# Development of Antiretroviral Resistance in Children With HIV in Low- and Middle-Income Countries

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**With antiretroviral therapy (ART) recommended by the World Health Organization (WHO) for children aged <2 years with human immunodeficiency virus (HIV) and continuing global ART roll-out, ART coverage in children is rising. However ART coverage in children lags considerably behind that in adults (28% vs 58%). Long duration of therapy needed for HIV-infected children requires maximal efficacy, minimal toxicity, and prevention of development of drug resistance. This requires consideration of ways to improve sequencing of regimens during childhood to minimize development of resistance and treatment failure. We consider aspects of virological failure and development of resistance in vertically HIV-infected children in resource-limited settings. We review evidence guiding choices of first- and second-line ART, the impact of drugs given to prevent mother-to-child transmission, adherence issues and, availability of appropriate drug formulations. Recommendations made during the Collaborative HIV and Anti-HIV Drug Resistance Network (CHAIN)/WHO meeting (October 2012) are summarized.**

***Keywords.*** children; mother-to-child transmission; HIV; antiretroviral therapy; resistance.

Only 28% of human immunodeficiency virus (HIV)–infected children in need of antiretroviral therapy (ART) were receiving it in 2011, lagging significantly behind the 58% coverage for adults [1]. World Health Organization (WHO) guidelines for ART initiation expanded in 2010 to include all HIV-infected children aged <24 months, not only infants aged <12 months [2]. This was because of recognition of the continued higher risk of disease progression and death among children aged 1–2 years and to bring young HIV-infected children into care. ART dramatically reduces morbidity and mortality in children of all ages, so duration of therapy is likely to be long as survival increases. Recent trial and programmatic data is encouraging in that approximately 80% of children appear to achieve viral load (VL) suppression (to <400 c/mL) at 1 year [3] (Table 1). However, early infant diagnosis continues to be a significant challenge for programmatic ART rollout [4].

Although there is no substantial evidence that development of resistance differs in children compared with adults, being associated in both with poor adherence and exposure to suboptimal regimens, there are some key differences. Resistance increases with continuing the same ART regimen in the presence of detectable VL. In general, children tend to be maintained longer than adults on failing regimens, mainly because of challenges with adherence and limited treatment options. Long-term treatment success requires maximizing effectiveness of first-line therapy and minimizing the generation of resistant virus.

In well-resourced countries, the rate of triple-class treatment failure in children and adolescents has been reported to be twice that observed in adults, with risk increasing with duration of therapy [5] and with entry into adolescent years [6]. A caveat is that much data from the developed world are now historic because of low incidence of new infections (subsequent to high prevention of mother-to-child transmission (PMTCT)

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coverage) and often includes old data from children on now outdated regimens.

A systematic review of resistance data in children from developing world settings found that 90% of those failing first-line regimens had ≥1 detectable resistance mutation, with mutations increasing in frequency with longer duration of treatment [7]. However many children included in this study were on suboptimal regimens, and data from programs in resource-limited settings may be limited by substantial loss to follow-up.

Sequencing of ART in children needs to take account of acquisition of resistance mutations as a result of exposure to ARVs as part of either treatment or PMTCT during pregnancy and breastfeeding. The use of nonnucleoside reverse-transcriptase inhibitors (NNRTIs) or protease inhibitor (PI)–based regimens requires careful consideration to balance effectiveness, adherence, and vulnerability to resistance generation [8]. Adherence is often affected by the palatability of pediatric formulations, dependence on caregivers (which may be multiple in many African cultures), and the psychological upheavals of adolescence. Finally, there are operational challenges that jeopardize the effectiveness of pediatric ART rollout in resource-limited settings and thus impact on the selection of viral resistance, such as the use of multiple formulations, which can compromise the reliability of supply chains. It is important to simplify and align child regimens with adult regimens where possible, particularly at lower-level health facilities.

## THE IMPACT OF PMTCT ON ART RESISTANCE

ART given for PMTCT may result in direct transmission of HIV drug-resistant virus, or, more often, drug resistance may be selected at any time from gestation to labor and breastfeeding as a result of exposure to maternal antiretrovirals or postnatal prophylaxis in the presence of viremia. This has been demonstrated in mother–infant pairs found to carry different mutations after exposure to single-dose neviripine (NVP) as PMTCT:K103N in mothers and Y181C in infants [9]. Increased NVP resistance increases the risk of treatment failure when the child starts NVP-based ART [10]. For this reason, where feasible, a boosted PI-based first-line regimen is recommended by all pediatric guidelines for children at high risk of NNRTI resistance (ie, those exposed to an NNRTI as part of a PMTCT regimen). Mutations from PMTCT may fade with time from birth, and the degree they affect response to treatment in older children exposed to non-ART PMTCT regimens is less clear.

The impact of any PMTCT program is dependent on HIV prevalence in pregnant women, the uptake and management of the PMTCT cascade, and the coverage of early infant diagnosis (EID). The key is cascade completion. Currently, many pregnant women at risk are still not being tested for HIV, and effective ART coverage for those in need was only 57% in 2011 for low- and middle-income countries [11]. Even with increased coverage, the majority of infected children will not be NNRTI exposed because PMTCT reduces transmission: it has been estimated that with 95% PMTCT coverage, 3-fold more children will be born to undiagnosed (non-NNRTI exposed) women [12]. Identification of these children who are not known to be at risk of HIV remains difficult and requires that provider-initiated HIV testing of children be increased at multiple entry points. Currently most children who have access to early infant diagnosis are from PMTCT programs.

With scale-up of more effective PMTCT regimens (option A: zidovudine [ZDV] in pregnancy, NVP at delivery and ZDV + lamivudine [3TC] tail; or option B: triple ART in pregnancy and through breastfeeding; or option B + life-long ART for the mother [13]), the detrimental effect of single-dose NVP is likely to decrease. Nevertheless, particularly in the context of suboptimal program performance, the resistance implications of different PMTCT options are an important consideration. As more babies are born to mothers taking ART long term, there are ongoing opportunities for transmission of resistant virus, including transmission during breastfeeding if the mother is not adherent. In east and southern Africa, surveillance of resistance has reported an increase in the prevalence of NNRTI-resistant virus, which may in part be because of PMTCT regimens [14].

## FIRST-LINE REGIMENS: NNRTI VS PI-BASED REGIMENS

For infants and children who are not exposed to PMTCT, current WHO 2010 recommendations are to start NVP-containing regimens. Efavirenz [EFV] pharmacokinetics result in underexposure and wide variability in children aged <3 years, so it is not licensed for this age group. However, there is now ongoing debate about use of NNRTI vs boosted PI as first-line therapy in young children not exposed to PMTCT [15]. Recent data from the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) 1060 cohort 2 randomized trial from Africa and India found a significantly higher rate of virological failure, treatment discontinuation, or death (as a composite endpoint) at 24 weeks in children aged <3 years on NVP-containing regimens compared with Ritonavir-boosted Lopinavir [LPV/r] despite no evidence of prior exposure to NVP [8]. Among children who had virological failure on a NVP-containing regimen, 19 of 32 for whom there were available data had evidence of virological resistance. In the LPV/r group, 11 of 20 with viral failure had resistance mutations to nucleoside reverse-transcriptase inhibitors (NRTIs) 33/147 children on a NVP containing regimen had viral failure versus 12/140 children on a PI regimen at 24 weeks [8]. By contrast, among children in the PENPACT-1 trial (Paediatric European Network for Treatment of AIDS (PENTA) and Pediatric AIDS Clinical Trials Group (PACTG/IMPAACT) PENTA 9/PACTG

390) (n = 266 ART-naive children; median age, 6 years), there was no difference in long-term (4 years) virological outcomes between those starting PI-based regimens vs NNRTIs [16]. However, in 48% children, the PI used was nelfinavir, which is no longer recommended for use in children or adults. Nevertheless, a nonrandomized comparison of LPV/r vs NNRTI in PENPACT-1 demonstrated only small differences in viral load suppression between the 2 regimens, irrespective of age, and possibly in favor of NNRTI.

Children failing first-line PI-based regimens do so with minimal development of PI resistance or thymidine-associated mutations (TAMs) and are most likely to have been nonadherent [16, 17]. Where VL is monitored (eg, in South Africa) and is not suppressed on LPV/r, the need to switch to protect from development resistance is much less urgent than for NNRTI. It is possible such children may be less likely to adhere and successfully respond to an NNRTI-based second-line regimen, which is more vulnerable to development of resistance [18].

Currently, LPV/r is the only PI formulation available in combination. For young children, it is available only as a liquid formulation, although data on a new LPV/r granule are being generated. Cost implications for programmatic rollout need consideration because LPV/r syrup is more costly and requires a cold chain: comparing drug costs for a 10-kg child, an NNRTI-containing regimen costs approximately $100 per annum, whereas a PI-based regimen costs >$300 (although including ABC may increase the cost to $240) [19]. Atazanavir/ritonavir is a once-daily booster PI that is cheaper than LPV/r but needs development as a fixed-dose combination (FDC) with ritonavir for children. Atazanavir is currently only licensed for children over 6 years of age. Ritonavir tablets are very large, and an alternative to the unpalatable liquid formulation for young children is urgently needed.

## FIRST-LINE REGIMENS: NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NRTI) BACKBONE

The Paediatric European Network for Treatment of AIDS (PENTA) 5 trial showed that abacavir (ABC) + 3TC is more efficacious than ZDV + 3TC [20]. ABC hypersensitivity is rare in African children: in the AntiRetroviral Research fOr Watoto [ARROW] trial only 0.3% of 1206 children had a possible ABC reaction [21]. In addition, the resistance profile of nonthymidine analogue NRTIs is such that they may be best suited for first-line treatment, as the most frequent mutation induced by ABC (M184V) and slowly accumulated ABC-specific mutations (K65R, L74V, T215Y) do not affect susceptibility to ZDV (and may induce hypersusceptibility), which can then be used in second-line treatment [22]. Conversely, although less costly initially, using ZDV first in settings where VL monitoring is rare or unavailable will result in accumulation of TAMs, such that with ≥2 TAMS, the efficacy of ABC in a second-line regimen will be reduced. Additional data on the comparative toxicity, virological response, and resistance profiles of ABC vs ZDV in first-line ART with an NNRTI are expected from a 96-week trial comparing the toxicity, acceptability, and pharmacokinetics of FDCs of ABC/3TC, ZDV/3TC, and stavudine [d4T]/3TC with NVP or EFV, ongoing in Uganda and Zambia Children with HIV in Africa – Pharmacokinetics and Adherence/Acceptability of Simple Antiretroviral Regimens (CHAPAS-3) (http://www.chapas3trial.org/index.php?option=com_content&view=article&id=45&Itemid=1).

Whether the advantage offered by ABC in first-line therapy is as important in combination with a potent PI such as LPV/r, which would protect from selection of TAMs, is unclear. As NNRTI-based regimens are currently the only available option after PI-based first-line therapy in young children, ABC could theoretically contribute to making this a more potent second-line regimen.

Tenofovir (TDF) was recently approved by the US Food and Drug Administration and European Medicines Agency for use in children aged ≥2 years. It is less costly than ABC and has the potential for harmonization with adult regimens (which increasingly use TDF). Similar to ABC, if resistance to TDF develops, susceptibility to ZDV as second-line treatment is maintained or enhanced. Tenofovir "baby tablets" have very recently been developed, and a powder formulation is available for younger children. However, there are no pediatric FDCs containing TDF, and the adult tablets (EFV + TDF + 3TC/FTC) are not scored. Concerns about renal and bone safety of TDF in young children require long-term evaluation.

## WHEN TO SWITCH TO SECOND-LINE ART

In settings where VL testing is available, only 1 trial has directly evaluated different VL thresholds for switching in either adults or children [16]. The predominantly European–US PENPACT-1 trial compared switching at VL ≥ 1000 copies/mL vs ≥ 30 000 copies/mL in children also randomized to either an NNRTI or PI-containing regimen in a factorial design. All children had VL and CD4 monitoring every 3 months; 71% were still on first-line therapy at median 5 years follow-up. There was no difference in the VL primary endpoint for either randomization (approximately 82% had VL < 400 at 4 years with no differences by randomized groups); CD4 responses were good and clinical progression was rare and similar in all groups. However, there was 10% additional NRTI resistance (predominantly TAMs and M184V) in the delayed switching NNRTI arm that was not seen in the PI arm (25% of those with a resistance test). NNRTI and 3TC resistance occurred early, with viral rebound to 1000 copies/mL in the NNRTI arms, and was not prevented by switching at the lower VL threshold of 1000 copies/mL vs 30 000 copies/mL. This trial demonstrates the increased

**Table 1. ART Resistance in Children: Summary of Trial and Cohort Data**

| Name/Location/ | Years | No. | Drugs Used | Follow-up | Age (median) | VL < 400 c/mL | Resistance Mutations Seen | PMTCT Exposure | Switched to Second Line | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Trial Data | | | | | | | | | | |
| PENPACT 1 trial Europe, North and South America [16] | 2002–2005 | 266 | NNRTI: 61% EFV, 38% NVP. PI: 49% LPV/r, 48% NFV. NRTI: 88% 3TC, 43% ZDV, 24% ABC 20% 3TC | 6 y Primary endpoint: 4 y | 6 y (68 <3 y) | 82% (PI)/82% (NNRTI) 83% switch 1000 80% switch 30 000 | NNRTI and M184V mutations developed early. Late switching on NNRTI regimen increased NRTI (TAMs) resistance. Late switching: no difference in PI mutations. Only 1 LPV/r mutation | 15% exposure balanced across groups | 23% | Comparing switch at VL>1000 c/mL vs >30 000 c/mL and start with PI vs NNRTI. |
| IMPAACT 1060 Cohort 2 trial Africa and India [8] | 2006–2010 | 288 | NVP vs LPV/r + ZDV&3TC | 48 w Primary endpoint: 24 w* | <3 y | 79% (NVP)/91% (LPV/r)[a] | 21 of 32 in NVP group had resistance to ≥1 drug; 11 of 20 in LPV/r group, 1 to PI. | No documented exposure to NVP | | [a]at 24 w. Viral failure also included <log10 decrease in VL |
| IMPAACT 1060 Cohort 1 trial Africa and India [10] | 2006–2009 | 164 | NVP vs LPV/r + ZDV&3TC | 48 w Primary endpoint: 24 w* | <3 y | 85% (NVP)/95% (LPV/r)[b] | 17 of 20 in NVP group had resistance to ≥1 drug; 1/5 in LPV/r group | Exposed to NVP | | [b]at 24 w. Viral failure also included <log10 decrease in VL |
| NEVEREST 1 trial South Africa [23] | 2005–2007 | 195 | NVP vs LPV/r + 3TC&d4T | 3 y | <2 | **VL < 1000** 90% (LPVr)/78% (NVP) **VL < 50** 33% (LPVr)/46% (NVP) | 86% ≥ 1 mutation (NVP); 45% ≥ 1 mutation (LPV/r) | Previous NVP exposure | In NVP group, 13 switched back, 3 to other regimens. | Previously stable on PI based regimen, switched to NVP-based or control group. |
| ARROW trial Uganda/ Zimbabwe [27] | 2007–2012 | 1206 | NNRTI, 3TC, ABC; ZDV, 3TC, ABC, induction + NNRTI; 3TC, ABC, induction + ZDV | 4 y | 6 y. 31% <3 y | 84% in the NNRTI + 2NRTI arm | Pending | 7% PMTCT (most sdNVP) | 5% | |
| CHER trial/South Africa (NB did not compare regimens) [17] [26] | 2005–2007 | 377 | LPV/r, ZDV, 3TC | 5 y | <3 m | 84% | 52% had ≥1: M184V most common.Only 2 PI mutations | Most exposed sd NVP | 2% | |
| Cohort Data | | | | | | | | | | |
| TREAT Asia Paediatric HIV Observational Database (TApHOD) and IeDEA cohort 2011 Asia and Africa [38] | 2008 (Africa) 2009 (Asia) | 1301 (Asia) 4561 (Africa) | Multiple (WHO recommended in <5%) | Cross sectional | First line: 10 (Asia), 7 (Africa); Second line 12 (Asia), 9 (Africa) | | | | 10% (Asia) 3% (Africa) | |

*Table 1 continued.*

| Name/Location/ | Years | No. | Drugs Used | Follow-up | Age (median) | VL < 400 c/mL | Resistance Mutations Seen | PMTCT Exposure | Switched to Second Line | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| IeDEA cohort Southern Africa [39] | 1999–2008 | 5485 | 89% d4T/3TC; 55% EFV; 33% LPV/r; 7% RTV; 5% NVP | 3 y | 3.5 y at ART start, 4.2 y at failure | **<1000 c/mL** 81% (Kaplan–Meier estimates of probability of virological failure) | | 10% known exposed, 30% known unexposed, 60% unknown | 6.2% (estimated probability) | NVP or RTV (alone) and PMTCT exposure associated with viral failure |
| Musiime et al 2012 Uganda [29] | 2004–2010 | 142 | LPV/r (second line) | 48 w | 11 | 85% suppressed | M184V in 91%, K103N in 51%, 2 of 12 tested had PI resistance | | 8.2% of original cohort | Cohort on 2nd line after viral failure |
| Vaz 2012 Mozambique [40] | 2007–2008 | 119 | 52% ZDV, 3TC, NVP; 46% d4T, 3TC, NVP;1.7% d4T, 3TC, LPV/r | 1 y | 2 y | **<1000 c/mL** 77% | 5.4% mutations prior to ART, 10.3% at 1 y. 9% NRTI, 8% NNRTI, 8% dual class | 11% | 0 | PMTCT, baseline resistance and missed medication associated with resistance |
| Shet 2012 India [41] | 2009–2011 | 80 | | 26 m | | **<1000 c/mL** 85% | 92% with failure M184V, 67% K103N/R. No PI resistance | | | |
| Kekitiinwa 2012 Uganda [42] | 2007–2010 | 108 | 53% ZDV, 3TC, EFV; 41% ZDV, 3TC, NVP | 3 y | 4.5 y | 74% | 13% mutations prior to starting therapy; in those with failure 70% M184V, 55% K103N. No PI mutations | 15% | 10% | Resistance mutations accumulated over time with viral failure |

Abbreviations: ABC, abacavir; ART, antiretroviral therapy; d4T, stavudine; EFV, efavirenz; LPV/r, lopinavir boosted with ritonavir; NFV, nelfinavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; PMTCT; prevention of mother-to-child transmission; RTV, ritonavir; sdNVP, single-dose nevirapine; TAMS, thymidine analogue mutations; VL, viral load; WHO, World Health Organization; ZDV, zidovudine; 3TC, lamivudine.

Bold is to indicate when threshold of VL is different to <400 as in column head.

[a] See corresponding Comment.

[b] See corresponding Comment.

robustness of PI regimens against development of PI resistance and their ability to protect NRTIs from developing TAMs. Similarly, in the Children with HIV Early Antiretroviral therapy (CHER) trial only 7 of 353 children switched to second-line treatment and only 2 of 31 children with VL >1000 and on ART at trial end (median 5 years) developed PI mutations. Although 52% of those with VL >1000 had at least 1 mutation, these were almost exclusively M184V, and there were no TAMs [17].

With the aim of preserving the future use of PI-based regimens in children exposed to NNRTIs as PMTCT, the Nevirapine Resistance Study (NEVEREST) trial compared outcomes of children randomized to change to an NVP-based regimen after reaching VL suppression using a PI vs those staying on the original PI regimen [23]. There was more virological failure (VL > 1000 copies/mL) at 3 years in children who moved from PI to NNRTI, but interestingly, also more suppression to VL < 50 copies/mL in this group. In this trial, only children with undetectable VL at 1 year from treatment initiation were randomized. This trial demonstrates that exposure to PMTCT does not rule out later effective use of NVP after suppression with an LPV/r. However, patients with NVP-resistance at baseline were more likely to fail after substituting to NVP, and virological monitoring and/or genotyping has been suggested to identify children who can safely undergo this strategy; these tests are unlikely to be available in many low-income countries. A similar but simpler approach, which does not require monitoring, is under investigation in the NEVEREST-3, trial which is evaluating preemptive substitution of LPV/r for an EFV-based regimen at age 3 years.

A South African study reported less drug resistance overall among children failing second-line ART if they started with an NNRTI-containing regimen and switched to a PI-containing regimen rather than vice versa [18]. It is important that the impact of monitoring strategies on the selection of drug resistance is further studied as concerns regarding the accumulation of resistance while on a failing regimen remain considerable: TAMs conferring some resistance to all NRTIs accumulate if maintained on a failing AZT or stavudine regimen [24].

The rate of switch to second-line therapy in children living in resource-limited settings appears low in country programs: only approximately 3% of children overall in resource-limited settings were on second-line ART in 2010 [11]. In a large Ugandan cohort study, 5.3% switched from first-line NNRTI-containing regimens over 3 years [25]. It is unclear how much low switch rates may be because of treatment success or limited second-line options, and there are challenges in defining treatment failure. However, excellent suppression rates have also been reported in trials: 84% had VL < 400 c/mL at the end of 5 years in the CHER trial, with only 7 out of 341 completing follow-up switching [17, 26]. Similarly 85% had VL < 400 c/mL in the NNRTI + 3TC + ABC standard arm in the ARROW trial (n = 1206 children; <5% had switched at median 4 years). These results show that with both PI and NNRTI regimens (albeit not randomized), children of all ages respond extremely well to ART [27].

## WHAT TO SWITCH TO

Children have a good response to PI-based second-line ART after NNRTI-based first-line ART. A Thai cohort documented that 81% of children on second-line therapy had VL < 400 c/mL at 48 weeks [28], and in a Ugandan cohort, 85% had a VL < 400 c/mL at 48 weeks on a second-line boosted PI regimen [29]. Current WHO guidelines are to switch to a boosted PI regimen with either ABC/3TC or ZDV/3TC depending on preceding usage. An alternative is TDF, although like ABC, it is better from a resistance standpoint to be used as first-line treatment because it can be followed by ZDV as second-line treatment. Both ABC and TDF with 3TC can be given once daily in children [30].

The current lack of availability of suitable formulations of PIs other than LPV/r is of concern for those failing second-line therapy. In the case of treatment failure using LPV/r-based regimens, when NNRTI-based regimens may be vulnerable to resistance, darunavir (DRV) boosted with ritonavir [DRV/r] would be preferable, but is not widely available. In a UK cohort, even in children with prolonged LPV/r exposure and nonsuppressed VL, resistance to DRV was rare [31]. DRV/r is currently expensive and not coformulated for children.

## AVAILABILITY OF PEDIATRIC FORMULATIONS AND ADHERENCE AND RETENTION IN CARE

Effective therapeutic options are limited in children by a lack of suitable FDCs that can be dosed according to simplified weight band tables. Inadequate or inaccurate dosing and poorly palatable drugs can both lead to development of ART resistance. In general, children aged >3 years can take minitablets, and dispersible pediatric tablets of FDCs can be given even to small babies [32]. Both children and caregivers have reported preference of tablets over syrups, citing ease of transportation and fewer problems with taste and swallowing [33]. Whereas NVP + 2NRTIs are available as FDCs across all ages that can be scored and broken (with good demonstrable pharmacokinetics [PK]), PIs are problematic as discussed above, and there is an urgent need to develop better combination FDCs (eg, as granules) for young children [34]. Children are vulnerable in their dependence on caregivers to ensure adequate adherence. The difficulties in administration of unpalatable liquids or large tablets to children impinge directly on inadequate adherence and the possibility of emerging viral resistance. For adolescents, adherence can be very challenging as children come to terms with their diagnosis. Approximately 10% of the UK adolescent cohort was not taking ART because of poor adherence/refusal [6]. Within the African International epidemiologic Databases to

Evaluate AIDS (IeDEA) cohort, 25% of adolescents were no longer retained in care 36 months after ART initiation [35].

## OPERATIONAL AND HEALTH SYSTEMS: SUPPLY CHAIN AND DRUG STOCKOUTS

Effective health systems are a necessity for the uninterrupted supply of pediatric formulations to clinics, particularly with further rollout of ART to rural areas. Drug stockouts clearly contribute to development of viral resistance, particularly if individual drugs within FDCs have different half-lives, leaving children on effective monotherapy if the FDC is stopped. Drug supply continuity appears to be globally one of the weaknesses in program performance. Thirty-five percent of countries monitoring early warning indicators at the national level have reported inconsistent drug supplies to be a major issue [36].

The supply of pediatric regimens is vulnerable to breakdown because of challenges in forecasting, supply, and storage requirements. In a survey of decentralized health centers providing ART in Malawi, Uganda, and Zimbabwe in 2012, a quarter of centers experienced stockouts of pediatric formulations in the preceding 90 days [37]. This underlines the importance of minimizing the number of formulations and harmonizing with adults. PK studies undertaken in Africa have shown that the PK of scored adult tablets used in children is satisfactory [34].

One risk of single drugs is that if there is a lack of availability of 1 drug, the child can be left on inadequate dual or single therapy, increasing the risks of resistance. This can be overcome by the use of FDCs and harmonizing with adult regimens so that adult tablets (dosed as per WHO weight bands) could be used in emergencies. The importance of health system strengthening to ensure an uninterrupted supply of ART as well as the development of FDCs cannot be overestimated.

## CHAIN RECOMMENDATIONS

After consideration of evidence discussed above, the CHAIN group meeting made the following recommendations to minimize the risk of resistance development in children:

### First-Line Treatment

In children aged <3 years with high risk of NNRTI-resistance, LPV/r + 2NRTIs is preferred but with a possible switch to NNRTI-based regimen once virological suppression is achieved or after a fixed period of time. If there is no NNRTI exposure, NVP-based ART is a good alternative (as FDC). From the resistance perspective, ABC in combination with 3TC is preferable to ZDV first line. ZDV can effectively be used in second line regimens following a non-thymidine analogue NRTI. TDF is unavailable for children aged <2 years, but in those aged >3 years, efforts should be made to harmonize with adults and to develop appropriate FDCs for children, including TDF + 3TC (as FDC) to be given with EFV (triple pediatric FDC) or NVP.

### Second-Line Treatment

To minimize resistance selection, children on NNRTIs should switch to PI/r + ZDV/3TC (or ABC + 3TC if started with ZDV). For those starting LPV/r, switching to DRV with ritonavir once children can take ritonavir tablets and if affordable, may be preferable to NNRTI-based second-line ART because of resistance fragility.

Moving forward, the most important message is that children on ART do very well, with little differences between ART regimens; the need is for early diagnosis and timely ART initiation. Key challenges include monitoring effects of changing PMTCT practices on the emergence of resistance in children, operational research into implementing treatment switch strategies in the absence of VL monitoring, improving the availability of weight-banded FDCs for children after pharmacokinetic assessment, harmonization of child and adult regimens, and finally and importantly the strengthening of healthcare systems to ensure adequate and continuous drug provision.

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