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Second-line protease inhibitor-based highly active antiretroviral therapy after failing non-nucleoside reverse transcriptase inhibitors-based regimens in Asian HIV-infected children

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Conflict of interest statement

All authors declare no conflict of interest and that member of their immediate families do not have a financial interest in or arrangement with any commercial organization that may have a direct interest in the subject matter of this article.

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Ethical approval

All participating sites received institutional review board approval for the study.

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Abstract

Background—The WHO recommends boosted protease inhibitor (bPI)-based highly active antiretroviral therapy (HAART) after failing non-nucleoside reverse transcriptase inhibitor (NNRTI) treatment. We examined outcomes of this regimen in Asian HIV-infected children.

Methods—Children from five Asian countries in the TREAT Asia Pediatric HIV Observational Database (TApHOD) with ≥24 weeks of NNRTI-based HAART followed by ≥24 weeks of bPI-based HAART were eligible. Primary outcomes were the proportions with virologic suppression (HIV-RNA <400 copies/ml) and immune recovery (CD4% ≥25% if age <5 years and CD4 count ≥500 cells/mm^3 if age ≥5 years) at 48 and 96 weeks.

Results—Of 3422 children, 153 were eligible; 52% were female. At switch, median age was 10 years, 26% were in WHO stage 4. Median weight-for-age z-score (WAZ) was −1.9 (n=121), CD4% was 12.5% (n=106), CD4 count was 237 (n=112) cells/mm^3, and HIV-RNA was 4.6 log_{10}copies/ml (n=61). The most common PI was lopinavir/ritonavir (83%).

At 48 weeks, 61% (79/129) had immune recovery, 60% (26/43) had undetectable HIV-RNA and 73% (58/79) had fasting triglycerides ≥130mg/dl. By 96 weeks, 70% (57/82) achieved immune recovery, 65% (17/26) virologic suppression, and hypertriglyceridemia occurred in 66% (33/50).

Predictors for virologic suppression at week 48 were longer duration of NNRTI-based HAART (p=0.006), younger age (p=0.007), higher WAZ (p=0.020), and HIV-RNA at switch <10,000 copies/ml (p=0.049).

Conclusion—In this regional cohort of Asian children on bPI-based second-line HAART, 60% of children tested had immune recovery by one year, and two-thirds had hyperlipidemia, highlighting difficulties in optimizing second-line HAART with limited drug options.

Keywords

Asian HIV-infected children; protease inhibitor; second-line HAART

Introduction

The most commonly recommended first-line highly active antiretroviral therapy (HAART) regimens for HIV-infected children in resource-limited settings are those using non-nucleoside reverse transcriptase inhibitors (NNRTI) (1). Where plasma HIV-RNA is not available, WHO recommends using clinical failure or immunological criteria to inform decisions to switch to second-line therapy (1, 2). In patients with first-line NNRTI-based treatment failure, ritonavir-boosted protease inhibitor (bPI)-containing regimens are recommended (1-3).

Small studies in antiretroviral-experienced HIV-infected children in resource-rich countries have reported virologic suppression rates of bPI-based HAART being as high as 87-92% (4, 5). However, there is limited information about the success of bPI-based second-line HAART among HIV-infected children in Asia (6, 7). One retrospective study from Thailand

showed a 76% virologic suppression rate after second-line bPI-treatment (8). We postulated that the efficacy of bPI second-line therapy may be lower in Asian children compared to children in Western settings because of limited access to HIV-RNA monitoring resulting in delayed diagnosis of first-line treatment failure and fewer drug options with which to design the most potent second-line regimen (9). Moreover, the known metabolic complications of bPIs, such as hyperlipidemia, may not be as well monitored in these settings (10).

The TREAT Asia Pediatric HIV Observational Database (TApHOD) was initiated to evaluate the outcomes of HIV-infected children and provide evidence to guide care and treatment practices and policies in Asia (11). In this study, we report the treatment outcomes and predictors of treatment failure in children using PI-based second-line HAART in the TApHOD cohort.

Materials and methods

The methods for, and structure of, the TApHOD cohort have previously been described (11). In brief, data from children with HIV ≤18 years of age receiving clinical care at participating sites are submitted biannually by electronic transfer to a central database maintained at the Kirby Institute for Infection and Immunity in Society, Sydney, Australia. The data set contains demographic information, clinical and laboratory monitoring data, and treatment outcomes collected as part of routine care. The frequency of visits and monitoring is determined by standard patient care indications and availability. Compiled data are subject to extensive, routine quality checks. All participating sites, the coordinating center (TREAT Asia/amfAR, Thailand) and the data management center (The Kirby Institute, Australia) received institutional review board approval for the study. Consent was waived by all review boards.

At the time of this study, the cohort included data up to the end of March 2010 from 14 sites (predominately public, university-based clinics and hospitals located in urban areas) in five Asian countries. For this analysis, we included all children who switched from first-line NNRTI-based HAART after at least 24 weeks of treatment to second-line bPI-based HAART, for at least 24 weeks. The children who had received mono- or dual-NRTI prior to NNRTI-based HAART were included. Children who received PIs at any time prior to switch, were ≥18 years of age at the start of second-line bPI-based HAART, or received double PI regimens were excluded. A treatment gap of up to 14 days was allowed between the completion of first-line and initiation of second-line treatment.

The primary outcomes were the proportions of children with virologic suppression and immune recovery after 48 and 96 weeks. Virologic suppression was defined as plasma HIV-RNA <400 or <50 copies/ml, depending on the assay. Immune recovery was defined as CD4% ≥25% if age <5 years and CD4 count ≥500 cells/mm^3 if age ≥5 years (12, 13). Potential predictors of these outcomes included demographic variables, treatment history, and medical outcomes measured at or prior to initiation of second-line HAART.

The baseline measurement (week 0) was the closest observation to the date of initiation of bPI-based HAART in the interval from 90 days prior to 14 days after - except for HIV-RNA level and WHO staging, where observations after second-line switch were excluded from the week 0 values. Weeks 48 and 96 measurements were defined as the closest measurements during the period from 24 weeks prior to 24 weeks after the anniversary date, as long as this was not more than 14 days after discontinuation of second-line treatment.

For height-for-age z-score (HAZ), the WHO 2006/2007 Child Growth Standards were used (14). WHO 1977 Standards were used for weight-for-age z-score (WAZ) in order to allow for scoring children >10 years of age (15). Previous assessments have confirmed the

applicability of the 1977 growth references in this cohort by comparing them to the WHO 2006/2007 reference curves in children <10 years (16).

All lipids and glucose tests were performed after fasting for at least 6-8 hours. Dyslipidemia and elevated fasting glucose were defined as: elevated fasting total cholesterol (TC) ≥200 mg/dl, elevated fasting triglyceride (TG) ≥130 mg/dl, reduced fasting high density lipoprotein (HDL) <35 mg/dl, and fasting glucose (FBS) ≥110 mg/dl (17-19). We calculated the proportions of children with ratios of TC/HDL ≥5 and TG/HDL ≥3.7, per American Heart Association reports showing that these values correlated with cardiovascular events in adults without HIV (20, 21).

Statistical analysis

The statistical significance of changes between baseline and week 48 or week 96 was tested using non-parametric methods: Wilcoxon's paired rank test for quantitative data and McNemar's Chi-square test for categorical data. Relationships between the predictor variables and outcomes were modeled using univariate and multivariate logistic regression. Results are summarized as odds ratios with associated p-values and 95% confidence intervals.

Results

Of the 3422 children in the TApHOD cohort, 2751 had commenced any ART and 153 children met inclusion criteria for the analysis. Reasons for failing inclusion criteria were current first-line NNRTI treatment (n=2194), use of unboosted or double PI regimens (n=222), duration of treatment less than specified (n=181), and age over 18 years (n=1). Eligible children came from five countries, 52% were female, and 97% were HIV-infected by vertical transmission (Table 1). Forty-seven (30.7%) children received ≥28 days of a mono- or dual-antiretroviral regimen prior to NNRTI-based HAART with a median (IQR) duration of 2.0 (0.9-3.9) years. Sixty-one percent of 153 children used nevirapine, 37% used efavirenz and 2% used both simultaneously before switching to bPI-based HAART. The median duration of NNRTI-based HAART was 2.6 years. The reasons for switching to bPI-based HAART were virological failure in 59 (38.6%) children, immunological failure in 46 (30.0%) children, and 48 (31.4%) had no record of either virological or immunological failure.

At the switch to bPI-based HAART, the median age was 10 years, median WAZ was −1.9 and 26% were in WHO stage 4. The median CD4% was 12.5% and, where available, HIV-RNA was 4.6 $\log_{10}$copies/ml. The most prescribed bPI was lopinavir/ritonavir (83%) and the most commonly used NRTI combination was zidovudine/lamivudine (34%) (Table 1). The median time on bPI-based HAART was 1.7 (0.9-2.4) years. All children were followed long enough to contribute to the 48-week follow-up analysis and 96 (63%) contributed to the 96-week analysis.

By 96 weeks, one child had progressed to WHO stage 4 (due to cryptococcal meningitis) and two children died (one from unknown causes at week 28 and one due to *Mycobacterium avium complex* and tuberculosis at week 36). Changes in weight, CD4, HIV-RNA, and lipids from baseline to week 48 and to week 96 are summarized in Table 2. The weight-for-height z-score significantly increased between commencement of bPI and week 48, and then plateaued. It took two years of bPI before a significant improvement in the HAZ-score was observed. Immune recovery rates were 79/129 (61%) at week 48 and 57/82 (70%) at week 96. Virologic suppression to <400 copies/ml for those with HIV-RNA tests were 26/43 (60%) at week 48 and 17/26 (65%) at week 96. Virologic suppression to <50 copies/ml was seen in 21/43 (49%) at week 48 and 16/26 (62%) at week 96. The statistically significant

increase in CD4 levels after initiation of second-line bPI-HAART was accompanied by statistically significant increases in TC and TG. Hypertriglyceridemia was the most common type of hyperlipidemia. High TC/HDL and TG/HDL ratios were found in 18% and 41% of participants at baseline and these rates did not change significantly over the course of treatment.

At week 48, 83 of the 153 children had HIV-RNA testing. Of those with previous mono- or dual-NRTI therapy, 33.3% (8/24) had virological suppression at 48 weeks. Of those without previous mono- or dual-NRTI therapy, 37.3% (22/59) had virological suppression at week 48 (p=0.73).

Predictors for immune recovery and virologic suppression

By multivariate analysis, predictors of immune recovery at week 48 after switching were younger age (OR 0.8, p<0.001) and CD4 count at switch of ≥200 cells/mm^3 (OR 7.7, p=0.003) (Table 3).

Predictors for virologic suppression to HIV-RNA <400 copies/ml at week 48 after switching were longer duration of first-line NNRTI-based HAART (OR 1.8 per additional year, p=0.006), younger age (OR 0.8 per additional year, p=0.007), higher WAZ (OR=1.7 per standard deviation, p=0.020), and HIV-RNA of <10,000 copies/ml (OR 12.6, p=0.049) at switch (Table 4).

Discussion

This study provides important initial insights into the implementation and effectiveness of second-line bPI-based HAART in Asian HIV-infected children, including information on the antiretroviral regimens being used for bPI-based HAART, estimates of the proportion reaching virologic control and immune suppression at weeks 48 and 96, predictors of virologic control and immune suppression, and estimates of dyslipidemia. We showed that immune recovery occurred in about 60% of children with CD4 monitoring by one year, and that hyperlipidemia was seen in about two-thirds of children with fasting lipid tests. Similar to other resource-limited settings, many Asian countries have limited antiretroviral and laboratory monitoring options. Recycling NRTIs is common in Asia in second-line regimens due to limited drug options (22), but using partially active or inactive NRTIs in subsequent regimens has been shown to impact treatment efficacy (23). These findings highlight the need to increase access to appropriate testing in order to optimize long-term HAART management in children.

A limited number of our children had HIV-RNA monitoring, which showed two-thirds achieving viral suppression. This rate is comparable to a previously reported 67% virologic suppression rate in Thai children using second-line lopinavir/ritronavir-based HAART (24). The PENPACT-1 study in US and European children reported a 7% virologic failure rate in children on PI-based second-line (25). Other reports from resource-rich settings showed virologic success in 87-92% of children on PI treatment; however, the numbers of children were small and many were on PIs as first-line treatment (4, 5). While this study cannot illuminate the causes of these disparities, we speculate that lack of regular access to HIV-RNA and genotypic resistance testing can delay the switch to second-line treatment and the selection of appropriate NRTI backbone combinations. Moreover, one-third of children in this analysis had mono- or dual-NRTI regimens prior to NNRTI-based HAART. This prior exposure to NRTI has been reported to lead to accumulation of reverse transcriptase mutations, impacting the future potential for virologic suppression (26). In our study, we did not see a significant difference between those with and without prior NRTI exposure, but the numbers of patients with HIV-RNA testing was small.

Tenofovir was not used in any of the children in this analysis. TApHOD sites have anecdotally confirmed using tenofovir subsequent to the period of data reporting, and anticipate this to increase in the future. Lopinavir/ritronavir was the most prescribed PI, and is widely available in the region as the co-formulated heat-stable tablet in adult and occasionally pediatric versions (22, 27). The use of indinavir is uncommon, due in large part to its renal toxicity (28). Only one child in this analysis was prescribed an atazanavir/ritonavir-containing regimen. Long-term metabolic side effects from lopinavir/ritonavir containing regimens are increasingly reported in HIV-infected children (10, 29). A notable proportion of the children tested had hyperlipidemia, which may contribute to future cardiovascular disease risk if unchanged. In addition, a significant number of these children had abnormal TC/HDL and TG/HDL ratios, both of which are associated with cardiovascular and mortality risks in uninfected adults (20, 21, 30). HIV-associated immune activation could further increase such risks (31). These observations indicate the need for evidence-based management guidelines for dyslipidemia in HIV-infected children (10).

The study has identified a range of statistically significant predictors of immune recovery and virologic response. Younger children and those with higher CD4, lower HIV-RNA, and better weight at the commencement of second-line bPI-based HAART recorded better treatment outcomes, similar to published reports (13, 32-34). Castro et al, reported older age at HAART initiation was associated with increased risk of triple-class failure in a retrospective cohort study of HIV-infected children in Europe (35). Longer duration of NNRTI first-line treatment was associated with better outcomes on second-line bPI. We speculate that this could imply better adherence in this group of children, as those children who continued for longer durations without failure on first-line NNRTI-based HAART may be more likely to be adherent on second-line HAART.

As TApHOD is an observational cohort, there are limitations on the depth and completeness of the available data. Three quarters of the patients were treated in Thailand, which limits the generalizability of the results for the Asia region. Since patients are primarily seen at urban referral centers, our sample may be biased toward centers with greater patient management experience and technical resources. Children in our study were generally older (median age 10 years), so the results may not apply to younger children on second-line HAART. As treatment was not randomly assigned, we cannot make comparisons of the relative effectiveness of alternate bPI-based HAART regimens. With the frequency and scope of laboratory testing being determined by local clinical and economic circumstances, we accepted wide time windows and varying levels of missing data in our principal outcome variables, which could have introduced additional bias. Lastly, data which could have helped to further assess reasons for failure, including adherence and HIV genotype, were not available.

In conclusion, lopinavir/ritonavir-based HAART with recycling of NRTIs was commonly used as second-line treatment in this regional Asian cohort. Of those with monitoring data, a notable percentage do not achieve successful treatment, and hyperlipidemia is common. Further investigations of the causes of first-line and second-line treatment failure in children in Asia are needed to guide future interventions to prevent HIV drug resistance and delay the need for increasingly expensive and frequently inaccessible antiretrovirals. As children infected with HIV grow to adulthood, treatment failure will occur more frequently, adding pressure on national programmes to reassess treatment guidelines with regards to monitoring and resistance testing, and expand procurement of necessary antiretrovirals. Our study raises the concern that unless there is improvement in the outcomes of children on second-line regimens, the HIV community will need to define and better prepare for third-line treatment options.

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References

1. Antiretroviral Therapy of HIV infection in infants and children: towards universal access: WHO recommendations for a public health approach - 2010 revision.
2. Antiretroviral Therapy of HIV infection in adults and adolescents: WHO recommendations for a public health approach - 2010 revision.
3. Sungkanuparph S, Anekthananon T, Hiransuthikul N, Bowonwatanuwong C, Supparatpinyo K, Mootsikapun P, et al. Guidelines for antiretroviral therapy in HIV-1 infected adults and adolescents: the recommendations of the Thai AIDS Society (TAS) 2008. J Med Assoc Thai. Dec; 2008 91(12): 1925–35. [PubMed: 19133532]
4. Rudin C, Wolbers M, Nadal D, Rickenbach M, Bucher HC. Long-term safety and effectiveness of lopinavir/ritonavir in antiretroviral-experienced HIV-1-infected children. Archives of disease in childhood. Jun; 2010 95(6):478–81. [PubMed: 20501542]
5. Delaugerre C, Teglas JP, Treluyer JM, Vaz P, Jullien V, Veber F, et al. Predictive factors of virologic success in HIV-1-infected children treated with lopinavir/ritonavir. Journal of acquired immune deficiency syndromes (1999). Oct 1; 2004 37(2):1269–75. [PubMed: 15385734]
6. Bunupuradah T, Aurpibul L, Ananworanich J, Puthanakit T. The effectiveness of highly active antiretroviral therapy among HIV-infected children in Asian countries. Asian Biomedicine. 2009; 3(1):89–100.
7. Pujades-Rodriguez M, O'Brien D, Humblet P, Calmy A. Second-line antiretroviral therapy in resource-limited settings: the experience of Medecins Sans Frontieres. AIDS (London, England). Jul 11; 2008 22(11):1305–12.
8. Puthanakit T, Jourdain G, Suntarattiwong P, Chokephaibulkit K, Siangphoe U, Suwanlerk T, et al. High virologic response rate after second-line boosted protease inhibitor-based antiretroviral therapy regimens in children from a resource limited setting. AIDS research and therapy. 2012; 9(1):20. [PubMed: 22709957]
9. Sungkanuparph S, Manosuthi W, Kiertiburanakul S, Piyavong B, Chumpathat N, Chantratita W. Options for a second-line antiretroviral regimen for HIV type 1-infected patients whose initial regimen of a fixed-dose combination of stavudine, lamivudine, and nevirapine fails. Clin Infect Dis. Feb 1; 2007 44(3):447–52. [PubMed: 17205457]
10. Rhoads MP, Lanigan J, Smith CJ, Lyall EG. Effect of specific antiretroviral therapy (ART) drugs on lipid changes and the need for lipid management in children with HIV. Journal of acquired immune deficiency syndromes (1999). Apr 14.2011
11. Kariminia A, Chokephaibulkit K, Pang J, Lumbiganon P, Hansudewechakul R, Amin J, et al. Cohort Profile: The TREAT Asia Pediatric HIV Observational Database. International journal of epidemiology. Feb; 2011 40(1):15–24. [PubMed: 20100820]
12. Puthanakit T, Kerr S, Ananworanich J, Bunupuradah T, Boonrak P, Sirisanthana V. Pattern and predictors of immunologic recovery in human immunodeficiency virus-infected children receiving non-nucleoside reverse transcriptase inhibitor-based highly active antiretroviral therapy. The Pediatric infectious disease journal. Jun; 2009 28(6):488–92. [PubMed: 19504731]

13. Larru B, Resino S, Bellon JM, de Jose MI, Fortuny C, Navarro ML, et al. Long-term response to highly active antiretroviral therapy with lopinavir/ritonavir in pre-treated vertically HIV-infected children. The Journal of antimicrobial chemotherapy. Jan; 2008 61(1):183–90. [PubMed: 18025025]

14. [Accessed September 8, 2010] WHO growth chart 2006. Available at: http://www.who.int/childgrowth/en/

15. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11. 2002; 246:1–190. [PubMed: 12043359]

16. Hansudewechakul R, Sirisanthana V, Kurniati N, Puthanakit T, Lumbiganon P, Saphonn V, et al. Antiretroviral therapy outcomes of HIV-infected children in the TREAT Asia pediatric HIV observational database. Journal of acquired immune deficiency syndromes (1999). Dec 1; 2010 55(4):503–9. [PubMed: 20842043]

17. Aldrovandi GM, Lindsey JC, Jacobson DL, Zadzilka A, Sheeran E, Moye J, et al. Morphologic and metabolic abnormalities in vertically HIV-infected children and youth. AIDS (London, England). Mar 27; 2009 23(6):661–72.

18. Botton J, Heude B, Kettaneh A, Borys JM, Lommez A, Bresson JL, et al. Cardiovascular risk factor levels and their relationships with overweight and fat distribution in children: the Fleurbaix Laventie Ville Sante II study. Metabolism: clinical and experimental. May; 2007 56(5):614–22. [PubMed: 17445535]

19. National Cholesterol Education Program (NCEP). highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics. Mar; 1992 89(3):495–501. [PubMed: 1741227]

20. [access 30 July 2010] The American Heart Association. http://www.americanheart.org

21. Bittner V, Johnson BD, Zineh I, Rogers WJ, Vido D, Marroquin OC, et al. The triglyceride/high-density lipoprotein cholesterol ratio predicts all-cause mortality in women with suspected myocardial ischemia: a report from the Women's Ischemia Syndrome Evaluation (WISE). American heart journal. Mar; 2009 157(3):548–55. [PubMed: 19249427]

22. A biregional survey and review of first-line treatment failure and second-line paediatric antiretroviral access and use in Asia and southern Africa. Journal of the International AIDS Society. 2011; 14:7. [PubMed: 21306608]

23. Scherrer AU, von Wyl V, Boni J, Yerly S, Klimkait T, Burgisser P, et al. Viral suppression rates in salvage treatment with raltegravir improved with the administration of genotypic partially active or inactive nucleoside/tide reverse transcriptase inhibitors. Journal of acquired immune deficiency syndromes (1999). Jan 28.2011

24. Puthanakit T, van der Lugt J, Bunupuradah T, Ananworanich J, Gorowara M, Phasomsap C, et al. Pharmacokinetics and 48 week efficacy of low-dose lopinavir/ritonavir in HIV-infected children. The Journal of antimicrobial chemotherapy. Sep 2.2009

25. Babiker A, Castro nee Green H, Compagnucci A, Fiscus S, Giaquinto C, Gibb DM, et al. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an open-label, randomised phase 2/3 trial. The Lancet infectious diseases. Apr; 2011 11(4):273–83. [PubMed: 21288774]

26. Bunupuradah T, Suntarattiwong P, Li A, Sirivichayakul S, Pancharoen C, Boonrak P, et al. Antiretroviral treatment outcome following genotyping in Thai children who failed dual nucleoside reverse transcriptase inhibitors. Int J Infect Dis. Aug 20.2009

27. Bierman WF, van Agtmael MA, Nijhuis M, Danner SA, Boucher CA. HIV monotherapy with ritonavir-boosted protease inhibitors: a systematic review. AIDS (London, England). Jan 28; 2009 23(3):279–91.

28. Duval X, Journot V, Leport C, Chene G, Dupon M, Cuzin L, et al. Incidence of and risk factors for adverse drug reactions in a prospective cohort of HIV-infected adults initiating protease inhibitor-containing therapy. Clin Infect Dis. Jul 15; 2004 39(2):248–55. [PubMed: 15307035]

29. Bunupuradah T, van der Lugt J, Kosalaraksa P, Engchanil C, Boonrak P, Puthanakit T, et al. Safety and efficacy of a double-boosted protease inhibitor combination, saquinavir and lopinavir/

ritonavir, in pretreated children at 96 weeks. Antivir Ther. 2009; 14(2):241–8. [PubMed: 19430099]

30. Quijada Z, Paoli M, Zerpa Y, Camacho N, Cichetti R, Villarroel V, et al. The triglyceride/HDL-cholesterol ratio as a marker of cardiovascular risk in obese children; association with traditional and emergent risk factors. Pediatric diabetes. Oct; 2008 9(5):464–71. [PubMed: 18507788]
31. Tebas P, Henry WK, Matining R, Weng-Cherng D, Schmitz J, Valdez H, et al. Metabolic and immune activation effects of treatment interruption in chronic HIV-1 infection: implications for cardiovascular risk. PloS one. 2008; 3(4):e2021. [PubMed: 18431498]
32. Machado DM, Gouvea Ade F, Cardoso MR, Beltrao SV, Cunegundes KS, Bononi F, et al. Factors associated with clinical, immunological and virological responses in protease-inhibitor-experienced Brazilian children receiving highly active antiretroviral therapy containing lopinavir-ritonavir. Braz J Infect Dis. Feb; 2007 11(1):16–9. [PubMed: 17625720]
33. Pujades-Rodriguez M, Balkan S, Arnould L, Brinkhof MA, Calmy A. Treatment failure and mortality factors in patients receiving second-line HIV therapy in resource-limited countries. Jama. Jul 21; 2010 304(3):303–12. [PubMed: 20639564]
34. Dollfus C, Le Chenadec J, Faye A, Blanche S, Briand N, Rouzioux C, et al. Long-term outcomes in adolescents perinatally infected with HIV-1 and followed up since birth in the French perinatal cohort (EPF/ANRS CO10). Clin Infect Dis. Jul 15; 2010 51(2):214–24. [PubMed: 20536367]
35. Castro H, Judd A, Gibb DM, Butler K, Lodwick RK, van Sighem A, et al. Risk of triple-class virological failure in children with HIV: a retrospective cohort study. Lancet. May 7; 2011 377(9777):1580–7. [PubMed: 21511330]

Key points summary

After one year of second-line, protease inhibitor-based treatment in children from five Asian countries, one-third of those tested did not achieve immune recovery or virologic suppression, and two-thirds had hyperlipidemia, highlighting the need for alternative drug options for treatment optimization.

Table 1

Baseline characteristics at commencement of single boosted Pl-based HAART

Characteristics	Total patients (N)	Median (IQR) or N (%)
Number (%) of children by country	153	
- Thailand		110 (71.9)
- Other *		43 (28.1)
Female, N (%)	153	79 (51.6)
Age, years	153	10 (7, 12)
Weight for age z-score	121	−1.9 (−3.0, 1.1)
Height for age z-score	121	−2.0 (−2.9, −1.2)
Weight for height z-score	121	−0.9 (−1.8, −0.2)
WHO stage 1:2:3:4, percent	147	7:25:42:26
CD4% at switch to PI-based HAART	106	12.5 (5.2, 20.0)
CD4 cells/mm^3 at switch to PI-based HAART	112	237 (90, 466)
HIV-RNA $\log_{10}$ copies/mL at switch to PI-based HAART	61	4.6 (3.9, 5.0)
NRTI combination with Pl-based HAART, N (%)	153	
- AZT/3TC		51 (34.2)
- AZT/ddI		28 (18.8)
- ddI/3TC		26 (17.5)
- d4T/ddI		13 (8.7)
- d4T/3TC		10 (6.7)
- Other (e.g., 3TC, ddI, no NRTI)		25 (16.3)
PI used, N (%)	153	
- LPV/r		127 (83.0)
- IDV/r		25 (16.3)
- ATV/r		1 (0.7)

HAART: highly active antiretroviral therapy, NNRTI: non nucleoside reverse transcriptase inhibitor, NRTI: nucleoside reverse transcriptase inhibitor, bPI; boosted protease inhibitor, AZT; zidovudine, 3TC; lamivudine, ddI; didanosine, d4T; stavudine, LPV/r lopinavir/ritonavir, IDV/r; indinavir/ritonavir, ATV/r; atazanavir/ritonavir

* Malaysia N=17, Indonesia N=9, Vietnam N=9, India N=8

Table 2

Efficacy and safety of second-line single boosted PI-based HAART

Characteristics	Children observed at week 0 and week 48				Children observed at week 0 and week 96			
	N=153	Week 0 Median (IQR) or N (%)	Week 48 Median (IQR) or N (%)	p*	N=96	Week 0 Median (IQR) or N (%)	Week 96 Median (IQR) or N (%)	p*
Weight for age z-score	115	−1.9 (−3.0, −1.2)	−1.9 (−2.9, −1.2)	0.452	73	−1.6 (−2.9,−1.2)	−1.7 (−2.7, −1.1)	0.763
Height for age z-score	115	−2.0 (−2.9, −1.2)	−1.9 (−2.7, −1.2)	0.794	73	−2.0 (−2.6,−1.1)	−1.8 (−2.3, −1.2)	0.034
Weight for height z-score	42	−0.9 (−2.1, −0.2)	−0.6 (−1.3, −0.1)	0.006	15	−0.3 (−2.4,−0.0)	−0.6 (−1.3, −0.5)	0.804
Median CD4% (IQR)	92	13.8 (6.1, 21.0)	20.3 (16.1, 25.3)	<0.001	63	13.4 (6.0,20.0)	22.8 (14.0, 27.9)	<0.001
Median CD4 cells/mm^3 (IQR)	96	256 (112, 542)	597 (399, 877)	<0.001	66	277 (119,482)	667 (370, 960)	<0.001
Immune recovery**, N (%)	129		79/129 (61)		82		57/82 (70)	
Median HIV-RNA, log 10 copies/ml (IQR)	43	4.4 (3.8, 4.9)	1.7 (1.7, 4.1)	N/A	26	4.5 (3.8,4.9)	1.7 (1.7,, 4.0)	N/A
HIV-RNA < 400 copies/ml, N (%)	43		26 (60)		26		17 (65)	
HIV-RNA < 50 copies/ml, N (%)	43		21 (49)		26		16 (62)	
Fasting lipids and glucose								
Median total cholesterol, mg/dl (IQR)	79	167 (139, 192)	180 (154, 217)	<0.001	50	158 (136, 191)	187 (150, 221)	0.002
Median triglycerides mg/dl (IQR)	79	120 (79, 200)	168 (117, 243)	<0.001	50	117 (69, 211)	160 (104, 240)	0.006
Median high-density lipoprotein mg/dl (IQR)	49	44 (36, 59)	49 (40, 60)	0.906	34	44 (34, 59)	47 (37, 59)	0.700
Median fasting glucose mg/dl (IQR)	63	84 (76, 90)	80 (76, 84)	0.083	43	84 (77, 90)	81 (78,87)	0.242
Number of children with with dyslipidemia								
Total cholesterol ≥200 mg/dl, N (%)	79	14 (18)	25 (32)	0.012	50	10 (20)	18 (36)	0.021
Triglyceride ≥130 mg/dl, N (%)	79	39 (49)	58 (73)	<0.001	50	24 (48)	33 (66)	0.029
High-density lipoprotein <35 mg/dl, N (%)	49	12 (24)	9 (18)	0.317	34	11 (32)	8 (24)	0.687
Fasting glucose ≥110 mg/dl, N (%)	63	1 (2)	1 (2)	N/A	43	0 (0)	2 (5)	N/A
Total cholesterol: high-density	49	9 (18)	11 (22)	0.414	34	7 (21)	9 (26)	0.317

Characteristics	Children observed at week 0 and week 48				Children observed at week 0 and week 96			
	N=153	Week 0 Median (IQR) or N (%)	Week 48 Median (IQR) or N (%)	p*	N=96	Week 0 Median (IQR) or N (%)	Week 96 Median (IQR) or N (%)	p*
lipoprotein ≥ 5, N (%) ***								
Triglyceride: high-density lipoprotein ≥ 3.7, N (%) ***	49	20 (41)	24 (49)	0.206	34	17 (50)	16 (47)	0.655

N/A: not available due to limited paired data from week 0

HAART: highly active antiretroviral therapy; UND: undetectable by available HIV-RNA assay

*compared to week 0, approximately 80% of all observations fall within +/− 12 weeks

**If we exclude the immune recovered and those with missing immune status at baseline, 35/72 (48.6%) of the remainder attain immune recovery by week 48 and 31/52 (59.6%) attain immune recovery by week 96.

***Based on American Heart Association recommendations (20)

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Table 3

Factors associated with immune recovery at 48 weeks of single boosted PI-based HAART (N=129)

Variables*	Total patients N	Univariate analysis OR (95% CI)	p-value	Multivariate analysis OR (95% CI)	p-value
Sex					
-male	63	1			
-female	66	1.03 (0.61,2.50)	0.568		
Age in years at start of PI-based HAART	129	0.83 (0.74,0.94)	0.003	0.78 (0.67,0.90)	<0.001
Weight for age z-score at start of PI-based HAART	105	1.11 (0.88,1.40)	0.380		
CD4 count at start of PI-based HAART					
- Unavailable	33	3.43 (1.29,9.13)	0.313	4.51 (1.55,13.11)	0.288
- <200 cells/mm^3	38	1		1	
- ≥200 cells/mm^3	58	4.91 (2.03,11.89)	0.012	7.73 (2.78,21.46)	0.003
HIV-RNA $\log_{10}$ copies/ml at start of PI-based HAART	58	1.14 (0.81,1.59)	0.457		
Years on NNRTI-based HAART before switching to PI-based HAART	129	1.03 (0.83,1.28)	0.809		
WHO stage at start of PI-based HAART					
- Stage 1 or 2	45	1			
- Stage 3	49	0.59 (0.25,1.39)	0.834		
- Stage 4	34	0.41 (0.16,1.03)	0.118		
PI used					
- IDV/r	24	0.58 (0.24,1.41)			
- LPV/r	104	1	0.226		

OR (95%CI): odds ratio (95% confidence interval); AZT: zidovudine; 3TC: lamivudine; ddl: didanosine; d4T: stavudine; IDV/r: indinavir/ritonavir; LPV/r: lopinavir/ritonavir

*Exposure to mono/dual antiretroviral regimens before first-line HAART, NRTI combination used in PI-based regimen, and hemoglobin at start of PI-based HAART had no association with immune recovery by univariate analysis (all p>0.10; data not shown)

Table 4

Factors associated with virologic suppression (HIV-RNA <400 copies/ml) at 48 weeks of single boosted PI-based HAART (N=83)

Variables*	Total patients N	Univariate analysis OR (95% CI)	p value	Multivariate analysis OR (95% CI)	p value
Sex					
-male	39	1			
-female	44	0.57 (0.24,1.37)	0.209		
Age in years at start of PI-based HAART	83	0.92 (0.81,1.05)	0.202	0.78 (0.65,0.93)	0.007
Weight for age z-score at start of PI-based HAART	71	1.55 (1.09,2.21)	0.014	1.71 (1.09,2.69)	0.020
CD4 count at starting PI-based HAART					
- Unavailable	18	4.94 (1.52,16.0)	0.089		
- <200 cells/mm^3	20	1			
- ≥200 cells/mm^3	45	6.00 (1.47,24.5)	0.138		
HIV-RNA $\log_{10}$ copies/ml at start of PI-based HAART					
- Unavailable	40	3.00 (1.08,8.32)	0.672	5.84 (1.47,23.28)	0.423
- <10000	16	6.00 (1.50,23.99)	0.050	12.56 (1.93,81.75)	0.049
- ≥10000	27	1		1	
Years on NNRTI-based HAART before switching to PI-based HAART	83	1.51 (1.11,2.05)	0.008	1.84 (1.19,2.85)	0.006
WHO stage at start of PI-based HAART					
- Stage 1 or 2	30	1			
- Stage 3	30	0.48 (0.16,1.48)	0.695		
- Stage 4	22	0.58 (0.21,1.62)	0.365		
PI type					
- IDV/r	10	0.31 (0.07,1.28)			
- LPV/r	72	1	0.105		

OR (95%CI): odds ratio (95% confidence interval); AZT: zidovudine; 3TC: lamivudine; ddl: didanosine; d4T: stavudine; IDV/r: indinavir/ritonavir; LPV/r: lopinavir/ritonavir

*Exposure to mono/dual antiretroviral regimens before first-line HAART, and NRTI combination used in PI-based regimen, and hemoglobin at start of PI-based HAART had no association with virologic suppression by univariate analysis (all p>0.10; data not shown)