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Equivalence of Boosted Atazanavir Based Regimens and Currently Effective HAART Regimens with Other PI's/NNRTI's in HIV + Children and Adolescents with Elevated Lipid Levels

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Abstract

Background: A frequent side-effect of antiretroviral therapy is elevation of plasma lipids and cholesterol. Atazanavir has been shown in adults to have a smaller elevation in plasma lipids in relation to other protease inhibitors. The purpose of this study was to determine the efficacy of Atazanavir in pediatric patients switching to Atazanavir from other HAART regimens and to compare the lipid levels after the switch.

Methods: Ten HIV infected pediatric patients with virologic suppression on HAART and elevated lipid levels were enrolled. Subjects were switched to boosted Atazanavir and followed for 24 weeks. CD4 + cell counts, viral loads and lipid levels were monitored at each study visit. Changes in lipid levels were analyzed with the non-parametric Friedman's test.

Results: Subjects were perinatally infected, not on lipid lowering medications, aged 6-18 years. Eight were male and 2 were female. Triglycerides trended from a mean of 288.5 at baseline to a mean of 193.3 at follow-up but the decrease was not statistically significant. Cholesterol trended from a mean of 214.3 at baseline to as low as 178.5 at 12 weeks post switch with a significant Friedman's Test ($\chi^2(3) = 12.6$, $p = 0.006$). Across all visits mean pre- and post-switch viral loads remained < 200 and CD4 + cell counts were not significantly different.

Conclusions: All patients maintained viral suppression and stable CD4 + cell counts after switching to Atazanavir. There was a statistically significant improvement in cholesterol levels with a trend to improvement in elevated triglyceride levels. Switch to Atazanavir is safe, efficacious and potentially beneficial in pediatric patients with elevated lipid levels.

Keywords

HIV, Antiretroviral, Patient care, Metabolism

Background

Children infected with HIV face a lifetime of treatment with antiretroviral medications. A frequent consequence of antiretroviral treatment is the elevation of plasma lipids [1]. Two analyses of data from a prospectively collected database of HIV infected children on highly active antiretroviral therapy (HAART), revealed that 13% of children had elevated cholesterol levels at baseline and an additional 13% developed elevated cholesterol levels during follow-up. Boosted protease inhibitor (PI) use, non-boosted PI use, virologic control and self-reported adherence were all associated with an increased risk for elevated cholesterol levels [1,2]. The second study also showed an increased risk for hypercholesterolemia for children on a non-nucleoside reverse transcriptase inhibitor (NNRTI) regimen [2]. Elevated cholesterol levels have even been shown in toddlers taking protease inhibitors [3]. Long-term effects of exposure to prolonged elevation of plasma lipids in HIV-infected children on HAART treatment are unknown. Early atherosclerotic changes and thickening of vascular intima have been described in HIV infected pediatric patients [4-6] and prolonged exposure to antiretroviral medications and elevated cholesterol and triglyceride levels could potentiate the development of these abnormalities.

Atazanavir (Reyataz®) has been shown in adults to result in smaller elevations in plasma lipids in relation to other protease inhibitors [7,8]. In addition, improvements in plasma lipid levels have been shown in adult patients with elevated lipid levels switching to Atazanavir from other protease inhibitors [9]. Early studies in pediatric patients taking Atazanavir with or without Ritonavir showed small increases in cholesterol and no increase in triglycerides in children with baseline plasma lipid levels within the normal range. Lipid levels remained in the normal range through 48 weeks [10,11]. A study by Macassa, et al. evaluated the results of switching 23 HAART treated pediatric patients to boosted Atazanavir. In their study, they reported a significant risk of virologic failure after the switch [12]. Lipid changes were not reported in that study. One recent retrospective review by Xiang, et al. showed maintenance of viral suppression and sustained improvement in mean total cholesterol in pediatric patients switching from suppressive LPV/r to boosted Atazanavir (ATV/r) or boosted Darunavir (DRV/r) [13]. In contrast Rutstein, et al. showed elevation of cholesterol and triglycerides in a sample of naïve and treatment experienced children treated with an atazanavir based regimen [14].

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The hypothesis for this study proposes that HIV-positive children on a HAART regimen with elevated lipids will maintain virologic control (VL stable) and will have improvement in their lipid levels when switched from a non-ATV/r containing regimen to an ATV/r based regimen. The primary objective of the study was to determine the equivalence of an ATV/r based regimen to stable non-ATV/r based HAART therapy in terms of absolute CD4+ cells, CD4 + cell% and viral load in children. The secondary objectives were to 1) evaluate changes in lipid levels (non-fasting cholesterol and triglycerides) in children switching to ATV/r from non-ATV/r regimens and 2) determine if an ATV/r based regimen results in an increase in patient satisfaction and patient reported adherence and a decrease in symptoms related to medication side effects.

Methods

The study design was a prospective, non-randomized, open-label, intervention study.The setting was a hospital-based pediatric HIV clinic in the southwestern US from 8/26/2009 to 10/16/2013. A convenience sample was drawn to include all eligible patients. Eight perinatally HIV-infected pediatric subjects with virologic suppression on HAART and elevated lipid levels (greater than 95% for age on the National Health and Nutrition Examination Survey [NHANES] data) [15-17] were enrolled in the study. Retrospective data was included from two additional patients who had been switched prior to the study for a total n of 10. Inclusion criteria included signed, written, informed consent/assent, subject age between 6 and 18 years, protocol defined contraception for young women of child bearing potential, stable on HAART therapy with a viral load < 1000 for 6 months prior to baseline visit, weight greater than or equal to 25 kg, and able or willing to learn to swallow pills. Exclusion criteria included women of child bearing potential who were pregnant or unwilling or unable to use contraception, underlying hepatitis B or C viral infections, previously demonstrated clinically significant hypersensitivity to any of the components of Atazanavir (Reyataz®), grade 3 or higher elevations in transaminases (> 10 X ULN), taking medications that are highly dependent on CyP3A or UGT1A1 for clearance.

Once enrolled with baseline measures of viral load, CD4 + cells and lipid levels (non-fasting cholesterol, triglycerides) and safety laboratories (CBC, creatinine, bilirubin, ALT, AST, glucose, serum protein) completed, subjects were switched to Atazanavir capsules dosed according to the CDC Guidelines [18] and boosted with 100mg of ritonavir (Table 1). Subjects continued the same background therapy and were followed for 24 weeks. CD4 + cell counts, viral loads, lipid levels and patient and parent satisfaction, as well as medication adherence and side effects were monitored at 4, 12 and 24 weeks post switch. Laboratory tests were processed by the lab preferred by the subject's insurance (Sonora Quest or LabCorp). Parent and patient satisfaction were measured with an investigator developed 7-item Likert scales. Adherence was measured at baseline and 4, 12 and 24 weeks post switch with parent/subject report for pre and post comparison. Pill counts were conducted at 4, 12 and 24 weeks post switch to give a more accurate estimation of how adherent subjects were and to provide evidence for validity of the data.

The two additional subjects who had been switched to ATV/r prior to the initiation of the study did not have patient or parent satisfaction data or pill counts available. Data collection, management, entry and analysis were completed by and under the direction of a PhD prepared research nurse.

Descriptive statistics for demographic variables were generated using frequencies in SPSS. Changes in outcome variables were analyzed with the non-parametric Friedman's test and Wilcoxon Signed Rank post hoc tests. The study was reviewed and approved by the Phoenix Children's Hospital Institutional Review Board. Parents signed informed consent and children over the age of 7 signed assents. Signed informed consent was waived by the IRB for participants in the retrospective chart review portion of the study.

Results

Subjects were all perinatally infected, not on lipid-lowering medications, aged 6-18 yrs. (median 9.5). Eight were male and 2 were female. Four were African-American, 3 were Caucasian, 2 were Hispanic and 1 was Asian. Seven subjects were on regimens containing lopinavir/ritonavir (LPV/r) plus 2 NRTI's. Two were on regimens containing LPV/r plus efavirenz plus 2 NRTI's, and 1 subject was on a regimen containing ritonavir plus Truvada® (Table 2). At baseline subject weights were quite varied (range = 25.6-118.4 kg, m = 30.1 kg), as were BMI's. All of the subjects showed appropriate growth for their developmental level throughout the study period (Table 3).

Lipid levels

Triglycerides trended from a mean of 288.5 at baseline to a mean of 193.3 at follow-up but the decrease was not statistically significant. Cholesterol trended from a mean of 214.3 at baseline to as low as 178.5 at 12 weeks post switch (Table 4) with a significant Friedman's test ($\chi^2(3) = 12.6$, $p = 0.006$). Post hoc Wilcoxon Signed Rank tests showed a significant difference between baseline and week 4 ($Z = -2.701$, $p = 0.007$).

Virologic and immune response

Viral loads (Friedman's Test $\chi^2(3) = 1.0$, $p = 0.801$) and CD4 + cell counts (Friedman's Test $\chi^2(3) = 1.8$, $p = 0.615$) and CD4 + cell percentages (Friedman's Test $\chi^2(3) = 6.918$, $p = 0.075$) were not significantly different between baseline and any of the follow-up visits. Mean viral loads (all < 200) and CD4 + cell counts and percentages are shown in Table 5. No subjects experienced virologic failure (> 200 copies/ml) or had to switch regimens while on study.

Table 1: Dosing of Atazanavir/Ritonavir taken together with food for treatment experienced children [18].

Weight (kg)	Once daily dose ATV	Once daily dose RTV
25 to < 32 kg	200 mg	100 mg
32 to < 39 kg	250 mg	100 mg
≥ 39 kg	300 mg	100 mg

Table 2: Baseline HAART regimens.

PID	PI	NNRTI	NNRTI's
102	LPV/r		ABC, DDI
103	LPV/r	EFV	FTC/TDF
104	RTV		FTC/TDF
105	LPV/r	EFV	3TC
106	LPV/r		ZDV, DDI
107	LPV/r		DDI, d4T
108	LPV/r		d4T, 3TC
109	LPV/r		d4T, 3TC
110	LPV/r		ABC, 3TC
111	LPV/r		TDF, 3TC

Table 3: Weight in Kg and BMI per subject by visit.

PID	Baseline Wt (BMI)	WK 4 Wt (BMI)	Wk 12 Wt (BMI)	Wk 24 Wt (BMI)
102	64.2 (24.3)	56.7 (24.1)	68.6 (25.0)	70.6 (24.9)
103	57.2 (21.2)	58.7 (21.8)	59.9 (22.1)	59.9 (21.8)
104	119.7 (33.5)	123 (35.0)	122.4 (35.8)	120.8 (34.1)
105	57.1 (25.2)	54.8 (23.6)	61.3 (26.3)	54.3 (22.7)
106	25.6 (15.6)	27.5 (16.5)	28.6 (16.8)	29.7 (17.2)
107	25.6 (17.2)	26.8 (15.4)	26.3 (15.0)	26.0 (14.4)
108	28.5 (15.0)	28.4 (14.7)	29.2 (15.0)	30.4 (15.3)
109	26.4 (17.1)	27.5 (17.7)	28.7 (18.2)	29.5 (18.1)
110	31.8 (17.7)	33.2 (18.4)	33.9 (18.4)	36.8 (19.6)
111	28.1 (15.9)	29.2 (16.3)	30.1 (16.8)	30.6 (16.7)

Table 4: Mean cholesterol and triglyceride values by visit.

Visit	Mean chol	Std dev chol	Mean trig	Std dev trig
Baseline	214.3	31.6	288.5	253.9
4 Wks	187.2	30.0	240.5	107.2
12 Wks	178.5	38.1	195.5	93.8
24 Wks	181.5	29.3	193.3	106.5

Table 5: Mean Viral Load (VL), Absolute CD4 counts (CD4) and CD4 percentages (CD4%) by visit.

Visit	Mean VL*	Std dev VL	Mean CD4	Std dev CD4	Mean CD4%	Std dev CD4%
Baseline	2.3	7.3	1233.1	473.8	33.4	5.7
4 Wks	Undetectable	0.0	1214.3	476.8	34.0	4.6
12 Wks	13.4	42.4	1151.9	442.7	33.5	6.4
24 Wks	2.6	8.2	1120.0	413.2	33.0	4.3

*Viral Loads that were undetectable were given a value of 0 for this analysis. Any other value was given the actual value.

Adherence results

Adherence, measure by pill counts, ranged from 90% to 100% (mean = 98.4%) of doses taken across all 3 post-switch visits.

Adverse events

One patient had grade 3 Bilirubin (4.4-6.3 mg/dl at all the post switch visits and a grade 2 amylase (200 IU/L) at 12 wks. There were no clinical symptoms and all other labs were within normal limits. Two subjects had signs/symptoms > grade 1 while on Atazanavir. These were grade 2 or 3 fever, cough and pain associated with upper respiratory tract infections or parotitis. No subjects withdrew from the study as a result of an adverse event (AE). There were no significant AST/ALT elevations in subjects on the study.

Patient/Parent satisfaction

Subjects started out with a high level of satisfaction (m = 34.2 out of 36). There was no significant difference between satisfaction with the prior regimen and the Atazanavir regimen (Friedman's Test Chi-Square (3) = 1.632, p = 0.652). Parents likewise started out with a mean satisfaction of 31.8 out of 36 and had no significant change over the course of the study (Friedman's Test, Chi-square (3) = 4.048, p = 0.256). There were positive comments from subjects who were able to switch to once a day regimens. One mother commented that her child had a better appetite after the switch from LPV/r.

Discussion

The effects of prolonged exposure to elevated lipid levels and elevated cholesterol due to HAART in children are not well known. However, these effects are problematic in adults and there is concern that children with HIV and prolonged exposure to elevated lipid levels may have increased risks of heart disease and stroke [19,20]. Efforts to adjust diet, nutrition and exercise can be very important in reducing these risks as well as the consideration of the use of statins, when indicated. One study has shown a modest improvement in cholesterol levels in pediatric patients with HIV switching to ATV/r [13]. Our study shows similar results. In addition, our study suggests that those children with very high lipid levels benefit the most from the switch, which is a question worth further study. The ability to decrease lipid elevations by using a more favorable protease inhibitor such as Atazanavir (or other lipid sparing medications) is an additional option for physicians choosing antiretroviral regimens or considering a switch in therapy for patients with elevated levels.

A previous study in children switched to Atazanavir raised a concern about the ability for patients to maintain virologic control, particularly in children with higher viral loads at initiation of therapy [12]. However, the retrospective study by Xiang [13] and our prospective study did not replicate those findings. Toxicity was minimal and no patients had to discontinue the Atazanavir due to side effects. Our study would also suggest that Atazanavir based regimens can be efficacious.

Limitations of this study included the small sample size and the wide variety of prior treatment regimens taken by the subjects. The self-reported adherence values may have been inflated as has been shown to frequently occur among many different subject populations. In addition, using non-fasting lipid levels may have introduced bias or increased variability in the secondary outcome variables. Theoretically the use of two different laboratories to determine lipid values may have been a source of bias. However the reference values for the lipid tests were the same for the two laboratories and there have been no indications that there are clinically significant differences between these laboratories on the lipid tests in our clinical practice.

Conclusions

All subjects maintained viral suppression and stable CD4 + cell counts and CD4 + cell percentages after switching to an Atazanavir containing regimen. There was a statistically significant improvement in cholesterol levels with a trend to improvement in elevated triglyceride levels. This study did not demonstrate virologic failure in stable pediatric patients switching to Atazanavir. Switching to Atazanavir appears safe and efficacious and can be beneficial in pediatric patients with elevated lipid levels.

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