

# Effects of Combined Use of Antiretroviral Agents and Atypical Antipsychotics on Lipid Parameters

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## Abstract

Human immunodeficiency virus (HIV) and psychiatric disorders frequently occur together and may result in concurrent use of atypical antipsychotic (AAP) agents and highly active antiretroviral therapy (HAART). Both classes of agents have been shown to cause clinically important dyslipidemia and metabolic dysregulation in a population at high baseline cardiovascular risk. The combined effects of concurrent use of these drug classes on lipids and other metabolic indices remain undetermined. This retrospective cohort included HIV(+) or HIV(-) patients at the Dallas Veterans Affairs Medical Center who received either HAART or AAP agents. Subjects were separated into three groups: HAART+AAP, HAART alone, and a control group of HIV(-) patients taking AAP agents. The combined HAART and AAP use on lipid parameters was examined. Included patients received treatment for at least 12 weeks and had baseline and follow-up lipids within 1 year. A total of 107 male patients were analyzed with a mean age of 51 years. Mean time on HAART regimen was 49 months (HAART+AAP; n=27) and 24 months (HAART alone; n=40), and mean time on AAPs was 20 months (HAART+AAP) and 22 months (AAP alone; n=40). The addition of an AAP agent to medication regimens in HIV(+) patients, resulted in trends toward worsening TC, LDL, and non-HDL cholesterol levels, although not statistically significant. Ratios of TC/HDL were insignificant between groups following initiation of HAART alone, AAP alone, or in combination; however a greater TG/HDL ratio was noted in those receiving HAART+AAP relative to HAART or AAP alone.

**Keywords:** Antiretrovirals; Atypical antipsychotics; Lipids

**Abbreviations:** HIV: Human Immunodeficiency Virus; HAART: Highly Active Antiretroviral Therapy; AAP: Antipsychotic, CV: Cardiovascular; CAD: Coronary Artery Disease; TC: Total Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; TG: Triglycerides; HDL-C: High-Density Lipoprotein Cholesterol; FPG: Fasting Plasma Glucose; BMI: Body Mass Index; VANTHCS: Veterans Affairs North Texas Healthcare System; NNRTI: Non-nucleoside Reverse Transcriptase Inhibitor; PTSD: Post-traumatic Stress Disorder

## Introduction

Human immunodeficiency virus (HIV)-infected patients are commonly burdened with a myriad of psychiatric comorbidities. Nearly one-half of HIV patients are affected by psychiatric disorders, with depressive symptoms and anxiety being the most prevalent, at 46% and 32% respectively [1]. Managing various target symptoms of these disorders often requires the use of atypical antipsychotic (AAP) agents, which may be co-prescribed with highly active antiretroviral therapy (HAART) in the HIV-infected patient. This combination of medications may cause a theoretical concern given that both of these therapeutic drug classes have been associated with metabolic abnormalities, particularly altered lipid and glucose metabolism [2].

Unfortunately, both HIV patients and those with psychiatric illness are known to be at greater cardiovascular (CV) risk relative to the general population. Several large studies [3,4] have shown that both HIV infection as well as antiretroviral therapy contribute to CV risk, especially an increased risk for myocardial infarction (MI) with long-term therapy. In addition, patients with certain psychiatric disorders have been shown to have a higher prevalence of CV risk

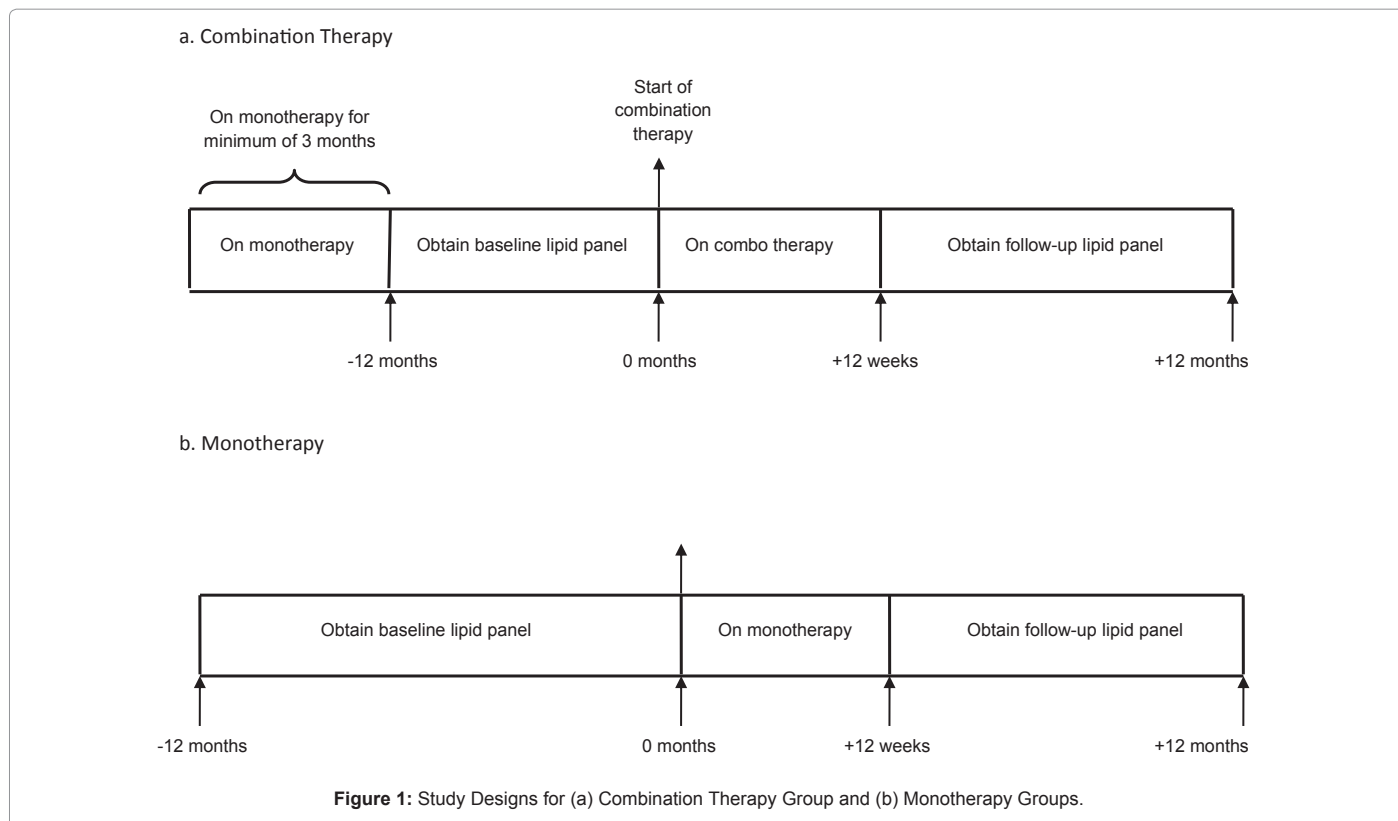
factors, which may result in a higher risk of new-onset coronary artery disease (CAD) compared to healthy individuals [5]. A review article examining the metabolic complications of both HIV and severe mental illness medications suggests a potential increased risk for metabolic abnormalities mediated by inherent physiologic changes as well as medication side effects [6]. Although, both HAART and AAP agents have been shown to cause adverse effects on cardiovascular risk factors such as serum lipids and impaired glucose metabolism [7-10], the effects of concurrent use on these metabolic indices with both classes of agents has yet to be reported in the literature. The primary aim of this study was to determine if combined use of antiretroviral therapy and atypical antipsychotic agents resulted in worsening lipid parameters and other metabolic indices compared to use of antiretroviral therapy or atypical antipsychotic agents alone. We hypothesized that the combined effects of antiretroviral therapy and atypical antipsychotic therapies on lipid parameters were additive.

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## Materials and Methods

### Objectives

The primary objective of the study was to determine if the introduction of the combined use of HAART and AAP agents resulted in a worsening of lipid parameters, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C), compared to baseline. The secondary objectives were to assess the following: change in lipid parameters from baseline with combination therapy versus HAART monotherapy or AAP monotherapy; change in fasting plasma glucose (FPG) from baseline; change in body mass index (BMI; calculated as kg/m<sup>2</sup>) from baseline; collect frequencies of newly developed metabolic syndrome based on the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) [11] diagnostic criteria; collect frequencies of change in lipid-lowering and glucose-lowering medications after initiation of combination therapy.

### Design and participants

This was a single-center, retrospective cohort study conducted at the Veterans Affairs North Texas Healthcare System (VANTHCS) located in Dallas, Texas. The study cohort included HIV-positive (+) or HIV-negative (-) patients who received either HAART or AAPs from 1/1/98 to 9/1/08. The subjects were separated into three groups: HAART + AAP, a control group of HAART alone, and a control group of HIV (-) patients taking AAP agents. These control groups were selected in order to examine metabolic effects of HAART or AAP monotherapy compared to combination therapy.

All patients 18 years and older were eligible for study inclusion if they had a diagnosis of HIV infection or were utilizing an AAP agent.

Patients were identified through a retrospective search of medication records within the HIV Registry at the VANTHCS. All patients with a diagnosis of HIV who ever received the combination of antiretroviral therapy and atypical antipsychotic therapy during the study period were screened for inclusion in the treatment group. All HIV-positive patients who received antiretroviral therapy alone were screened for inclusion in one of the control groups and the second control group consisted of a random sample of HIV-negative patients receiving atypical antipsychotics. For the combination therapy (treatment) group, patients must have been maintained on HAART or AAP monotherapy for a minimum of 12 weeks prior to the initiation of the second class of medication. Patients were required to be maintained on combination therapy for a minimum of 12 weeks. Also, they must have had a lipid profile obtained within a 1-year period prior to the initiation of combination therapy, and a follow-up lipid profile within a 12- 52 week period after the initiation of combination therapy (Figure 1). To be included in the monotherapy groups, patients must have been maintained on only HAART or AAP therapy for a minimum of 12 weeks. Additionally, patients must have a lipid profile obtained within a 12- 52 week period prior to the initiation of the AAP or HAART, and a follow-up lipid profile within a 12- 52 week period after the initiation of either monotherapy agent (Figure 1). Patients were excluded from the study if they exhibited a significant change in baseline diabetes control considered not related to HAART or AAP therapy (defined as a change in hemoglobin A1c of  $\pm 1\%$  or increase in FPG of  $> 30\text{-}40\text{ mg/dL}$ ), evidence of significant changes in dietary and/or exercise patterns, new diagnosis of alcoholism or significant change in alcohol consumption, evidence of poor compliance based on prescription refill history and progress notes, or a diagnosis of nephrotic syndrome. Details regarding other disease states known to affect lipids and/or glucose, such as hypothyroidism, were collected in effort to reduce

possible confounders. After initial screening was conducted based on inclusion and exclusion criteria, all eligible patients in the HAART + AAP and HAART alone groups were included. Patients from the AAP alone group were randomly selected using a random number generator, in order to meet the minimum group size necessary based on the pre-defined power calculation.

### Data collection

The comprehensive, real-time, computerized patient record system (CPRS) was used to access medical records for eligible patients, including progress notes, laboratory values, medications, and International Classification of Diseases, version 9 (ICD-9) codes. Data gathered for each study participant included demographic information, height/weight, past medical history, social history, family history, medications utilized during the time-frame of interest (specifically known metabolic effects), duration of HAART and/or AAP use, lipid parameters, plasma glucose and A1c, blood pressures, liver enzymes, CD4+ and HIV viral load, and thyroid stimulating hormone (TSH).

### Statistical analysis

A sample size of 22 patients in each group was necessary to show a 7% difference in LDL-C ( $\alpha = 0.05$  and with 80% power). An LDL-C reduction of 7% has been shown to predict a 15% reduction in coronary heart disease ( $p < 0.04$ ) [12], and was deemed clinically significant by the authors. Between-group comparisons were performed using ANOVA with Bonferroni correction and within-group comparisons were performed using paired t-tests (SPSS®v.17).

### Results

Three hundred and fifty HIV (+) patients were identified from the VANTHCS database, with 112 patients identified as eligible for the combination therapy group (HAART + AAP) and 238 patients eligible for the HAART monotherapy group (HAART alone). After application of the inclusion and exclusion criteria, 85 patients in the HAART + AAP group were excluded based on inadequate treatment duration ( $n=64$ ), lack of laboratory data ( $n=11$ ), misdiagnosis of HIV ( $n=4$ ), poor compliance ( $n=3$ ), or use of more than one study agent ( $n=3$ ), leaving 27 patients eligible for inclusion. One-hundred ninety-eight patients were excluded from the HAART alone group due to lack of adequate lipid panels ( $n=150$ ), misdiagnosis of HIV ( $n=16$ ), HAART treatment duration  $< 12$  weeks ( $n=21$ ), death ( $n=7$ ), or poor compliance ( $n=4$ ), leaving 40 patients included in the analysis.

A total of 13,723 HIV (-) patients were eligible for the AAP monotherapy (AAP alone) group. Individuals were screened at random until 40 cases were eligible for inclusion. The reasons for exclusion from this AAP alone group were inadequate lipid panels ( $n=80$ ), AAP duration of  $< 12$  weeks ( $n=28$ ), noncompliance ( $n=18$ ), use of more than one study agent ( $n=5$ ), and death ( $n=1$ ).

Baseline characteristics ( $\pm$  SD) were similar between all three groups (Table 1). All patients included in the study were male with a majority being overweight (BMI  $> 26$  kg/m<sup>2</sup> for all groups), but the patients in the HIV (+) groups tended to be younger ( $47.6 \pm 7.7$  years). HAART regimens were more likely to be non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing (46.3%) and quetiapine was the most commonly-used AAP (47.8%). Mean duration of HIV was 9.8 years with patients averaging 22.3 months on HAART. The most common indications for AAP initiation were for insomnia and post-traumatic stress disorder (PTSD)-related symptoms, such as nightmares. The mean duration of AAP use  $20.3 \pm 20.1$  months for the HAART + AAP group and  $22.5 \pm 24.9$  months for the AAP alone group.

	HAART + AAP (n=27)	HAART alone (n=40)	AAP alone (n=40)
Mean age $\pm$ SD (y)	48.9 $\pm$ 8.61	47.6 $\pm$ 7.7	55.8 $\pm$ 11.9
Male (%)	100	100	100
Baseline BMI $\pm$ SD (kg/m <sup>2</sup> )	26.1 $\pm$ 4.3	27.1 $\pm$ 6.4	27.0 $\pm$ 5.1
HIV Duration $\pm$ SD (y)	10.4 $\pm$ 7.3	9.2 $\pm$ 7.1	N/A
Time on HAART $\pm$ SD (months)	20.3 $\pm$ 20.1	24.3 $\pm$ 18.7	N/A
Time on AAP $\pm$ SD (months)	20.3 $\pm$ 20.1	N/A	22.5 $\pm$ 24.9

HAART: highly active antiretroviral therapy; AAP: atypical antipsychotic; BMI: body mass index

**Table 1:** Baseline Characteristics.

### Effect of HAART and/or AAP therapy on lipid parameters

**HAART + AAP:** The introduction of HAART or an AAP to a patient already stabilized on one class of medication, resulted in non-significant worsening of some lipid parameters. The mean total cholesterol (TC) increased ( $+8.5 \pm 36.0$  mg/dL,  $p=0.23$ ), the triglycerides (TG) increased ( $+54.5 \pm 171.9$  mg/dL,  $p=0.11$ ), and the non-high density lipoprotein (non-HDL) increased ( $+7.5 \pm 36.0$  mg/dL,  $p=0.61$ ), although none of these changes were statistically significant when compared to baseline. Low density lipoprotein cholesterol and HDL-C trended towards improvement ( $-1.3 \pm 26.4$  mg/dL,  $p=0.81$  and  $+1.0 \pm 10.0$  mg/dL,  $p=0.61$ , respectively), though neither reached statistical significance. Lipid ratios, including TC/HDL and TG/HDL also showed worsening trends from baseline ( $+0.1 \pm 1.3$  and  $+1.8 \pm 6.4$ , respectively) (Figures 2 and 3).

**HAART alone:** When compared to a baseline, the addition of HAART resulted in worsening of TC ( $+16.9 \pm 44.9$  mg/dL,  $p=0.21$ ), LDL ( $+4.9 \pm 36.5$  mg/dL,  $p=0.41$ ), TG ( $+7.0 \pm 110$  mg/dL,  $p=0.69$ ), and non-HDL ( $+9.4 \pm 39.8$ ,  $p=0.15$ ); however, none of these were statistically significant. A significant increase was seen in HDL ( $+8.0 \pm 12.7$  mg/dL,  $p < 0.001$ ), but the slight improvements seen with TC/HDL ( $-0.5 \pm 1.3$ ), and TG/HDL ( $-1.0 \pm 4.0$ ) were not significant.

**AAP alone:** The addition of an AAP agent in patients without previous AAP utilization resulted in non-significant improvement of several lipid parameters, including TC ( $-6.9 \pm 30.1$  mg/dL,  $p=0.16$ ), LDL ( $-4.1 \pm 23.8$  mg/dL,  $p=0.28$ ), TG ( $-8.2 \pm 87.2$  mg/dL, 0.56), and non-HDL ( $-4.7 \pm 31.9$  mg/dL,  $p=0.36$ ), but non-significant trends toward further worsening for HDL ( $-3.9 \pm 12.2$  mg/dL,  $p=0.51$ ), TC/HDL ( $+0.1 \pm 1.3$ ) and TG/HDL ( $+0.03 \pm 2.7$ ).

**Between group comparisons:** Compared to those receiving AAP monotherapy, patients in the HAART alone group showed significant worsening in TC from baseline (HAART:  $+16.9 \pm 44.9$  mg/dL; AAP:  $-6.9 \pm 30.1$  mg/dL;  $p=0.017$ ), but significantly-improved HDL (HAART:  $+8.0 \pm 12.7$  mg/dL; AAP:  $-3.9 \pm 12.2$  mg/dL;  $p < 0.0001$ ). With respect to lipid ratios, combination HAART + AAP therapy resulted in a significant increase, or worsening, in TG/HDL ratio ( $+1.8 \pm 6.4$ ) compared to HAART monotherapy ( $-1.0 \pm 4.0$ ) ( $p=0.035$ ). Although other variations were noted between each of the three study groups, none were found to be statistically significant.

### Changes in metabolic indices and medication utilization from baseline

A trend in worsening glucose was seen in the HAART + AAP group and the AAP alone group, while a slight improvement was found in the HAART alone cohort. Patients in all three groups exhibited worsening body mass index (BMI), with the BMI change from baseline in the combination therapy group being significant. While 7% of the patients in the combination therapy group met criteria for new development

of metabolic syndrome, 27.5% in the AAP monotherapy met the same criteria. The effects of these classes of medications on lipid parameters and plasma glucose resulted in over one-half of the patients in the combination and HAART-only groups requiring the addition or adjustment of one or more lipid- or glucose-lowering medication (55.5% and 52.5%, respectively), while 72.5% of patients in the AAP monotherapy group underwent a similar medication change (Table 2).

## Discussion

In this real-world exploratory clinical study, the addition of an AAP agent to medication regimens in HIV(+) patients, already stabilized on HAART for at least 3 months, resulted in trends toward worsening TC, LDL, and non-HDL cholesterol levels. Although these values were not statistically significant, any worsening of metabolic parameters could be clinically concerning. To our knowledge, this is the first study examining the combined metabolic effects of these two classes of medications, although the individual class-specific effects on lipid and glucose metabolism have been well-described. As expected, the lipid parameter that seemed to be most greatly affected by the use of any of the aforementioned medication combinations was triglycerides.

This is consistent with previous metabolic studies independently evaluating HAART and AAP effects on lipids where TG elevations are

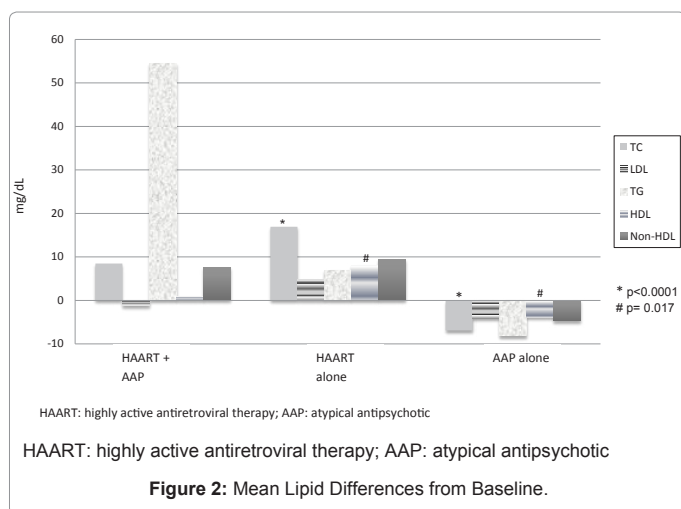


Figure 2: Mean Lipid Differences from Baseline.

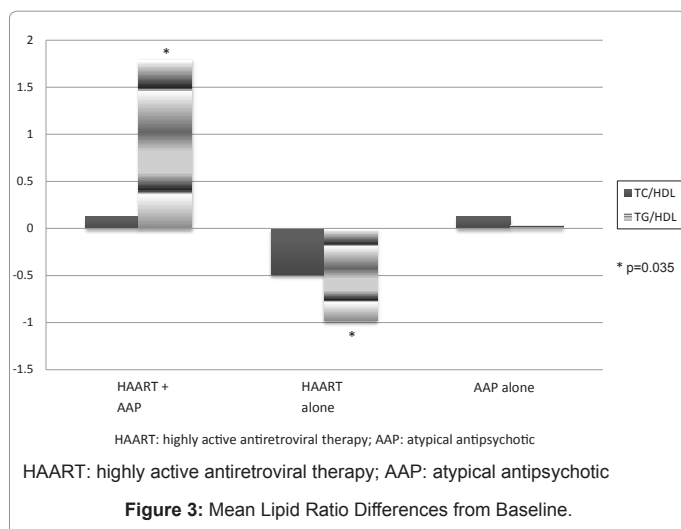


Figure 3: Mean Lipid Ratio Differences from Baseline.

	HAART +AAP (n=27)	HAART alone (n=40)	AAP alone (n=40)
Mean Change in Glucose ± SD (mg/dL)	+2.2 ± 41.0	-3.6 ± 38.5	+1.1 ± 50.3
Mean Change in BMI ± SD (kg/m <sup>2</sup> )	+0.8 ± 4.9*	+0.5 ± 6.3	+0.9 ± 5.8
New Development of Metabolic Syndrome, no. (%)	2 (7)	0 (0)	11 (27.5)
Diabetes Meds Added/Changed, no. (%)	2 (7)	7 (14.5)	12 (30)
Lipid Meds Added/Changed, no. (%)	13 (48)	14 (35)	17 (42.5)
Total Meds Added/Changed, no. (%)	15 (55.5)	21 (52.5)	29 (72.5)

HAART: highly active antiretroviral therapy; AAP: atypical antipsychotic; BMI: body mass index

\*p=0.013 for within-group comparison

Table 2: Changes in Metabolic Indices and Medication Utilization from Baseline.

of greater magnitude than other lipid indices. Previous reports include incidents of hypertriglyceridemia exceeding 1000mg/dL with ritonavir based antiretroviral regimens [13] as well as reports of AAPs increasing TGs by 11-31% [14,15]. Such drastic triglyceride alterations are likely due to the effect of both of these drug classes on insulin resistance [16,17]. The further increase in TGs (+54.5 ± 171.9 mg/dL, p=0.11) seen following co-administration of HAART and AAP suggests that the combined effects could be additive. Probable mechanisms of HAART-associated dyslipidemia are: impaired glucose uptake noted with protease inhibitors as they may inhibit GLUT-4 transporter, resulting in elevated serum glucose levels to serve as a substrate for hepatic TG synthesis [18], reduced suppression or stimulation of lipolysis leading to increased serum free fatty acids [18,19], and down regulation of steroid regulatory element-binding protein (SREBP-1c) resulting in fat accumulation in insulin-sensitive tissues, such as the liver [20], all of which can lead to increased TGs. These mechanisms differ somewhat from those proposed for AAP-associated dyslipidemia, which implicate weight gain, possibly induced by disruption of the feeding regulatory system via dysregulation in insulin, leptin, and ghrelin levels [21], or action at serotonin (5-HT), dopamine (D), and histamine (H) receptors, all known to affect food intake [22-24]. Since both HAART and AAPs seem to cause metabolic derangement by different metabolic pathways, it is possible that the combinatory effects are additive. Our data regarding lipid ratios are consistent with these findings, specifically the trend toward further worsening seen with the TG/HDL ratio in the HAART + AAP group, suggesting increased insulin resistance [25]. These findings uncover a challenging scenario from a medication-therapy management perspective, especially for those with HAART-associated dyslipidemia that is difficult to control even in the absence of AAP use.

Other noteworthy findings that further support worsening metabolic control with concomitant HAART and AAP therapy include a significant increase in BMI. Increasing weight, waist circumference, and ultimately, BMI can further place an individual at higher risk for insulin resistance and premature cardiovascular disease, especially in those with central obesity [26,27]. Rates of metabolic syndrome also increased in both the HAART + AAP and AAP alone groups though this finding did not reach statistical significance. The data obtained in this study imply that co-administration of HAART and AAP may have a clinically meaningful impact on lipid parameters. This may warrant monitoring and management of these various lipid and other metabolic risk factors in patients taking HAART and/or AAP therapy as suggested by consensus statement [28].

While worsening in lipid indices is of concern, perhaps an even more important observation made was the notable increase in utilization of lipid-lowering medications following the introduction of combination use of HAART + AAP. Over 50% of the patients in the combination therapy group received intensification of medications used to manage glucose or lipids, with 48% of these involving cholesterol-lowering medications. In the HIV (+) groups, despite the regular clinic follow-up in the HIV clinic, close monitoring, and fairly aggressive use of medications used to manage metabolic side effects, we still noticed a global trend toward worsening lipid parameters. It is possible that if these medication interventions were not performed, the post-therapy lipid changes may have been of greater magnitude, or possibly could have reached statistical significance, since use of these medications during the follow-up period may have contributed to the large variability observed in our lipid endpoints. It is important, however, to recognize that the large number of glucose- and lipid-lowering medication adjustments suggest that clinicians were concerned with worsening control of these metabolic parameters and were following published consensus recommendations [23] regarding the monitoring of these patients. In light of this pattern, perhaps a future study focusing on rates and trends of medication utilization would be valuable.

While our findings support a qualitative worsening in serum lipids following combined use of HAART and AAP, our study is not without limitations. One-year of follow-up may have been too brief to capture any further lipid changes beyond this time period, and this makes it difficult to account for subsequent introduction of lipid and/or glycemic controlling medications. Future research should examine laboratory values and interventions over a longer period of time. Secondly, the variation in triglycerides was much wider than expected, making the reproducibility and applicability of this study difficult. Also, triglyceride values are used in the determination of total cholesterol and non-HDL cholesterol, resulting in wide variability in these values as well. Since our study was not powered to detect a difference with such wide variability, type II error is highly possible. Reasons for the wide triglyceride variability include fasting versus non-fasting patient status, the introduction, change, and discontinuation of lipid-lowering medications throughout the course of the study period, and, possibly, fluctuation in glycemic control of the patients that is not reflected by hemoglobin A1c. In this study there was potential confounding due to inconsistent lipid testing, seeing as about half of the eligible patients were excluded from the analysis due to absent pre or post drug initiation lipid testing for the monotherapy groups. However, only 10% of eligible patients were excluded in the combination group suggesting the more risk factors present at baseline, the closer the patients are monitored. Finally, in the AAP monotherapy group, the lipid parameters improved without a change in lipid medications. This may have been due to the overall management of the patients by clinicians acutely aware of metabolic complications associated with these drugs, possibly conferring some bias in the results. All patients were males which is an inherent limitation due to our facility, thus limiting the ability to generalize this data to other population groups. Patient ethnicity was not collected and therefore cannot be utilized to draw any possible genetic conclusions about the population studied. Additionally, the number of patients reported in this study was small as it was meant to be an exploratory study to possibly generate future prospective studies. These limitations restrict the overall applicability to apply our results to a broad population. Re-design of this study in a prospective manner would allow for control of many of these real-life variables, including fasting status, medication introduction and discontinuation, analysis

of separate HIV and AAP agents, and close monitoring and regulation of glycemic control.

## Conclusion

The use of combination antiretroviral therapy and atypical antipsychotic agents suggests worsening metabolic control in patients already at higher baseline cardiovascular risk. This study focused mainly on lipids, and found that combination therapy may result in further worsening of TC, LDL, and non-HDL. Although the lipid and glucose medication interventions may have confounded our findings, it is clinically noteworthy that over 50% of the patients in each group required the addition or adjustment of one of these classes of medications, simply to maintain adequate control of these important metabolic parameters. This suggests that both HAART and AAP alone, and in combination, may potentially result in clinically meaningful metabolic sequelae, specifically, qualitative worsening lipids, however this study was not designed to identify a cause and effect relationship. The increased BMI and TG/HDL ratio in the combination therapy group might signify that these metabolic changes might be facilitated through increased insulin resistance, further implying that efforts should be employed to monitor metabolic status. If a future study examining similar effects was to be conducted, we would recommend standardization of medication choices, mechanism of ensuring fasting states of lipid panels, and a longer follow-up period.

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