Sequencing paediatric antiretroviral therapy in the context of a public health approach

Ragna S Boerma,1,2 T Sonia Boender,1 Michael Boele van Hensbroek,1 Tobias F Rinke de Wit1 and Kim CE Sigaloff1,3

Abstract
Introduction: As access to prevention of mother-to-child transmission (PMTCT) efforts has increased, the total number of children being born with HIV has significantly decreased. However, those children who do become infected after PMTCT failure are at particular risk of HIV drug resistance, selected by exposure to maternal or paediatric antiretroviral drugs used before, during or after birth. As a consequence, the response to antiretroviral therapy (ART) in these children may be compromised, particularly when non-nucleoside reverse transcriptase inhibitors (NNRTIs) are used as part of the first-line regimen. We review evidence guiding choices of first- and second-line ART.

Discussion: Children generally respond relatively well to ART. Clinical trials show the superiority of protease inhibitor (PI)-over NNRTI-based treatment in young children, but observational reports of NNRTI-containing regimens are usually favourable as well. This is reassuring as national guidelines often still recommend the use of NNRTI-based treatment for PMTCT-unexposed young children, due to the higher costs of PIs. After failure of NNRTI-based, first-line treatment, the rate of acquired drug resistance is high, but HIV may well be suppressed by PIs in second-line ART. By contrast, there are currently no adequate alternatives in resource-limited settings (RLS) for children failing either first- or second-line, PI-containing regimens.

Conclusions: Affordable salvage treatment options for children in RLS are urgently needed.

Keywords: paediatric HIV; antiretroviral therapy; HIV drug resistance; protease inhibitor; non-nucleoside reverse transcriptase inhibitor; low- and middle-income countries.

Introduction
The treatment of HIV-1 in children is more challenging than treatment of adults and is associated with an increased risk of virological failure. Children are vulnerable to developing HIV drug resistance due to various reasons, such as variability in pharmacokinetics, limited paediatric treatment options and lack of adherence support [1]. Moreover, drug exposure as part of the prevention of mother-to-child transmission (PMTCT) can lead to pre-treatment drug resistance [2–4], thus diminishing the chance of treatment success.

Clinical trials have found that children under three years of age on protease inhibitor (PI)-based, antiretroviral therapy (ART) experience less virological failure and death than children on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens, both in PMTCT-exposed and -unexposed children [5–7]. The World Health Organization (WHO) therefore recommends all children below three years of age to receive a PI-based regimen [lopinavir/ritonavir (LPV/r)], regardless of history of PMTCT exposure [8]. Unfortunately, despite these recommendations, the use of PIs for young children in low- and middle-income countries (LMIC) in routine programmes is limited due to practical barriers. PIs are more costly than NNRTIs, and infant formulations were, until recently, only available as a liquid that requires refrigeration [7,9,10].

In this commentary, we will compare PI-based versus NNRTI-based, first-line ART for children, and also discuss feasible ART sequencing approaches in children.

Discussion
More than half of HIV-infected children who do not receive treatment are estimated to die before the age of two years [11]. ART dramatically reduces morbidity and mortality in HIV-infected children of all ages. Findings of previous systematic reviews are encouraging as up to 70 to 80% of children achieve virological suppression after 12 months of first-line treatment [12,13]. In young children under three years of age, data from clinical trials and observational studies in resource-limited settings (RLS) show that, on average, the HIV suppression rate is sustained around 60 to 70% up to 24 months after treatment initiation (Figure 1, Table 1).

NNRTI- versus PI-based, first-line ART
Based on data from clinical trials [5,6,27], the WHO has moved to recommending PI-based, first-line ART for all children below three years, regardless of previous PMTCT exposure. Comparison of trials and observational data reveals higher rates of virological suppression among children receiving PI-based regimens (Figure 1). However, data on
The virological failure rate was 6.7% after one year, 804 children starting on EFV- or NVP-based, first-line cohort study in Botswana with five years of follow-up included concordant results. Lowenthal et al.[32] describe a cohort study in Botswana with five years of follow-up including 804 children starting on EFV- or NVP-based, first-line treatment. The virological failure rate was 6.7% after one year, 10.2% after two years and 12.8% after five years of follow-up on EFV-based treatment, and 12.8, 19.8 and 25.1%, respectively, for NVP-based treatment[32]. In a Zambian cohort, 198 ART-naive and mostly PMTCT-unexposed children started either NVP- or EFV-based treatment. Six to twenty-four months after treatment initiation, the virological failure rate increased from 11.5 to 22.2%[16].

Interpretation of the differences between PI- and NNRTI-treated children is limited by the heterogeneity of studies in terms of design, study participants and setting. It is difficult to draw firm conclusions on the benefits of PI over NNRTI treatment in programmatic settings, especially in PMTCT-unexposed young children. However, results from randomized controlled trials have convincingly shown the superiority of PI-over NNRTI-based treatment[5,6], and PI-based treatment should be implemented for all HIV-infected children under three years of age, as recommended by the WHO[8]. The outcomes of observational studies reporting on programmatic data remain relevant, because the dispensation of PIs may be influenced by financial and logistical issues. LPV/r, currently the only PI combination available for children, is at least five times more expensive than EFV or NVP[33]. Recently, the United States Food and Drug Administration approved LPV/r in pellet form for paediatric usage, which, in contrast to the up-to-now only available LPV/r syrup, does not require refrigeration[10]. This is an important step towards increased access to PI treatment for children in LMIC.

**HIV-TB coinfection**

Tuberculosis (TB) is one of the most common co-infections affecting children with HIV, and cotreatment occurs in up to one-third of children[21]. Comedication for TB adds significant complexity to the treatment of children who also require or are already receiving ART. For children on LPV/r-based regimens, guidelines suggest to add ritonavir to achieve the full therapeutic dose[8]. An alternative is to change to a triple NRTI regimen[34] or to substitute NVP for LPV/r[8]. Children on NVP- or EFV-based ART can usually continue the same regimen (ensuring that NVP dose is 200 mg/m2) or can also be changed to a triple NRTI regimen. These changes in the ART regimen, as well as simultaneous use of TB drugs, put children at risk of developing drug toxicity, virological failure[21] and HIV drug resistance[35].

**Development of resistance on first-line therapy**

Virological failure is defined by the WHO as two consecutive measurements of plasma viral load > 1000 cps/mL at least six months of treatment[8]. However, WHO definitions have changed over time and studies have reported different virological cut-offs to define failure. A systematic review of resistance data in children from resource-poor settings found that 90% of those failing first-line regimens had at least one HIV drug-resistance mutation, with mutations increasing in frequency with duration of treatment[36]. This review included mostly cross-sectional studies and included children who were treated with suboptimal regimens.

More recent studies also show high rates of HIV drug resistance among children with treatment failure. In a study conducted in the Central African Republic, 83 and 85% of children on first-line therapy with a detectable viral load after...
18 months had NRTI and NNRTI mutations, respectively. The most prevalent NRTI mutations were M184V (73%), T69D/N/S (17%), L74I/V (8%), K65R (8%) and Q151M (2%), and the most prevalent NNRTI mutations were Y181C (44%), K103H/N/S (39%), K101E/P (39%), G190A (30%) and A98G/S (19%) [37].

In Thai children treated with NVP- or EFV-containing therapy, NRTI mutations were found in 89% of children at the time of virological failure, with M184V/I (85%), K65R (11%) and K219Q/E (8%) being the most prevalent. NNRTI mutations were detected in 97% of the children, of which Y181C/I (58%), K103N (34%), G190S/A (18%) and V108I (13%), were most common [31].

It is clear from these studies that children who fail NNRTI-based, first-line regimens, generally report similarly high rates of NNRTI- and NRTI-associated mutations, with the Y181C and M184V mutations being among the most prevalent mutations within the respective drug classes. Accumulated NRTI resistance can have consequences for the construction of an effective, second-line, PI-based regimen, in which NRTIs are used as the backbone. This implies that a timely switch to second-line ART after failure is warranted, to prevent clinical consequences as well as the accumulation of drug resistance. Timely switching is, however, challenged by lack of virological monitoring in RLS. Reluctance of clinicians to change therapy in children, for whom limited drug options are available, may be an additional barrier.

In a European study, the development of both PI and NRTI resistance among children failing first-line, PI-based regimens was negligible [38]. In RLS, there are few reports of acquired protease mutations on first-line treatment. A recent

**Table 1. Studies reporting virological suppression rates in children <3 years on first-line ART 6–24 months after treatment initiation**

| Study                            | Median year of treatment initiation | Regimen      | Total number of patients | Number of patients with viral suppression | % children with virological suppression | Time after treatment initiation |
|----------------------------------|------------------------------------|--------------|--------------------------|------------------------------------------|----------------------------------------|---------------------------------|
| Lockman 2007<sup>a</sup> [2]     | 2001                               | NNRTI-based  | 12                       | 11                                       | 91.7                                   | 6 months                        |
| Lockman 2007<sup>b</sup>         | 2001                               | NNRTI-based  | 11                       | 1                                        | 9.1                                    | 6 months                        |
| Puthanakit 2009 [14]             | 2004                               | NNRTI-based  | 25                       | 14                                       | 56.0                                   | 6 months                        |
| Germanaud 2010 [15]              | 2007                               | NNRTI-based  | 68                       | 43                                       | 63.2                                   | 6 months                        |
| Van Dijk 2011 [16]               | 2008                               | NNRTI-based  | 96                       | 85                                       | 88.5                                   | 6 months                        |
| Cotton 2013 [17]                 | 2006                               | PI-based     | 230                      | 192                                      | 83.5                                   | 6 months                        |
| Romano Mazzotti 2009 [18]        | Not reported                       | PI-based     | 56                       | 21                                       | 37.5                                   | 6 months                        |
| Technau 2014 [19]                | 2006                               | PI-based     | 2612                     | 1763                                     | 67.5                                   | 6 months                        |
| Lindsey 2014<sup>a</sup> [20]    | 2008                               | NNRTI-based  | 116                      | 86                                       | 74.1                                   | 6 months                        |
| Lindsey 2014<sup>b</sup>         | 2008                               | PI-based     | 124                      | 112                                      | 90.3                                   | 6 months                        |
| Lindsey 2014<sup>c</sup>         | 2008                               | NNRTI-based  | 68                       | 55                                       | 80.1                                   | 6 months                        |
| Lindsey 2014<sup>d</sup>         | 2008                               | PI-based     | 71                       | 67                                       | 94.4                                   | 6 months                        |
| Meyers 2011 [21]                 | 2006                               | PI-based     | 617                      | 323                                      | 52.4                                   | 6 months                        |
| Lockman 2007<sup>e</sup>         | 2001                               | NNRTI-based  | 11                       | 10                                       | 90.9                                   | 12 months                       |
| Lockman 2007<sup>f</sup>         | 2001                               | NNRTI-based  | 10                       | 1                                        | 10.0                                   | 12 months                       |
| Jaspan 2008 [22]                 | 2004                               | PI-based     | 85                       | 60                                       | 70.6                                   | 12 months                       |
| Jaspan 2008<sup>g</sup>          | 2004                               | NNRTI-based  | 115                      | 47                                       | 40.9                                   | 12 months                       |
| Prendergast 2008 [23]            | 2004                               | PI-based     | 49                       | 44                                       | 89.8                                   | 12 months                       |
| Puthanakit 2009                  | 2004                               | NNRTI-based  | 24                       | 19                                       | 79.2                                   | 12 months                       |
| Van Dijk 2011                    | 2008                               | NNRTI-based  | 77                       | 68                                       | 88.3                                   | 12 months                       |
| Romano Mazzotti 2009             | Not reported                       | PI-based     | 56                       | 30                                       | 53.6                                   | 12 months                       |
| Soeters 2014 [24]                | 2011                               | PI-based     | 118                      | 61                                       | 51.7                                   | 12 months                       |
| Technau 2014                     | 2006                               | PI-based     | 2165                     | 1595                                     | 73.7                                   | 12 months                       |
| Puthanakit 2009                  | 2004                               | NNRTI-based  | 19                       | 16                                       | 84.2                                   | 18 months                       |
| Van Dijk 2011                    | 2008                               | NNRTI-based  | 53                       | 46                                       | 86.8                                   | 18 months                       |
| Kay2012 [25]                     | 2007                               | NNRTI-based  | 34                       | 19                                       | 55.9                                   | 18 months                       |
| Lockman 2007<sup>f</sup>         | 2001                               | NNRTI-based  | 9                        | 1                                        | 11.1                                   | 24 months                       |
| Lockman 2007<sup>e</sup>         | 2001                               | NNRTI-based  | 11                       | 9                                        | 81.8                                   | 24 months                       |
| Puthanakit 2009                  | 2004                               | NNRTI-based  | 15                       | 14                                       | 93.3                                   | 24 months                       |
| Van Dijk 2011                    | 2008                               | NNRTI-based  | 27                       | 21                                       | 77.8                                   | 24 months                       |
| Musilime 2014 [26]               | 2011                               | NNRTI-based  | 349                      | 294                                      | 84.2                                   | 24 months                       |

<sup>a</sup>PMTCT-unexposed cohort; <sup>b</sup>PMTCT-exposed cohort. NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
South African study found that 8 out of 75 (10.7%) children with virological failure on a first-line PI had LPV/r mutations [39]. Within the NRTI drug class, the M184V and thymidine analogue mutations were found in seven out of eight and two out of eight children, respectively. Data among adults have shown that with intensified adherence support, viral load suppression on PI-based ART is possible, despite drug resistance [40]. In this study, performed in Khayelitsha, South Africa, two-thirds of participants resuppressed within three months while remaining on PI-based regimens. The consequences of this study obviously extend to children receiving PIs; intensive adherence counselling should be offered before switching.

Second-line ART
As per WHO recommendation, failure of an NNRTI-based regimen is followed by switching to a boosted PI plus two NRTIs. There are limited data about the response to second-line ART in children [41]. A recent study from Thailand reported on 111 children among whom the risk of virological failure 24 months after second-line initiation was 41% [42]. Children with longer duration of first-line ART were at higher risk of second-line failure. The latter suggests that continued first-line failure may have led to the accumulation of NRTI mutations, diminishing the response to subsequent second-line therapy. However, in the study’s multivariate analysis, resistance to NRTIs did not appear as a risk factor for failure.

For children for whom a PI-based, first-line regimen has failed, NNRTIs remain the only new drug class that can be introduced. However, potential re-emergence of archived NNRTI mutations may limit the effectiveness of this ART sequencing approach. Moreover, NNRTIs have a much lower genetic barrier for resistance [43], and without the protection of an effective NRTI backbone (due to acquired resistance), NNRTI resistance will rapidly emerge. Recently, the first reports on the outcome of second-line NNRTI in children have been published. One small study from South Africa found that six months after regimen change, the proportion with virological failure was 75% (6 out of 8) in children receiving NNRTI-based second-line versus 20% (13 out of 66) in children on PI-based second-line [44]. A second study, again from South Africa, reported on 12 children who were switched to NNRTI-based therapy. Of these, 8 out of 12 (67%) did not achieve virological suppression [39]. Although these findings are based on a small number of children, it is apparent that NNRTI-based, second-line ART is not an optimal choice and is expected to have limited durability.

Salvage options
Constructing third-line regimens using novel, robust drugs such as darunavir, raltegravir or dolutegravir, may be possible for children. Studies have demonstrated the efficacy of darunavir in heavily ART-experienced patients [45]. In a UK cohort, even in children with prolonged PI exposure, resistance to darunavir was rare [46]. Darunavir could therefore be an option after failure of first-line, LPV/r-based treatment in children above three years of age. Raltegravir is the first integrase inhibitor approved for paediatric usage (> 4 weeks of age) and has been evaluated in the IMPAACT P1066 trial, showing virological suppression (< 400 cps/mL) in approximately 80% of participants after 48 weeks of follow-up [47]. In adults, co-administration of rifampicin decreases raltegravir concentrations, thereby potentially limiting the efficacy of this drug in children with HIV-TB coinfection [48]. Dolutegravir, an integrase strand transfer inhibitor with a very favourable resistance profile, has to date only been approved in children > 12 years of age. Results of two cohorts of the IMPAACT 1093 trial have been presented in an abstract form and showed virological suppression in 17 out of 23 treatment-experienced adolescents (aged 12 to 18 years) after 48 weeks of treatment with dolutegravir, and in 9 out of 11 treatment-experienced children (aged 6 to 12 years) after 24 weeks of treatment [49,50]. These newer antiretroviral agents, however, are currently unavailable in RLS. Substantial cost-reduction and/or generic production of these drugs are vital to ensure salvage options for children failing PI-based regimens.

Conclusions
Despite the challenges of paediatric antiretroviral treatment, especially in RLS, studies have shown relatively high rates of virological suppression in children on first-line treatment. For young children, randomized controlled trials have shown the superiority of PI-over NNRTI-based treatment. Observational studies, however, also report favourable results of NNRTI-based, first-line treatment. This has important implications for settings in which PI treatment is unavailable due to logistic and financial barriers. Unquestionably, early initiation of treatment is vital and should be prioritized even if NNRTIs are the only obtainable drugs.

After NNRTI-based, first-line treatment failure, the rates of acquired drug resistance among children are strikingly high. However, these children are likely to still benefit from PIs in second-line. By contrast, the development of resistance mutations after failure of PI-based first-line is limited. If children do have continued failure on first-line LPV/r, the chances of resuppression after switching to second-line NNRTI are very low. Suitable formulations of additional PIs are urgently needed for children who fail either first- or second-line LPV/r. Darunavir boosted with ritonavir would be a suitable candidate, but it is not widely available. Newer antiretroviral agents including second-generation NNRTIs and integrase inhibitors should also be evaluated. The future of an increasing number of children will depend on the availability of these salvage medications. To make these regimens accessible on a global scale, low-cost generic drugs or major price reductions of patented versions are necessary.

Authors’ affiliations
1Amsterdam Institute for Global Health and Development and Department of Global Health, Academic Medical Center of the University of Amsterdam, The Netherlands; 2Global Child Health Group, Emma Children’s Hospital/Academic Medical Center of the University of Amsterdam, The Netherlands; 3Division of Infectious Diseases, Department of Internal Medicine, Academic Medical Center, University of Amsterdam, The Netherlands

Competing interests
We declare no competing interests.

Authors’ contributions
KCES conceived the manuscript and wrote the first draft. RSB performed the literature review and finalized the manuscript. TSB, MBH and TFRW participated in the discussion of results and critically reviewed the final paper.
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References

1. Havens PL, Gibb DM. Increasing antiretroviral drug access for children with HIV infection. Pediatrics. 2007;119(4):838–45.
2. Lockman S, Shapiro RL, Smeaton LM, Wuster C, Thor I, Stevens L, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. N Engl J Med. 2007;356(2):135–47.
3. Musoke PM, Barlow-Mosha L, Bagenda D, Mduiope P, Mubiru M, Ajuna P, et al. Response to antiretroviral therapy in HIV-infected Ugandan children exposed and not exposed to single-dose nevirapine at birth. J Acquir Immune Defic Syndr. 2009;52(5):560–8.
4. Sigaloff KC, Calis JC, Geelen SP, van Vught M, de Wit TF. HIV-1 resistance-associated mutations after failure of first-line antiretroviral treatment among children in resource-poor regions: a systematic review. Lancet Infect Dis. 2011;11(10):769–79.
5. Violari A, Lindsay JC, Hughes MD, Mujuru HA, Kamthunzi P, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. N Engl J Med. 2012;366(25):2380–9.
6. Palumbo P, Lindsay JC, Hughes MD, Bobat R, Meyers T, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. N Engl J Med. 2010;363(15):1510–20.
7. Penazzato M, Prendergast AJ, Muhe L, Tindiyebwa D, Abrams E. Optimisation of antiretroviral therapy in HIV-infected children under 3 years of age (Review). Cochrane Database Syst Rev. 2014;(5):CD004772.
8. World Health Organization (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2013.
9. Fitzgerald F, Penazzato M, Gibb D. Development of antiretroviral resistance in children with HIV in low- and middle-income countries. J Infect Dis. 2013;207(Suppl 2):S85–92.
10. Cipla. Cipla announces US FDA approval for the world’s first paediatric lopinavir and ritonavir oral pellets for the treatment of AIDS in infants and young children [Internet]. Press release. 2015 [cited 2015 Aug 3]. Available from: http://www.cipla.com/getattachment/50550369-81cf-4870-9d4d-58b77207(Suppl 2):S85
11. Newell M-L, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet. 2004;364(9441):1236–43.
12. Sudcliffe CG, van Dijk JH, Bolton C, Persaud D, Moss WJ. Effectiveness of antiretroviral therapy among HIV-infected children in sub-Saharan Africa. Lancet Infect Dis. 2009;9(8):477–89.
13. Giangrossi AC, Chang Y, Margulis AV, Bernstein A, Bassett IV, Losina E, et al. Effectiveness of pediatric antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis. Clin Infect Dis. 2009;49(12):1915–27.
14. Puthanakit T, Auripibul L, Sirisanthana S, Sirisanthana V. Efficacy of non-nucleoside reverse transcriptase inhibitor-based highly active antiretroviral therapy in Thai HIV-infected children aged two years or less. Pediatr Infect Dis J. 2009;28(3):246–8.
15. Germain R, Derache A, Traore M, Maged Y, Toure S, Dieko F, et al. Level of viral load and antiretroviral resistance after 6 months of non-nucleoside reverse transcriptase inhibitor-first-line treatment in HIV-infected children in Mali. J Antimicrob Chemother. 2010;65(1):118–24.
16. Van Dijk JH, Sudcliffe CG, Munsanje B, Sandison T, Akunga B, Biga M, et al. Adherence and viral suppression among infants and young children initiating protease inhibitor-based antiretroviral therapy. Pediatr Infect Dis J. 2013;32(5):489–94.
17. Van Zyl GU, van der Merwe L, Claassen M, Kennedy C, Gidney HW, et al. Protease inhibitor resistance in South African children with virologic failure. Pediatr Infect Dis J. 2009;28(12):1139–20.
18. Davies M-A, Keiser O, Eley B, Rabie H, van Culem G, Giddy J, et al. Outcomes of the South Africa National Antiretroviral Treatment Programme for children: the iDeSA Southern Africa collaboration. South Afr Med J. 2009;99(10):730–7.
19. Oittamata P, Puthanakit T, Chaissarue S, Sirisanthana V. Predictors of virologic failure and genotypic resistance mutation patterns in Thai children receiving non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. Pediatr Infect Dis J. 2009;28(9):826–30.
20. Lowenthal ED, Ellenberg JH, Machine E, Sagdeo A, Boiditswe S, Steenhoff AP, et al. Association between efavirenz-based compared with nevirapine-based antiretroviral regimens in a South African pediatric antiretroviral program. Pediatr Infect Dis J. 2010;29(12):1176–80.
21. Rossouw TM, Feucht UD, Melikian G, Van Dijk JH, Thomas W, du Plessis NM, et al. An open-label randomised factorial trial. Lancet. 2013;381(9875):1391–403.
22. Rossouw TM, Feucht UD, Melikian G, Van Dijk JH, Thomas W, du Plessis NM, et al. Factors associated with the development of drug-resistance mutations in HIV-1 infected children failing protease inhibitor-based antiretroviral therapy in South Africa. PLoS One. 2015;10(7):e0133452.
23. Sigaloff KC, Calis JC, Geelen SP, van Vught M, de Wit TF. HIV-1 resistance-associated mutations after failure of first-line antiretroviral treatment among children in resource-poor regions: a systematic review. Lancet Infect Dis. 2011;11(10):769–79.
24. Charpentier C, Gody J, Mbilokon O, Moscou S, Matta M, Pere H, et al. Virological response and resistance profiles after treatment: a cross-sectional evaluation in HIV type 1-infected children living in the Central African Republic. AIDS Res Hum Retroviruses. 2012;28(1):87–94.
38. 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. Lancet Infect Dis. 2011;11(4):273–83.
39. Meyers T, Savvy S, Wong YJ, Moultrie H, Pinillos F, Fairlie L, et al. Virologic failure among children taking lopinavir/ritonavir-containing first-line antiretroviral therapy in South Africa. Pediatr Infect Dis J. 2015;34(2):175–9.
40. Garone DB, Conradie K, Patten G, Cornell M, Frontières MS, Town C, et al. High rate of virological re-suppression among patients failing second-line antiretroviral therapy following enhanced adherence support?: a model of care in Khayelitsha, South Africa. South Afr Med J. 2013;14(4):166–9.
41. Ajose O, Mookerjee S, Mills EJ, Bouille A, Ford N. Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings. AIDS. 2012;26(8):929–38.
42. Suaysod R, Ngo-Giang-Huong N, Salvadori N, Cressy TR, Kanjanavanit S, Techakunakorn P, et al. Treatment failure in HIV-infected children on second-line protease inhibitor-based antiretroviral therapy. Clin Infect Dis. 2015;61:91–101.
43. Van den Vijver D, Wensing A, Angarano G, Asjo B, Balotta C, Boeri E, et al. The calculated genetic barrier for antiretroviral drug resistance substitutions is largely similar for different HIV-1 subtypes. J Acquir Immune Defic Syndr. 2006;41(3):352–60.
44. Zanoni BC, Sunpath H, Feeney ME. Pediatric response to second-line antiretroviral therapy in South Africa. PLoS One. 2012;7(11):5–9.
45. Violari A, Bologna R, Kumarasamy N, Pilotto JH, Hendrickx A, Kakuda TN, et al. Safety and efficacy of darunavir/ritonavir in treatment-experienced pediatric patients. Pediatr Infect Dis J. 2015;34(5):132–7.
46. Donegan KL, Walker AS, Dunn D, Judd A, Pillay D, Menson E, et al. The prevalence of darunavir-associated mutations in HIV-1-infected children in the UK. Antivir Ther. 2012;17(4):599–603.
47. Nachman S, Zheng N, Acosta EP, Teppler H, Homony B, Graham B, et al. Pharmacokinetics, safety, and 48-week efficacy of oral raltegravir in HIV-1-infected children aged 2 through 18 years. Clin Infect Dis. 2014;58(3):413–22.
48. Eley BS, Meyers T. Antiretroviral therapy for children in resource-limited settings. Pediatr Drugs. 2011;13(5):303–16.
49. Viani RM, Alvero C, Fenton T, Acosta E, Hazra R, Gara EO, et al. Safety and efficacy of dolutegravir in HIV treatment-experienced adolescents: 48-week results. Conference on Retroviruses and Opportunistic Infections (CROI); 2014 Mar 3–6, Boston, Massachusetts.
50. Viani RM, Alvero C, Fenton T, Acosta E, Hazra R, Gara EO, et al. Safety, pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV+ children. Conference on Retroviruses and Opportunistic Infections (CROI); 2014 Mar 3–6, Boston, Massachusetts.