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Antiretroviral concentrations in small hair samples as a feasible marker of adherence in rural Kenya

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Abstract

Antiretroviral hair levels objectively quantify drug exposure over time and predict virologic responses. We assessed the acceptability and feasibility of collecting small hair samples in a rural Kenyan cohort. 95% of participants (354/373) donated hair. Although median self-reported adherence was 100% (IQR 96–100%), a wide range of hair concentrations likely indicates overestimation of self-reported adherence and the advantages of a pharmacologic adherence measure. Higher nevirapine (NVP) hair concentrations observed in women and older adults

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require further study to unravel behavioral versus pharmacokinetic contributors. In resource-limited settings, hair antiretroviral levels may serve as a low-cost quantitative biomarker of adherence.

Keywords

Adherence; nevirapine; hair concentrations; resource-limited setting; feasibility and acceptability; pharmacologic measure

INTRODUCTION

Sub-optimal antiretroviral exposure has been linked to adverse clinical outcomes in HIV-infected individuals, and may be a useful early predictor of subsequent virologic failure.[1–3] Medication adherence is a key determinant of exposure, but self-reported adherence can be limited by recall bias, forgetfulness, or social desirability bias.[4–6] Other adherence measures, such as clinic attendance, pill-counts, medication event monitoring systems, or antiretroviral (ARV) plasma levels all have challenges and biases.[4,5,7–10] Reliable adherence measures are needed to predict impending failure and for monitoring the effectiveness of adherence interventions, especially in resource-limited settings.

Our group has worked extensively on measuring ARV levels in small hair samples to monitor adherence and exposure,[1,11–17] after others reported proof-of-concept analyses.[18–21] Because drug concentrations in hair reflect uptake from the systemic circulation over weeks to months, hair analysis provides advantages over plasma monitoring in assessing long-term adherence.[20,22] We have developed methods to extract and analyze prevalent-use ARVs from hair.[13,1413,14] In U.S.-based studies, hair ARV levels predict virologic response more strongly than self-reported adherence.[11,12]

The relationship between self-reported adherence and ARV hair concentrations has not previously been explored in a resource-limited setting. Here, we examine this association in a large prospective cohort of HIV-infected individuals in rural Kenya. We additionally examine age and sex differences in ARV hair concentrations. Finally, we discuss feasibility and acceptability of this approach to objectively measure adherence in this community.

METHODS

Participants

This study occurred within the Mfangano Island Healthy Networks Impact Study (MIHNIS), a community-based cluster nonrandomized controlled trial conducted on Mfangano Island in Lake Victoria, Kenya.[23] MIHNIS evaluates the impact of a social- support “microclinic” intervention on adherence amongst HIV-infected individuals. Participants were recruited from a rural level-3 health facility on Mfangano Island supported by Family AIDS Care & Education Services, a President’s Emergency Plan for AIDS Relief-funded collaboration between the University of California San Francisco (UCSF) and the Kenya Medical Research Institute (KEMRI).[24] Patients were eligible if currently taking antiretrovirals, ≥18 years, and conversant in English or DhoLuo. Baseline pre-intervention data was collected

during routine clinic visits or at scheduled home visits between November 2011-March 2012. We present here baseline data correlating nevirapine (NVP) hair levels with self-reported adherence in the cohort. All study procedures received ethical approval from UCSF and KEMRI and all participants provided informed consent. MIHNIS is registered at ClinicalTrials.gov (NCT01912521)

Measures

The AIDS Clinical Trials Group (ACTG) 4-day adherence questionnaire[25] was used to measure self-reported adherence, and small hair samples were collected for analyses of NVP concentrations.[14] ACTG 4-day, as well as modified 3-, 7-, and 30-day, medication recall measures have been validated against virologic responses in both the US[26–28] and resource-limited settings.[29] Hair was collected privately at either the clinic or the participant's home using previously-described procedures.[11] Participants with hair too short for collection (<1.0 centimeter (cm)) were scheduled for a repeat appointment 2–4 weeks later for collection. Hair samples were shipped at room temperature to UCSF for analysis by previously described liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods.[13,14]

Statistical Analysis

Because hair grows at approximately 1 cm/month,[30] ARV concentrations were measured in the proximal centimeter of hair to represent ~28 days of exposure. We calculated number of missed doses in the previous 28 days as 7 times the self-reported missed doses over the previous four days. If no missed doses were reported for those four days, we assumed four total missed doses if the participant reported the last missed dose was within the past week, two total missed doses if last missed dose was 1–2 weeks ago, and one missed dose if the last missed dose was 2–4 weeks ago; otherwise, we assumed no missed doses in the preceding 28 days. Because all participants were on twice-daily dosing, we calculated percent adherence by subtracting number of missed doses from number of expected doses (56) and dividing by total expected doses.

To reduce skewness, NVP hair levels were log-transformed using log(5 + hair level in ng/ml). The small constant 5 was added to mitigate the size of differences between low hair levels after log transformation. We did not dichotomize hair levels because studies have shown graded relationships of hair ARV concentrations to virologic outcomes.[11,12,15] We calculated approximate fold-effects on hair NVP levels by exponentiating regression coefficients. Percent self-reported adherence was logarithmically transformed (adding 1 to permit inclusion of one observation with zero adherence). Using percent adherence as an untransformed predictor of hair level did not improve fit to the data.

Univariate and multivariate regression models explored the degree to which age, sex and self-reported adherence were associated with NVP hair levels. All analyses were conducted using SAS version 9.2 (Cary, NC), using the Mixed procedure with robust standard errors to mitigate the influence of non-normal residuals.

RESULTS

Demographic information and acceptability of hair collection

Of 441 eligible patients, 373 (85%) agreed to participate in the longitudinal MIHNIS Study. Participants ranged from 18–78 years old and ~two-thirds were women (Table 1). Median duration on antiretrovirals was 2.8 years (IQR 1.3–4.4 years) at baseline. Of those enrolled, 354 (95%) donated hair. Study staff were unable to collect hair samples in 19 participants (16 men; 3 women). Only two explicitly refused hair collection, citing concern about disclosure of HIV status if others were to witness the procedure. The remaining 17 signed the study's separate hair collection consent form, but on repeated occasions cut their hair immediately prior to scheduled collection. Though motives were uncertain, study staff interpreted these actions as attempts to non-confrontationally avoid hair collection.

Of participants who donated hair, 307 (87%) were on NVP-based regimens and included in the present analysis. Over 60% of these participants reported 100% adherence (no missed doses in the past 28 days). Median self-reported adherence was 100% (IQR 96–100%).

Relationship between self-reported adherence and NVP hair levels

Univariate analysis between log-adherence and log-hair level indicated a statistically significant correlation (1.61-fold increase in hair level per 2-fold increase in self-reported adherence, 95% CI 1.48–1.75). One participant reported zero adherence, an outlier from the remaining participants (mean adherence (%) ±SD, 96.6 ± 7.69). Self-report of zero adherence generally eliminates the utility of biologic confirmatory testing. Excluding this participant from the analysis maintained the estimated effect (1.91–fold, 95%CI 0.42–8.7), but the confidence interval was much wider, eliminating the association's statistical significance. (Table 2)

In multivariate modeling with the outlier removed, women averaged an estimated 67% increase in NVP hair concentrations compared to men (p=0.0001). Each 10-year increment in age was associated with a 25% (p<0.0001) increase. The estimated effect of self-reported adherence was a 72% increase in NVP hair levels per 2-fold increase in adherence, but with wide uncertainty.

Cost considerations

The costs for hair collection ($1.10/sample) and hair storage/shipment ($0.25/sample) were minimal. Measurement of NVP concentrations via LC-MS/MS is approximately $30/hair sample, although a newly-described method using thin-layer chromatography would cost significantly less (~$5/hair sample).[31] Of note, the cost of an HIV viral load in the region is ~$50.

DISCUSSION

Self-report vs. Hair

Though we observed a relationship between self-reported adherence and NVP hair concentrations, the confidence interval for this estimate was wide and included one. Self-

reported adherence was high, with nearly all participants reporting >85% adherence over the preceding 28 days; median self-reported adherence was 100%. Hair levels, however, varied widely even amongst those reporting complete adherence.

Because we were unable to measure HIV viral load due to cost, we have no direct evidence about whether self-report or hair measures more accurately reflect true adherence. No prior study has related hair NVP levels to virologic outcomes, although hair levels of other ARVs have demonstrated graded relationships with virologic response, rather than simple thresholds.[11,12,15] Nevertheless, we have previously demonstrated that hair ARV concentrations more strongly predict virologic success than self-reported adherence in large cohorts.[11,12,15] Others have reported on biases in self report that cause overestimation of adherence.[5,32–35] Therefore, a weak association between self-reported adherence and a pharmacologic measure of adherence is not unexpected, and likely reflects the limits of self-report.[33,36,37]

Feasibility and Acceptance

Our report describes the first experience with collecting and analyzing hair samples from a rural African setting. The high level of hair sample donation (95%) was striking. Though 15% of eligible subjects declined participation in the larger parent study, a lack of interest or time were cited as reasons, rather than concerns regarding hair collection. Separate consent for hair collection facilitated selective participation in hair sampling. Previous ethnographic research by our group had raised local concerns regarding hair collection and the potential for “witchcraft”.[38] Based on discussions with community and clinic stakeholders, we incorporated hair sample collection into the regular clinic flow when possible, framing the procedure as a “new hair test” that may eventually help providers make better decisions about HIV treatment. When participants were unable to come to the clinic, specimens were collected confidentially at participant homes.

Other challenges included very short hair-styles popular among both sexes in rural Kenya, necessitating training for collection from recently-shaved subjects or those with “weaves”. We set a minimum length of 1.0cm for hair collection, approximating one month of exposure. Participants with occipital hair of <1.0cm were requested at the time of consent not to cut their hair, and were scheduled for return appointments after 2–4 weeks. These strategies, along with the provision of transportation costs of 50 Kenyan Shillings (~$0.58), likely improved acceptability.

Because hair collection requires minimal training and samples can be stored and shipped at room temperature without biohazardous precautions, the costs of hair collection, storage and shipment are minimal. Although the costs to analyze the samples using LC/MS-MS were higher, we have developed a low-cost assay for analyzing NVP in hair semiquantitatively that will significantly lower costs[31] and similar low-cost assays for other ARVs (including efavirenz) are in development.

Factors associated with higher NVP exposure

Hair levels of ARVs serve as a marker of long-term exposure, mediated predominantly by behavior (adherence) and biology (pharmacokinetics).[6] We found higher drug exposure at

older ages. Evidence is limited regarding the effects of aging on ARV concentrations, with one large study showing higher protease inhibitor levels with age,[39] and another demonstrating sub-therapeutic ARV concentrations in older adults.[2] The contribution of pharmacokinetic versus adherence differences by age in this Kenyan population merits further study.

We also found higher NVP hair concentrations in females. Though the observed increase in NVP exposure was independent of self-report, assessing the contribution of behavioral versus biologic variability to this finding in a cohort with such high rates of self-reported adherence is difficult. A trend toward higher adherence among women in resource-limited settings was summarized in a recent meta-analysis[40]; the hair data in this cohort supports this finding. Sex differences in ARV pharmacokinetics may also play a role.[41]

Further Applications and Conclusions

Though not a replacement for HIV viral loads, hair ARV drug levels strongly correlate with virologic suppression in other studies.[11,12,15] Moreover, hair measurement of ARV levels can predict subsequent virologic failure in longitudinal models.[11] By the time a regimen fails virologically, opportunities for adherence interventions may have been missed, and expensive second-line therapies are often needed.[42] Hair ARV levels may predict impending virologic failure, suggesting useful algorithms to enhance adherence interventions and treatment outcomes in clinical settings.

ARV hair measures may also provide clinicians with important information on underlying reasons for virologic failure once it occurs. In two large urban clinics in South Africa,[1] virologic failure was strongly associated with low hair levels of ARVs. Moreover, few patients had evidence of resistance mutations upon failing, suggesting inadequate medication exposure as the most frequent cause of virologic failure.

In conclusion, our study in Kenya found that hair collection was highly acceptable and feasible for local research staff and participants. With similar mobilization efforts and community engagement strategies, these results are likely generalizable to other rural sub-Saharan African communities. The wide variability in drug exposure in hair at similar levels of self-reported adherence reinforces the limited utility of self-report.[34] Hair ARV measures, especially those using lower-cost methods,[31] may supplement assessment of ART adherence in remote, resource-limited settings and provide an objective tool to predict impending virologic failure and improve outcomes.

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References

1. van Zyl GU, van Mens TE, McIlleron H, et al. Low lopinavir plasma or hair concentrations explain second-line protease inhibitor failures in a resource-limited setting. J Acquir Immune Defic Syndr. 2011; 56(4):333–339. [PubMed: 21239995]

2. Fabbiani M, Di Giambenedetto S, Bracciale L, et al. Pharmacokinetic variability of antiretroviral drugs and correlation with virological outcome: 2 years of experience in routine clinical practice. The Journal of Antimicrobial Chemotherapy. Jul; 2009 64(1):109–117. [PubMed: 19398461]
3. Li JZ, Gallien S, Ribaudo H, Heisey A, Bangsberg DR, Kuritzkes DR. Incomplete adherence to antiretroviral therapy is associated with higher levels of residual HIV-1 viremia. AIDS. Dec 19.2013
4. Berg KM, Arnsten JH. Practical and conceptual challenges in measuring antiretroviral adherence. J Acquir Immune Defic Syndr. Dec 1; 2006 43 (Suppl 1):S79–87. [PubMed: 17133207]
5. Kagee A, Nel A. Assessing the association between self-report items for HIV pill adherence and biological measures. AIDS Care. 2012; 24(11):1448–1452. [PubMed: 22670758]
6. Gandhi M, Greenblatt RM. Hair it is: the long and short of monitoring antiretroviral treatment. Annals of Internal Medicine. 2002; 137:696–697. [PubMed: 12379072]
7. Haberer JE, Kahane J, Kigozi I, et al. Real-time adherence monitoring for HIV antiretroviral therapy. AIDS Behav. Dec; 2010 14(6):1340–1346. [PubMed: 20809380]
8. Wendel CS, Mohler MJ, Kroesen K, Ampel NM, Gifford AL, Coons SJ. Barriers to use of electronic adherence monitoring in an HIV clinic. The Annals of Pharmacotherapy. Sep; 2001 35(9):1010–1015. [PubMed: 11573846]
9. Liu H, Golin CE, Miller LG, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. Ann Intern Med. May 15; 2001 134(10):968–977. [PubMed: 11352698]
10. Muller AD, Jaspan HB, Myer L, et al. Standard measures are inadequate to monitor pediatric adherence in a resource-limited setting. AIDS Behav. Feb; 2011 15(2):422–431. [PubMed: 20953692]
11. Gandhi M, Ameli N, Bacchetti P, et al. Atazanavir concentration in hair is the strongest predictor of outcomes on antiretroviral therapy. Clinical Infectious Diseases. 2011; 52(10):1267–1275. [PubMed: 21507924]
12. Gandhi M, Ameli N, Bacchetti P, et al. Protease inhibitor levels in hair strongly predict virologic response to treatment. AIDS. 2009; 23(4):471–478. [PubMed: 19165084]
13. Huang Y, Gandhi M, Greenblatt RM, Gee W, Lin ET, Messenkoff N. Sensitive analysis of anti-HIV drugs, efavirenz, lopinavir and ritonavir, in human hair by liquid chromatography coupled with tandem mass spectrometry. Rapid Commun Mass Spectrom. 2008; 22(21):3401–3409. [PubMed: 18837069]
14. Huang Y, Yang Q, Yoon K, et al. Microanalysis of the antiretroviral nevirapine in human hair from HIV-infected patients by liquid chromatography-tandem mass spectrometry. Analytical and Bioanalytical Chemistry. 2011; 401:1923–1933. [PubMed: 21847531]
15. Gandhi, M.; Ameli, N.; Bacchetti, P.; Huang, Y.; Gange, SJ.; Anastos, K. Concentrations of Efavirenz in Hair Are Strongly Correlated with Virologic Response. 16th Conference on Retroviruses and Opportunistic Infections (CROI); 2009; Montreal, Canada.
16. Gandhi M, Mwesigwa J, Aweeka F, et al. Hair and Plasma Data Show That Lopinavir, Ritonavir, and Efavirenz All Transfer From Mother to Infant In Utero, But Only Efavirenz Transfers via Breastfeeding. J Acquir Immune Defic Syndr. Aug 15; 2013 63(5):578–584. [PubMed: 24135775]
17. Bartelink IH, Savic RM, Mwesigwa J, et al. Pharmacokinetics of lopinavir/ritonavir and efavirenz in food insecure HIV-infected pregnant and breastfeeding women in tororo, uganda. Journal of Clinical Pharmacology. Aug 23.2013
18. Bernard L, Peytavin G, Vuagnat A, de Truchis P, Perronne C. Indinavir concentrations in hair from patients receiving highly active antiretroviral therapy. Lancet. Nov 28; 1998 352(9142):1757–1758. [PubMed: 9848361]
19. Bernard L, Vuagnat A, Peytavin G, et al. Relationship between levels of indinavir in hair and virologic response to highly active antiretroviral therapy. Annals of Internal Medicine. 2002; 137:656–659. [PubMed: 12379065]
20. Duval X, Peytavin G, Breton G, et al. Hair versus plasma concentrations as indicator of indinavir exposure in HIV-1-infected patients treated with indinavir/ritonavir combination. AIDS. Jan 2; 2007 21(1):106–108. [PubMed: 17148976]

21. Servais J, Peytavin G, Arendt V, et al. Indinavir hair concentration in highly active antiretroviral therapy-treated patients: association with viral load and drug resistance. AIDS. 2001; 15(7):941–943. [PubMed: 11399971]
22. Beumer JH, Bosman IJ, Maes RA. Hair as a biological specimen for therapeutic drug monitoring. International Journal of Clinical Practice. Jul-Aug;2001 55(6):353–357. [PubMed: 11501221]
23. Salmen, CR.; Hickey, MD.; Fiorella, KJ., et al. Redefining the unit of intervention: a novel social network approach for optimizing community-based HIV treatment and prevention in rural Western Kenya. In submission
24. Kulzer JL, Penner JA, Marima R, et al. Family model of HIV care and treatment: a retrospective study in Kenya. J Int AIDS Soc. 2012; 15(1):8. [PubMed: 22353553]
25. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). AIDS Care. 2000; 12:255–266. [PubMed: 10928201]
26. Ickovics JR, Cameron A, Zackin R, et al. Consequences and determinants of adherence to antiretroviral medication: results from Adult AIDS Clinical Trials Group protocol 370. Antiviral Therapy. Sep; 2002 7(3):185–193. [PubMed: 12487386]
27. Mannheimer S, Thackeray L, Huppler Hullsiek K, et al. A randomized comparison of two instruments for measuring self-reported antiretroviral adherence. AIDS Care. Feb; 2008 20(2): 161–169. [PubMed: 18293124]
28. Lu M, Safren SA, Skolnik PR, et al. Optimal recall period and response task for self-reported HIV medication adherence. AIDS Behav. Jan; 2008 12(1):86–94. [PubMed: 17577653]
29. Oyugi JH, Byakika-Tusiime J, Charlebois ED, et al. Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. J Acquir Immune Defic Syndr. Aug 15; 2004 36(5):1100–1102. [PubMed: 15247564]
30. Henderson GL. Mechanisms of drug incorporation into hair. Forensic Science International. Dec; 1993 63(1–3):19–29. [PubMed: 8138221]
31. Gandhi M, Yang Q, Bacchetti P, Huang Y. A Low-Cost Method for Analyzing Nevirapine Levels in Hair as a Marker of Adherence in Resource-Limited Settings. AIDS Research and Human Retroviruses. Nov 22.2013 2013
32. Thirumurthy H, Siripong N, Vreeman RC, et al. Differences between self-reported and electronically monitored adherence among patients receiving antiretroviral therapy in a resource-limited setting. AIDS. Nov 28; 2012 26(18):2399–2403. [PubMed: 22948266]
33. Wiens MO, MacLeod S, Musiime V, et al. Adherence to antiretroviral therapy in HIV-positive adolescents in Uganda assessed by multiple methods: a prospective cohort study. Paediatric Drugs. Oct 1; 2012 14(5):331–335. [PubMed: 22765225]
34. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. Aug 4; 2005 353(5):487–497. [PubMed: 16079372]
35. Nieuwkerk PT, de Boer-van der Kolk IM, Prins JM, Locadia M, Sprangers MA. Self-reported adherence is more predictive of virological treatment response among patients with a lower tendency towards socially desirable responding. Antiviral Therapy. 2010; 15(6):913–916. [PubMed: 20834104]
36. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. Dec 30; 2010 363(27):2587–2599. [PubMed: 21091279]
37. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. Aug 2; 2012 367(5):411–422. [PubMed: 22784040]
38. Salmen, C. Towards an Anthropology of Organic Health: The Relational Fields of HIV/AIDS among the Suba of Lake Victoria. Institute of Social and Cultural Anthropology, Oxford University; 2009.
39. Winston A, Jose S, Gibbons S, et al. Effects of age on antiretroviral plasma drug concentration in HIV-infected subjects undergoing routine therapeutic drug monitoring. The Journal of Antimicrobial Chemotherapy. Jun; 2013 68(6):1354–1359. [PubMed: 23435690]

40. Ortego C, Huedo-Medina TB, Santos P, et al. Sex differences in adherence to highly active antiretroviral therapy: a meta-analysis. AIDS Care. 2012; 24(12):1519–1534. [PubMed: 22533692]

41. Gandhi M, Aweeka F, Greenblatt RM, Blaschke TF. Sex differences in pharmacokinetics and pharmacodynamics. Annual Review of Pharmacology and Toxicology. 2004; 44:499–523.

42. Hoffmann CJ, Charalambous S, Sim J, et al. Viremia, resuppression, and time to resistance in human immunodeficiency virus (HIV) subtype C during first-line antiretroviral therapy in South Africa. Clin Infect Dis. Dec 15; 2009 49(12):1928–1935. [PubMed: 19911963]

Table 1

Characteristics of the 373 participants enrolled in the MIHNIS study

Characteristic	Percentage or Median (IQR)
Female	64%
Age (in years)	37 (20–54)
Median time on ART (years)[1]	2.8 (1.3–4.4)
Body mass index (BMI, kg/m2)	21.9 (20–23.8)
CD4 count (cells/mm[3])	361 (228–494)[2]
Current ARV regimen[3]	
NVP-3TC-AZT	40.2%
NVP-3TC-D4T	34.6%
NVP-3TC-TDF	9.9%
NVP-3TC	1.1%
NVP-AZT-D4T	0.8%
NVP-3TC-EFV	0.5%
Other Regimens[§]	12.9%
Participants providing hair samples	95%
Self-reported NVP adherence (n=307)	100% (96–100%)[5]
NVP hair concentration (ng/mg) (n=307)	75.1 (42.1–108.1)

[1] Participants initiated ART at least one month prior to hair collection.

[2] n=371, two participants did not have CD4 measurements recorded in their charts. Most recent CD4 count was used. Results were unchanged when restricting CD4 counts to only those performed within the last 90 (n=151) or 180 days (n=283).

[3] 3TC = lamivudine, AZT = zidovudine, d4T = stavudine, TDF = tenofovir disoproxil fumarate, EFV = efavirenz

[4] Includes efavirenz, lopinavir/ritonavir, or dual nucleoside reverse transcription inhibitor based regimens

[5] Mean adherence (%) ± standard deviation (SD), 96.6 ± 7.69

Table 2

Univariate and multivariate models of self-reported adherence, age and gender on changes in NVP hair concentrations among 306 participants on NVP-based regimens*

Characteristic	Univariate fold estimate (95% CI)	Univariate p-value	Multivariate fold estimate† (95% CI)	Multivariate p-value
Adherence (Log2)	1.91 (0.42–8.7)	0.43	1.72 (0.42–7.1)	0.45
Age (per 10 years)	1.18 (1.08–1.29)	0.0004	1.25 (1.14–1.37)	< 0.0001
Male (n=99)	1		1	
Female (n=207)	1.41 (1.10–1.81)	0.0066	1.67 (1.29–2.2)	0.0001

*Of the 307 participants prescribed NVP, one outlier was excluded from analysis for self reporting 0% adherence

†Multivariate model includes adherence (Log2), age (10-year increments) and gender