Title

Brief Report: Ritonavir Concentrations in Hair Predict Virologic Outcomes in HIV-Infected Adolescents With Virologic Failure on Atazanavir-Based or Ritonavir-Based Second-Line Treatment

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Ritonavir concentrations in hair predict virologic outcomes in HIV-infected adolescents with virologic failure on atazanavir/ritonavir-based second-line treatment

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Abstract

Background: Sub-optimal adherence to antiretroviral therapy (ART) is responsible for most virologic failure among adolescents with HIV. Methods for objectively measuring adherence to ART are limited. This study assessed the association between ritonavir concentrations in hair, self-reported adherence and modified directly administered antiretroviral therapy on virologic outcomes among HIV-infected adolescents who were virologically failing second-line ART in Harare, Zimbabwe.

Methods: HIV-infected adolescents on atazanavir/ritonavir-based second-line treatment for >6 months with viral load ≥1,000 copies/mL were randomized to either modified directly administered antiretroviral therapy (mDAART) plus standard-of-care (intervention) or standard-of-care alone (control). Questionnaires were administered; viral load and hair samples were collected at baseline and after 90 days. Virological suppression was defined as <1,000 copies/mL after follow-up.

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Preliminary findings: Results were submitted to the International Workshop on HIV Pediatrics 2021 Virtual Workshop for presentation from 16–17 July 2021 if accepted.

Results: Fifty adolescents (13–19 years old) were enrolled, and 42 adolescents had ritonavir concentrations measured in hair at baseline and 90 days. Twenty-three (46%) were randomised to mDAART. Viral load suppression at follow-up [regression co-efficient(standard error); 95% confidence interval; p-value] [−0.3(0.1); −0.5- −0.06; 0.01], self-reported adherence at follow-up [0.01(0.005); 0.004–0.02; 0.006] and being male [0.3(0.1); 0.08–0.5; 0.008] were associated with ritonavir concentrations in hair. The intervention, mDAART, was not associated with ritonavir concentrations [0.2(0.1); −0.07–0.4; 0.2].

Conclusion: Ritonavir concentrations in hair predicted virological suppression and were associated with self-reported adherence and being male in this cohort of adolescents with treatment failure to atazanavir/ritonavir-based second-line ART. Measuring ritonavir concentrations in hair in adolescents on protease inhibitor-based regimens could assess adherence in this vulnerable group to avert subsequent virologic failure.

Keywords

Adolescents; virologic treatment failure; ritonavir hair concentrations; adherence

Introduction

Lifelong antiretroviral therapy (ART) significantly reduces HIV-related morbidity and mortality. However, maintaining and measuring antiretroviral adherence is challenging. The most traditional method to assess adherence is self-report, but that is subjective, and can be inaccurate among adolescents with HIV where adherence is a particular challenge[1–3]. More objective methods are being evaluated since measuring antiretroviral levels in biomatrices such as dried blood spots and hair assesses both adherence and long-term exposure in one assay, which is strongly predictive of virologic outcomes[4].

Adolescents have been and will be on treatment for long periods of time and could have metabolic changes due to chronic HIV-infection and long-term ART[5]. Nearly half of adolescents are virologically failing ART and could harbour drug resistance mutations[6;7]. Furthermore, nearly half of new HIV infections worldwide occur in adolescents, possibly leading to propagation of drug resistant strains of HIV[6–8]. Drug levels in hair could help assess if viral resistance is present which could be important in resource-limited settings where drug resistance testing is expensive and largely unavailable in the public sector[8–10]. Specifically, adequate drug levels in the presence of viremia could imply drug resistance, while sub-optimal levels with viremia could imply poor adherence or other causes of reduced drug exposure[10]. Measuring antiretroviral levels directly allows drug resistance testing to be targeted to the former group and adherence interventions to the latter group. In addition, hair collection is painless and easy, which is helpful for adolescents who may be afraid of needles[11;12]. Moreover, samples can be stored indefinitely at room temperature and shipped without biohazardous precautions[11;12]. Antiretroviral hair concentrations reflect drug exposure and adherence over the past weeks to months, whereas plasma drug concentrations reflect exposure and adherence over the past day or two and are affected by white coat effects[13].

Although hair collection is easy and cheap, analysis of concentrations with high performance liquid chromatography coupled with tandem mass spectrometry is expensive. However, lower cost POC methods using thin layer chromatography are in development and might prove more cost effective than the laboratory-based methods and by reducing risk of high-level drug resistance[13].

Adolescent studies measuring antiretroviral levels in hair are scarce. In addition, ritonavir concentrations in hair are under-studied in both adolescents and adults, although this drug is widely co-formulated with other protease inhibitors as a pharmacokinetic enhancer in second-line treatment in resource limited settings[14]. Ritonavir is metabolised via the CYP3A4 pathway and inhibits metabolism of other protease inhibitors by inhibiting CYP3A4 enzymes, allowing lower doses of otherwise toxic protease inhibitors (PIs) to be prescribed[14]. There is therefore no therapeutic efficacy from ritonavir when used at such low doses. Adolescents failing 1st line therapy in sub-Saharan Africa are usually switched to ritonavir-boosted PIs. The reason we analyzed ritonavir is because it is taken together with protease inhibitors (such as atazanavir and lopinavir) and therefore serves as a surrogate for adherence to all boosted protease inhibitors. Ritonavir analysis is adherence-related and no emphasis on individual contribution of each of the ARV concentration was intended.

To evaluate the utility of ritonavir levels among adolescents, this study assessed the association between ritonavir concentrations in hair and virological outcomes and self-reported adherence among adolescents living with HIV and failing atazanavir/ritonavir-based 2nd line ART at a large clinic in Harare, Zimbabwe. The study also assessed if there was an association between ritonavir concentrations in hair and a home-based adherence intervention.

Methods

Study procedures were described earlier[15–17]. Briefly, a randomised, controlled trial of modified directly administered antiretroviral therapy (mDAART) was conducted among 50 adolescents living with HIV, on atazanavir/ritonavir-based 2nd line ART for at least 6 months, with virological treatment failure (defined as viral load ≥1,000 copies/ml) and registered at Harare hospital, Zimbabwe. The intervention, mDAART, consisted of home visits on scheduled days during the week to observe dose ingestion, SMS text messages during weekends to remind dose ingestion, and standard of care. The control arm received standard of care alone, which consisted of 3 monthly clinic visits for assessment, drug refill and adherence counselling by peer counsellors. Participants were followed-up for 3 months.

Hair samples were collected, stored and shipped according to a standard protocol[18]. Samples were analysed at the University of California San Francisco Hair Analytical Laboratory (UCSF-HAL) using peer reviewed and approved hair assays[19]. Ritonavir hair concentrations were measured using liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS), with an assay range of 0.01–4.0ng/mg hair[19].

The study was registered with the Pan African Clinical Trial Registry (PACTR201502001028169) and NIH Clinical Trials.gov (NCT02689895), and approved

by the Harare hospital institutional review board, Joint Research Ethics Committee (JREC/51/14), Biomedical and Research Training Institute, Medical Research Council of Zimbabwe (MRCZ/A/1840), Research Council of Zimbabwe (Ref: 02810) and the UCSF Committee on Human Research (CHR #11–07442)[15–17].

Statistical analysis

Data was entered into Research Electronic Data Capture (REDCap) and analysed in Stata 14. Analyses examined the relationship between ritonavir hair concentrations and virologic outcomes, self-reported adherence and mDAART. Treatment outcome was defined as ritonavir concentrations in hair. Ritonavir concentrations were treated as continuous in linear regression analysis and were first checked for normality and collinearity. Ritonavir concentrations were log transformed during analysis to meet normality assumptions. Stepwise regression analysis was used in multivariate linear regression models. We report regression coefficients back transformed using the exponentiality function. P-values ≤0.05 were considered statistically significant. Variables with p-values <0.25 were considered in multi-variate analysis. Self-reported adherence was assessed by a visual analogue scale[20].

Results

Participant demographics and characteristics were described previously[15–17]. Two female participants refused hair collection citing cosmetic disruption of their hairstyles and 6 participants were excluded from analysis because their hair had been shaved too short either at baseline or follow-up visits. Mean(SD); 95% CI ritonavir concentrations were 0.3(0.4); 0–0.9ng/mg hair and 0.6(0.4); 0–1.3ng/mg hair at baseline and follow-up respectively. After follow-up, suppressed (VL<1,000 copies/ml) participants, n(%) [18(43%)] had higher ritonavir concentrations [mean(SD); 95% CI] (0.7(0.4); 0.01–1.4ng/mg hair) compared to unsuppressed (VL ≥ 1,000 copies/ml) participants [24(57%)] (0.5(0.4); 0–1.1ng/mg hair)].

In bivariate analysis (table 1), ritonavir concentrations in hair were associated with decreased viral load from baseline to follow-up and virological suppression at follow-up [regression co-efficient(standard error); 95% confidence interval; p-value] [−0.1(0.04); −0.2- −0.01; 0.03] and [−0.3(0.1); −0.5- −0.02; 0.04 respectively]. Ritonavir concentrations in hair were also associated with attending school consistently over the past 3 months [−0.3(0.2); −0.7- −0.0008; 0.05] and self-reported adherence by visual analogue scale at follow-up [0.01(0.005); −0.00005–0.02; 0.05]. Ritonavir concentrations were not associated with mDAART [−0.04(0.1); −0.3– 0.2; 0.7].

In multivariate analysis (table 2), ritonavir concentrations in hair were associated with being male [regression co-efficient(standard error); 95% confidence interval; p-value] [0.3(0.1); 0.08–0.5; 0.008], self-reported adherence by visual analogue scale at follow-up [0.01(0.005); 0.004–0.02; 0.006] and viral load suppression at follow-up [−0.3(0.1); −0.5- −0.06; 0.01]. Ritonavir concentrations were not associated with mDAART [0.2(0.1); −0.07–0.4; 0.2].

Discussion

Our findings concur with previous studies that showed that antiretroviral concentrations in hair are associated with decreases in viral load and predict virological outcomes among HIV-infected adolescents with virological treatment failure on second-line ART, including atazanavir and tenofovir concentrations in hair in the same cohort[2;11;12;16;17;21]. Ritonavir concentrations in hair were the strongest predictor of virological suppression at follow-up in this study, as well as viral load decrease in bivariate analysis. Although tenofovir concentrations in hair in the same cohort did not predict viral load suppression, they were associated with decreased viral load[17]. This difference could be explained by differences in the number of samples analysed. Only 34 participants had hair samples analysed for tenofovir concentrations at baseline and follow-up, compared to 42 participants whose hair samples were analysed for atazanavir and ritonavir concentrations at the same timepoints. Antiretroviral levels in hair are important for identifying reduced adherence and exposure accurately before clinical and immunological treatment failure set in, and before drug resistance occurs.

Ritonavir is a protease inhibitor that is, in lower doses, co-formulated with other protease inhibitors as a booster[14]. Measuring ritonavir concentrations in hair could prove useful as a marker of adherence and exposure in adolescents on protease inhibitor-based regimens. Protease inhibitors remain the backbone of 2nd line ART in resource limited settings in all age groups[22]. In addition, antiretroviral concentrations in hair could be useful not only in assessing long term adherence and exposure, but in predicting drug resistance as well. Future studies could assess if antiretroviral levels in hair predict drug resistance by incorporating drug level measurement in hair among participants that are virologically failing treatment. To the best of our knowledge, this is the 1st study to measure ritonavir hair concentrations in adolescents.

The home-based adherence intervention, mDAART, was not associated with ritonavir concentrations in hair. This concurs with findings from the same cohort which found that mDAART was not associated with atazanavir concentrations in hair[16]. This was an unexpected finding which could be a result of the short duration of the intervention and could reflect a lag in accumulation of antiretroviral drugs in hair compared to initial plasma antiretroviral level increases and viral load decrease[16]. We suspect that the lag is only at the early stages as drug concentrations increase after a period of non-adherence and start accumulating in hair, which grows relatively slowly at a rate of approximately 1cm /month. Thereafter, drug levels in hair will accurately reflect drug exposure and adherence. Directly administered ART is unsustainable in lifelong treatment compared to shorter treatment courses such as anti-TB treatment but may be beneficial when targeted to “high risk” adolescents living with HIV over defined time periods. Studies of longer duration could provide more clarity.

Ritonavir concentrations in hair were associated with self-reported adherence in this cohort of adolescents with treatment failure to second-line ART. Self-reported adherence is often over-estimated and is unreliable due to recall bias[23]. In addition, previous studies showed that self-reported adherence was not associated with ARV levels in hair, including atazanavir

and tenofovir concentrations in the same cohort[1;3]. This finding could be a result of bias which occurred because of unblinding. Blinding was not possible because of the nature of the intervention. All participants were aware of their study arm and that they were in a study where their adherence was being monitored. This finding therefore needs to be evaluated further.

Being male was associated with ritonavir concentrations in hair, and this concurs with previous findings in the same cohort[16]. Although males are known to have lower health seeking behaviour and adherence to treatment in adults, adolescent males tend to have higher adherence to ART compared to adolescent females during adolescence[16;24–26]. This could be because girls enter adolescence earlier than boys, are more susceptible to peer pressure and conformity, and have earlier sexual debut. Contraception use and child-bearing may reduce adherence and exposure to ART. Interventions to improve adherence in adolescent girls are therefore indicated.

Our study has some limitations. Firstly, the sample was small. Secondly, the intervention, mDAART, was administered over 3 months only. Studies of longer follow-up and larger samples are indicated. In addition, both the participants and study staff were not blinded, and this might have introduced bias.

Conclusion

Ritonavir concentrations in hair predicted virologic outcomes and were associated with self-reported adherence among HIV-infected adolescents with virologic treatment failure to atazanavir/ritonavir-based second line ART in Zimbabwe. A home-based adherence intervention was, however, not associated with ritonavir hair concentrations in this cohort of adolescents. Measuring ritonavir concentrations in hair in adolescents on protease inhibitor-based regimens could assess adherence in this vulnerable group and help avert subsequent virologic failure.

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Table 1:

Linear logistic regression to determine factors associated with ritonavir concentrations in hair

Variable	Regression co-efficient (standard error); 95% confidence interval (n=42)	p-value
Age- 15–19 years	0.2(0.1); −0.1– 0.5	0.2
Age in years	0.03(0.04); −0.04– 0.1	0.4
Gender- male	0.2(0.1); −0.04– 0.5	0.1
Treatment arm- mDAART	−0.04(0.1); −0.3– 0.2	0.7
Consistent school attendance in the past 3 months	−0.3(0.2); −0.7– −0.0008	0.05
Time on 1st line ART (months)	−0.0001(0.003); −0.006– 0.006	0.9
Time on 2nd line ART (months)	−0.01(0.008); −0.03– 0.006	0.2
Total time on ART (months)	−0.0006(0.003); −0.006– −0.005	0.8
BMI-for-age	−0.05(0.08); −0.2– 0.1	0.5
Average VAS adherence at baseline (%)	0.006(0.003); −0.001– 0.01	0.09
Average VAS adherence after follow-up (%)	0.01(0.005); −0.00005– 0.02	0.05
Log baseline viral load (copies/ml)	0.01(0.09); −0.2– 0.2	0.9
Log viral load change decrease (copies/ml)	−0.1(0.04); −0.2– −0.01	0.03
Follow-up viral load <1,000 copies/ml	−0.3(0.1); −0.5– −0.02	0.04

mDAART- modified directly administered antiretroviral therapy; ART- antiretroviral therapy; BMI- body mass index; VAS- visual analogue scale

Table 2:

Multivariate linear regression to determine factors associated with ritonavir concentrations in hair

Variable	Regression coefficient(standard error); 95% confidence interval (n=42)	p-value
Age- 15–19 years	0.2(0.1); −0.07 – 0.4	0.2
Gender- male	0.3(0.1); 0.08 – 0.5	0.008
Treatment arm: mDAART	0.2(0.1); −0.07 – 0.4	0.2
Average VAS adherence after follow-up (%)	0.01(0.005); 0.004 – 0.02	0.006
Follow-up viral load <1,000 copies/ml	−0.3(0.1); −0.5 – −0.06	0.01

mDAART- modified directly administered antiretroviral therapy; VAS- visual analogue scale