Title

Brief Report

Journal

JAIDS Journal of Acquired Immune Deficiency Syndromes, 76(4)

ISSN

1525-4135

Authors

Pintye, Jillian

Bacchetti, Peter

Teeraananchai, Sirinya

et al.

Publication Date

2017-12-01

DOI

10.1097/qai.0000000000001527

Peer reviewed

HHS Public Access

Author manuscript

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2017 December 01; 76(4): 367–371. doi:10.1097/QAI.0000000000001527.

Brief Report: Lopinavir Hair Concentrations are the Strongest Predictor of Viremia in HIV-infected Asian Children and Adolescents on Second-line Antiretroviral Therapy

Jillian Pintye[1], **Peter Bacchetti**[2], **Sirinya Teeraananchai**[3], **Stephen Kerr**[3,4], **Wasana Prasitsuebsai**[3,5], **Thida Singtoroj**[6], **Karen Kuncze**[7], **Alexander Louie**[7], **Catherine A. Koss**[7], **Chengshi Jin**[2], **Nhi Phung**[7], **Howard Horng**[7], **Annette H. Sohn**[6], and **Monica Gandhi**[7]

[1]Department of Global Health, University of Washington [2]Department of Epidemiology and Biostatistics, University of California, San Francisco [3]HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand [4]The Kirby Institute, University of New South Wales, Sydney, Australia [5]GlaxoSmithKline (Thailand) Ltd., Bangkok, Thailand [6]TREAT Asia/amfAR-The Foundation for AIDS Research, Bangkok, Thailand [7]Department of Medicine, University of California, San Francisco

Abstract

Background—Children/adolescents display suboptimal antiretroviral therapy (ART) adherence and outcomes versus adults. Hair ART concentrations are objective adherence measures that predict viremia in adults but longitudinal data on hair levels in pediatric populations is limited. We assessed the predictive utility of hair lopinavir levels on viremia among youth on second-line ART.

Methods—We examined predictors of viremia (HIV-1 RNA >400 and >1000 copies/ml) at least 24 weeks after switch to lopinavir-based second-line ART in a cohort of HIV-infected Asian children followed between 2011 and 2014. Small hair samples, HIV-1 RNA, and self-reported adherence were collected biannually. Hair concentrations of lopinavir were measured via liquid-chromatography/tandem-mass-spectrometry using validated methods. Time-to-first viremia was examined using discrete-time Cox models.

Results—Overall, 244 children met inclusion criteria for the present analysis. Approximately half (55%) were males and the median age 10 years (interquartile range [IQR] 7–13); 40% were >11 years. At switch to second-line ART, median CD4 count was 300 (IQR 146–547) cells/mm^3 and median HIV-RNA level was 5.0 (IQR 4.3–5.6) $\log_{10}$/mL. Median time of study follow-up was 48 weeks and a median of 3 (range 1–5) hair samples collected from each participant. Adjusting for age, sex, country, self-reported adherence, CD4, and HIV-RNA, higher lopinavir hair

Corresponding Author: Monica Gandhi, M.D., M.P.H., Division of HIV, Infectious Diseases, and Global Medicine, San Francisco General Hospital, University of California, San Francisco, Box 0874, San Francisco, CA 94143-0874, Tel 415-476-4082, Fax 415 476 6953, monica.gandhi@ucsf.edu.

Potential conflicts of interest.

All authors. No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

These data were presented in part at the Conference on Retroviruses and Opportunistic Infections (CROI), February 13–16, 2017, Seattle, Washington, USA and the International AIDS Society (IAS) Conference on HIV Science, July 23–26, 2017, Paris, France

concentrations were the strongest predictor of lower odds of viremia (HIV-RNA >400 copies/ml adjusted odds ratio [aOR]=0.41 per doubling in hair concentration, 95% 0.29–0.58, p<0.001; HIV-RNA >1000 copies/ml aOR=0.54, 95% CI 0.45–0.65, p<0.001).

Conclusions—Hair concentrations predict viremia among children with HIV on 2nd-line ART and could guide clinical decisions for this population.

Keywords

Asia; pediatrics; antiretroviral therapy; adherence; viral load; protease inhibitors; hair concentrations; lopinavir

Introduction

Access to third-line antiretroviral therapy (ART) for HIV-infected individuals in low- and middle-income countries (LMICs) is limited, making prevention of second-line ART failure an urgent global HIV priority [1]. HIV-infected children and adolescents on ART have suboptimal virologic outcomes compared to adults, which may be due to both adherence challenges and the flux in pharmacokinetics unique to these age groups [2]. For children and adolescents on second-line ART, antiretroviral (ARV) drug levels—integrating both adherence and pharmacokinetics—could help explain virologic outcomes and guide subsequent treatment decisions. Earlier detection of those at risk for treatment failure via quantitative measurement of ARV concentrations could be important for targeting adherence interventions to at-risk individuals in order to prolong the duration of second-line ART, especially among pediatric populations in LMIC settings where alternative regimens and resistance testing may not readily be available.

Hair concentrations of ARVs are a non-invasive measure that reflect cumulative systemic drug exposure and predict viral suppression in adults better than self-reported adherence, [3, 4] single plasma ARV levels, [5] and host or viral characteristics, such as immune status and pre-treatment viral loads [4, 6, 7]. Hair sampling may be a particularly desirable approach for monitoring adherence/exposure in pediatric populations, since hair collection is painless and avoids phlebotomy [8]. We previously demonstrated an association of ARV hair concentrations with virologic responses among HIV-infected children on second-line ART in Southeast Asia [5]. The prior analysis was cross-sectional and did not allow for the predictive utility of hair concentrations on viremia to be examined. In this longitudinal study, we determine for the first time whether ARV hair concentrations predict viremia in a cohort of HIV-infected Asian children and adolescents on lopinavir (LPV)-based second-line ART.

Methods

Study Design and Population

We analyzed data from the Prospective Monitoring of Second-line Antiretroviral Therapy Failure and Resistance in Children (TASER-P) study, a longitudinal cohort study which monitored second-line ART failure and resistance from 2011–2014 in HIV-infected children from Vietnam, Thailand, and Indonesia. Eligibility and recruitment at the 8 sites of TASER-

P have been previously described [9]. Briefly, children were enrolled if they were HIV-infected, <18 years old, experienced first-line treatment failure and had already switched or were currently switching to second-line ART (defined as an ARV class switch from a non-nucleoside reverse transcriptase inhibitor [NNRTI] to a protease inhibitor [PI]). Children on nonstandard treatment regimens (i.e., once-daily boosted LPV/ritonavir (LPV/r) or a boosted PI without any nucleoside transcriptase inhibitors [NRTIs]) were ineligible. Clinical and laboratory assessments for treatment response and safety were performed every 6 months. Self-reported adherence assessments (reported by parent/guardian when appropriate) were collected using the WHO 30-day visual analogue scale [10]. Small hair samples for LPV concentrations and plasma for HIV-1 RNA levels were collected every 6 months by study personnel.

Hair Collection and Analyses of ARV Hair Concentrations

Small samples of hair were collected according to previously described methods [11]. Approximately 20 strands of hair (1–3 mg) are required to measure the concentration of PIs [12]. Hair samples were cut from underneath the top layer of hair from the occiput, [7] placed in aluminum foil, stored at room temperature, and shipped to the University of California, San Francisco (UCSF) for analysis.

The Hair Analytical Laboratory (HAL) at UCSF has developed, validated, and published the methods for analyzing LPV in hair using liquid chromatography-tandem mass spectrometry (LC-MS/MS) [13]. Briefly, the LPV in each finely cut hair specimen is extracted with methanol (MeOH) : trifluoroacetic acid (TFA) (*v:v*) overnight at 37°C. The resulting solution is evaporated, sodium phosphate buffer added, followed by extraction with methyl *t*-butyl ether:ethyl acetate (1:1) (*v:v*). The organic layer is isolated, evaporated, and reconstituted for LC-MS/MS analysis. The extracted samples are separated by reverse phase chromatography and detected by tandem mass spectrometry using electrospray positive ionization with multiple reaction monitoring (MRM) mode. The assay range is 0.05 – 20.0 ng/mg for LPV and the UCSF HAL assay has been peer reviewed and approved by the Division of AIDS (DAIDS) Clinical Pharmacology and Quality Assurance (CPQA) program [14].

Statistical Analysis

Participants were included in the present analysis if they had one or more hair specimens collected at least 3 months after switching to second-line therapy and were on a LPV-based regimen (91% of participants were on LPV/r-based regimens in the TASER-P cohort) [9]. At any visit where the HIV RNA level was >1000 copies/ml, standard genotyping of the viral reverse transcriptase and protease gene was performed. If ARV resistance to any class was detected at a visit, we censored the data at that point and only used previous observations from that person. Since virologic failure from viral resistance can be independent of adherence, we wanted to focus in this analysis on viremia likely to be related to adherence. In two cases, virologic failure due to resistance occurred at the participant's first visit in the hair substudy, so data from these two participants did not contribute to the time-to-event analyses.

Demographic and clinical characteristics were summarized with medians for continuous measures and proportions for categorical variables. We used separate time-to-first-event discrete-time Cox regression models to identify predictors of experiencing viremia defined as either an HIV-1 RNA level >400 copies/ml or an HIV-1 RNA level >1000 copies/ml. Characteristics assessed as potential predictors of viremia were those evaluated in the parent study [9] and included age ≤11 years, sex, country, self-reported adherence over the last 30 days, LPV hair concentrations, CD4 percentage and HIV-1 RNA level upon switching to second-line ART; hair levels and self-reported adherence were included in models as time-varying covariates. Statistical significance was based on a 2-sided p-value of <0.05. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Ethics Statement

All participating study sites and coordinating centers obtained local Institutional Review Board approvals for study participation. Informed consent was provided by primary caregivers; assent was provided by children >7 years who were aware of their own HIV status when required by the local review board.

Results

Characteristics of study participants

Overall, 277 children were enrolled in the TASER-P study between February 2011 and December 2012 [9] of whom 244 met inclusion criteria for the present analysis. At enrolment, 55% of participants were Vietnamese, 34% were Thai and 11% were Indonesian (Table 1). There were slightly more males (55%) than females and the median age was 10 years (interquartile range [IQR] 7–13); 40% of participants were >11 years. Overall, 88% of children or guardians reported more than 95% adherence to the ART regimen over the past 30 days. At switch to second-line ART, the median CD4 count was 300 (IQR 146–547) cells/mm^3 and the median HIV-RNA level was 5.0 (IQR 4.3–5.6) $\log_{10}$/mL.

Predictors of Time-to-First Viremia

Median time of study follow-up was 48 weeks and a median of 3 (range 1–5) hair samples were collected from each participant. Overall, 83 cases of viremia with HIV-1 RNA >400 copies/ml and 56 episodes with HIV-1 RNA >1000 copies/ml occurred during the follow-up period without accompanying ARV resistance.

In unadjusted models, higher hair concentrations of LPV were strongly associated with a decreased likelihood of experiencing viremia with HIV-1 RNA >400 copies/ml (Table 2, odds ratio [OR]=0.56 per doubling in hair concentration, 95% confidence interval [CI] 0.47–0.67, p<0.001); the association was similar with the outcome of HIV-1 RNA >1000 copies/ml (OR=0.54, 95% CI 0.45–0.65, p<0.001). Self-reported adherence ≥95% of the time was also associated with a decreased likelihood of having viremia in unadjusted analyses (OR=0.24 ≥95% vs <95% adherence 95% CI 0.13–0.44, p<0.001 for HIV-1 RNA >400 copies/ml; OR=0.26, 95% 0.13–0.51, p<0.001 for HIV-1 RNA >1000 copies/ml). Compared to participants with CD4 percentage >15% at switch to second-line ART, those

with CD4 percentage ≤15% had a 2-fold higher odds of having viremia of HIV-1 RNA >1000 copies/ml (OR=1.97, 95% CI 0.99–3.90, p=0.053).

After adjustment for age, sex, country, self-reported adherence, CD4 percentage and HIV-RNA copies/ml, LPV hair concentrations remained the strongest independent predictor of viremia, both for HIV-1 RNA >400 copies/ml (Table 2, adjusted odds ratio (aOR)=0.41 per doubling in hair concentration, 95% 0.29–0.58, p<0.001) and HIV-1 RNA >1000 copies/ml (aOR=0.54, 95% CI 0.45–0.65, p<0.001). Self-reported adherence was no longer associated with viremia in the multivariate models (Table 2).

Discussion

Our study is the first to prospectively examine the association of lopinavir hair concentrations with viremia in a cohort of HIV-infected children and adolescents on second-line ART. We show that LPV hair concentrations are the strongest predictor of viremia among children and adolescents on second-line LPV-based ART, even when controlling for sex, age, self-reported adherence and other characteristics. The association between hair levels and virologic outcomes was very similar for viremia defined as either HIV-1 RNA >400 copies/ml or HIV-1 RNA >1000 copies/ml. Our results add to the previously limited data on using non-invasive objective measures of ART adherence and drug exposure in pediatric populations. These findings – and a recently-published study showing a similar finding for atazanavir (ATV) hair levels among adolescents on ATV-based 2nd line-ART [15]- suggest that hair concentrations of ARVs can inform clinical decision-making around the management of viremia among HIV-infected children and adolescents by identifying those at risk for treatment failure due to chronically low drug levels.

There are several constraints currently impeding the availability and use of third-line ART for pediatric populations in LMICs, including limited laboratory capacity to diagnose treatment failure, lagging development of ARV formulations tailored for children, limited access to genotypic resistance testing, and cost [1]. Given these barriers to delivery of third-line ART, understanding who may be at risk for virologic failure among pediatric populations on second-line ART is critical. Our results suggest that hair concentrations could guide clinical decision making in at-risk children and future studies of real-time point-of-care hair assays are needed [16]. Low hair concentrations in the face of virologic failure could trigger adherence interventions to prevent resistance and prolong the duration of second-line ART. Adequate drug concentrations in the face of persistent virologic failure could inform cost-effective decision-making around when to perform genotypic resistance testing. Additionally, identifying patients with low hair concentrations who indeed have adequate adherence could trigger more personalized and potentially more aggressive dosing strategies.

Our study has some limitations. Hair testing for ARV levels has not been implemented at a regulated laboratory within Asia to date, requiring shipment of hair samples to CPQA-validated laboratories outside of the region. Our study used standardized and validated high-performance assays, but required the use of an expensive LC-tandem MS machine. Low-cost hair assays, currently in development, are needed prior to widespread applicability of this

non-invasive approach to assessing ARV adherence and exposure in LMIC clinical settings [16]. Additionally, plasma ARV levels were not assessed as part of the parent study and therefore we were unable to compare the predictive ability of hair levels with plasma concentrations on viremia.

In conclusion, this is the first study to demonstrate a longitudinal and strong association of lopinavir hair concentrations with viremia among HIV-infected children and adolescents on second-line ART. Future studies that examine the clinical application and cost-effectiveness of adherence monitoring via ARV hair concentrations are needed, especially now that viral load testing in LMICs is being expanded, while genotypic resistance testing remains limited. Early detection of those at risk for treatment failure with non-invasive approaches like hair sampling could be clinically important for pediatric populations in LMIC settings.

Acknowledgments

The authors would like to thank the participants and their families, as well as the TASER-P investigators and site staff for taking part in this study. We would also like to thank Dr. Leslie Z. Benet, General Director of the HAL.

Financial support

This study was funded by TREAT Asia, a program of amfAR, The Foundation for AIDS Research, with support from ViiV Healthcare, the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Cancer Institute, National Institute of Mental Health, and National Institute on Drug Abuse as part of the International Epidemiology Databases to Evaluate AIDS (IeDEA; U01AI069907), the U.S. National Institutes of Health's National Center for Advancing Translational Sciences (UCSF-CTSI Grant Number UL1 TR001872), and LIFE+, Austria. Statistical analysis support and partial support for hair assays came from the National Institutes of Allergy and Infectious Diseases (NIAID)/NIH R01 AI098472 (M. Gandhi, P. Bacchetti and C. Jin). This study was also supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (K12 HD052163 [P.I. Brindis, Adler] to support Dr. Koss) and NIAD T32 AI07140 to support J. Pintye. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

TASER-Pediatrics Study Group

N Kurniati and P Wicaksana, Cipto Mangunkusumo General Hospital, Jakarta, Indonesia; V Sirisanthana, L Aurpibul, and T Sudjaritruk, Chiang Mai University, Chiang Mai, Thailand; P Kosalaraksa, P Lumbiganon, and C Sopharak, Khon Kaen University, Khon Kaen, Thailand; W Prasitsuebsai, S Kerr, T Bunupuradah, S Teeraananchai, T Jupimai, J Intasan, N Thammajaruk, and C Ruengpanyathip, The HIV Netherlands, Australia, Thailand Research Collaboration (HIV-NAT), Bangkok, Thailand; K Chokephaibulkit, S Sricharoenchai, W Phongsamart, and N Kongstan, Siriraj Hospital, Mahidol University; KH Truong and TPK Le, Children’s Hospital 1, Ho Chi Minh City, Vietnam; VC Do, TM Ha, and VT An, Children’s Hospital 2, Ho Chi Minh City, Vietnam; LV Nguyen, KDT Khu, and TTT Giang, National Hospital of Pediatrics, Hanoi, Vietnam; AH Sohn, N Durier, T Singtoroj, and JL Ross, TREAT Asia, amfAR - The Foundation for AIDS Research, Bangkok, Thailand

References

1. World Health Organization. Access to antiretroviral drugs in low- and middle-income countries: technical report July 2014. Geneva, Switzerland: 2014.

2. Agwu AL, Fairlie L. Antiretroviral treatment, management challenges and outcomes in perinatally HIV-infected adolescents. J Int AIDS Soc. 2013; 16:18579. [PubMed: 23782477]
3. Gandhi M, Ameli N, Bacchetti P, Gange SJ, Anastos K, Levine A, et al. Protease inhibitor levels in hair strongly predict virologic response to treatment. AIDS. 2009; 23(4):471–478. [PubMed: 19165084]
4. Koss CA, Natureeba P, Mwesigwa J, Cohan D, Nzarubara B, Bacchetti P, et al. Hair concentrations of antiretrovirals predict viral suppression in HIV-infected pregnant and breastfeeding Ugandan women. AIDS. 2015; 29(7):825–830. [PubMed: 25985404]
5. Prasitsuebsai W, Kerr SJ, Truong KH, Ananworanich J, Do VC, Nguyen LV, et al. Using Lopinavir Concentrations in Hair Samples to Assess Treatment Outcomes on Second-Line Regimens Among Asian Children. AIDS Res Hum Retroviruses. 2015; 31(10):1009–1014. [PubMed: 26200586]
6. van Zyl GU, van Mens TE, McIlleron H, Zeier M, Nachega JB, Decloedt E, 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]
7. Hickey MD, Salmen CR, Tessler RA, Omollo D, Bacchetti P, Magerenge R, et al. Antiretroviral concentrations in small hair samples as a feasible marker of adherence in rural Kenya. J Acquir Immune Defic Syndr. 2014; 66(3):311–315. [PubMed: 24694932]
8. ter Heine R, Beijnen JH, Huitema AD. Bioanalytical issues in patient-friendly sampling methods for therapeutic drug monitoring: focus on antiretroviral drugs. Bioanalysis. 2009; 1(7):1329–1338. [PubMed: 21083054]
9. Prasitsuebsai W, Teeraananchai S, Singtoroj T, Truong KH, Ananworanich J, Do VC, et al. Treatment Outcomes and Resistance Patterns of Children and Adolescents on Second-Line Antiretroviral Therapy in Asia. J Acquir Immune Defic Syndr. 2016; 72(4):380–386. [PubMed: 27355415]
10. Giordano TP, Guzman D, Clark R, Charlebois ED, Bangsberg DR. Measuring adherence to antiretroviral therapy in a diverse population using a visual analogue scale. HIV Clin Trials. 2004; 5(2):74–79. [PubMed: 15116282]
11. Gandhi M, Ameli N, Bacchetti P, Anastos K, Gange SJ, Minkoff H, et al. Atazanavir concentration in hair is the strongest predictor of outcomes on antiretroviral therapy. Clin Infect Dis. 2011; 52(10):1267–1275. [PubMed: 21507924]
12. Kosuge K, Uematsu T, Araki SI, Matsuno H, Ohashi K, Nakashima M. Comparative dispositions of ofloxacin in human head, axillary, and pubic hairs. Antimicrob Agents Chemother. 1998; 42(5): 1298–1302. [PubMed: 9593174]
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. DiFrancesco R, Rosenkranz SL, Taylor CR, Pande PG, Siminski SM, Jenny RW, et al. Clinical pharmacology quality assurance program: models for longitudinal analysis of antiretroviral proficiency testing for international laboratories. Ther Drug Monit. 2013; 35(5):631–642. [PubMed: 24052065]
15. Chawana TD, Gandhi M, Nathoo K, Ngara B, Louie A, Horng H, et al. Defining a cut-off for atazanavir in hair samples associated with virological failure among adolescents failing second-line antiretroviral treatment. J Acquir Immune Defic Syndr. 2017
16. Gandhi M, Yang Q, Bacchetti P, Huang Y. Short communication: A low-cost method for analyzing nevirapine levels in hair as a marker of adherence in resource-limited settings. AIDS Res Hum Retroviruses. 2014; 30(1):25–28. [PubMed: 24164410]

Table 1

Demographic and clinical characteristics of HIV-infected children using second-line antiretroviral therapy at enrollment into the hair sub-study of TASER-P

Characteristic		N[1]	N (%) or Median (IQR)	
Demographic				
Age, years		244	10	(7–13)
Age ≤ 11 years		244	97	(40%)
Male sex		244	135	(55%)
Country		244		
	Indonesia		27	(11%)
	Vietnam		133	(55%)
	Thailand		84	(34%)
Clinical				
Self-reported adherence ≥95%[2]		244	196	(88%)
Time on 2nd line ART, years		244	1.9	(0.7–3.9)
CD4 cell count, cells/mm^3		204	300	(146–547)
CD4 percentage[3]		185	12.6	(7.0–19.0)
HIV-RNA, $\log_{10}$ (copies/mL)[3]		244	5.0	(4.3–5.6)
Had a viremic episode > 1000 copies/mL[4]		244	56	(23.1%)
Had a viremic episode > 400 copies/mL[4]		244	83	(34.3%)
Lopinavir hair levels (ng/mg)		244	9.66	(7.00–13.11)

IQR = interquartile range; ART = antiretroviral therapy

[1] No. of observations with data available

[2] Defined by WHO's adherence visual analogue scale [10]

[3] At time of switching to second-line antiretroviral therapy

[4] These are totals over all available follow-up. Excludes viremia with detected antiretroviral resistance.

Table 2

Predictors of viremia during follow up among HIV-infected children on second-line antiretroviral therapy in TASER-P

	HIV-RNA >400 copies/mL				HIV-RNA >1000 copies/mL			
	Bivariate[1]		Multivariate[2]		Bivariate[1]		Multivariate[2]	
	Crude OR (95% CI)	p-value	Adj OR (95% CI)	p-value	Crude OR (95% CI)	p-value	Adj OR (95% CI)	p-value
Age[3]								
≤ 11 years	0.61 (0.37–1.01)	0.054	1.35 (0.45–4.00)	0.59	0.75 (0.42–1.34)	0.32	0.87 (0.25–3.10)	0.83
> 11 years	ref				ref			
Sex								
Male	1.67 (1.03–2.70)	0.037	0.94 (0.43–2.10)	0.88	1.72 (0.97–3.00)	0.062	1.25 (0.50–3.10)	0.63
Female	ref				ref			
Country								
Indonesia	0.81 (0.29–2.30)	0.69	1.49 (0.30–7.30)	0.63	0.35 (0.08–1.55)	0.39	0.38 (0.04–3.80)	0.41
Vietnam	2.10 (1.21–3.60)	0.008	4.10 (1.35–12.50)	0.013	1.31 (0.71–2.40)	0.16	1.78 (0.53–6.00)	0.35
Thailand	ref				ref			
Self-reported adherence ≥95% [4]	0.24 (0.13–0.44)	<0.001	0.40 (0.15–1.11)	0.079	0.26 (0.13–0.51)	<0.001	0.60 (0.19–1.91)	0.39
CD4 percentage[5]								
<15%	1.45 (0.84–2.50)	0.190	1.33 (0.61–2.90)	0.48	1.97 (0.99–3.90)	0.053	2.00 (0.77–5.40)	0.15
≥15%	ref				ref			
HIV-RNA $\log_{10}$ [5]								
>5	2.50 (1.38–4.6)	0.003	1.58 (0.66–3.80)	0.31	2.20 (1.10–4.40)	0.026	1.09 (0.40–3.00)	0.87
≤5	ref				ref			
LPV hair levels, $\log_2$	0.56 (0.47–0.67)	<0.001	0.41 (0.29–0.58)	<0.001	0.54 (0.45–0.65)	<0.001	0.46 (0.34–0.63)	<0.001

OR = odds ratio; CI = confidence interval; LPV = lopinavir

[1]Bivariate models include time in hair substudy (the discrete time scale) as the second predictor. For bivariate analyses of HIV-RNA >400 copies/ml, total person-visits analyzed ranged from 493 to 661 and number of events ranged from 59 to 83, while the multivariate model included 411 person-visits and 47 events. For bivariate analyses of HIV-RNA >1000 copies/ml, total person-visits analyzed ranged from 521 to 710 and number of events ranged from 41 to 56, while the multivariate model included 436 person visits and 33 events.

[2]Multivariate models adjusted for time on 2nd line regimen, age, sex, country, self-reported adherence, CD4 percentage, HIV-RNA $\log_{10}$, and LPV hair levels

[3]At enrollment into hair sub-study

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2018 December 01.

Author Manuscript

Author Manuscript

Author Manuscript

[4] Self-reported adherence in the last 30 days

[5] At time of switch to second-line therapy.