.017
>=30 kg/cm^2	6.76	3.78-12.10	<0.001	4.92	2.42-10.00	<0.001	5.51	2.83-10.71	<0.001
FU- FIB-4 score									
<1.5	1.00			1.00			1.00		
1.5-3.25	3.12	1.84-5.27	<0.001	1.97	1.01-3.87	0.048	1.72	0.92-3.19	0.088
>3.25	4.58	2.14-9.81	<0.001	2.91	1.10-7.72	0.031	2.38	0.92-6.19	0.074
NRTIs in the current regimen									
Tenofovir + emtricitabine	1.00			1.00			1.00		
Tenofovir + lamivudine	0.92	0.28-3.07	0.896	1.37	0.37-5.07	0.639	1.32	0.36-4.81	0.679

Abacavir + lamivudine	1.10	0.42-2.89	0.847	1.13	0.32-3.98	0.850	1.43	0.47-4.38	0.529
Zidovudine + lamivudine	1.39	0.77-2.54	0.277	2.16	0.84-5.54	0.110	1.83	0.75-4.49	0.184
Stavudine + lamivudine	3.92	1.82-8.48	0.001	6.31	1.95-20.40	0.002	4.48	1.52-13.24	0.007
Didanosine + lamivudine	2.55	0.88-7.37	0.084	2.09	0.44-9.90	0.352	2.74	0.74-10.21	0.132
Other	1.99	1.05-3.77	0.034	2.38	0.65-8.63	0.189	3.29	1.09-9.95	0.035
Third drug in the current regimen									
Efavirenz	1.00			1.00			1.00		
Nevirapine	0.93	0.39-2.19	0.863	1.19	0.42-3.33	0.745	0.87	0.33-2.34	0.790
Lopinavir/ritonavir	1.81	0.92-3.59	0.087	1.20	0.47-3.10	0.702	1.12	0.48-2.65	0.788
Atazanavir/ritonavir	1.55	0.74-3.24	0.240	3.23	1.30-7.98	0.011	2.40	1.03-5.63	0.043
Fosamprenavir/ritonavir	0.87	0.12-6.47	0.890	1.53	0.19-12.40	0.692	1.35	0.17-10.69	0.776
Indinavir ± ritonavir	3.13	1.26-7.79	0.014	1.25	0.26-6.16	0.780	1.54	0.54-4.44	0.422
Saquinavir ± ritonavir	3.23	0.76-13.83	0.114	-	-	0.999	3.55	0.76-16.62	0.108
Nelfinavir	1.35	0.40-4.55	0.626	1.59	0.34-7.37	0.557	1.56	0.43-5.64	0.497
Only NRTI	1.73	0.79-3.81	0.171	1.51	0.39-5.86	0.552	0.90	0.28-2.89	0.857
Other	0.97	0.41-2.29	0.943	0.95	0.29-3.15	0.931	0.72	0.24-2.19	0.567
Calendar year of cART start (per 1 yr more)	0.95	0.90-1.01	0.099	1.02	0.92-1.14	0.689	1.00	0.91-1.10	0.956

Legend to the table: RR (Relative Risk), ARR (Adjusted Relative Risk), HCV-Ab (Hepatitis C Virus Antibodies), FU (follow-up), TRG (Triglycerides), FIB-4 (Fibrosis-4 score),HCV (Hepatitis C Virus Antibodies), HBV (Hepatitis B Virus Antibodies), BMI (Body Mass Index), HDL (High Density Lipoproteins Cholesterol), NRTI (nucleoside reverse transcriptase inhibitors), NNRTI (non- nucleoside reverse transcriptase inhibitors), PI (Protease Inhibitors), FU (follow-up),.