Proposal for the Inclusion of Darunavir/Ritonavir 120 mg/20 mg Tablets on the WHO Model List of Essential Medicines for Children (EMLc) for the Treatment of HIV/AIDS in Children

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1. Summary statement of the proposal

This document proposes the addition of darunavir/ritonavir 120 mg/20 mg (pDRV/r), as a fixed-dose combination (FDC) pediatric-strength tablet for treatment of HIV/AIDS among pediatric patients, on the core list of the Model List of Essential Medicines for Children (EMLc). Currently, the single products darunavir (as 75 mg tablets) and ritonavir (as 25 and 100 mg tablets) are included in the 9th EMLc published in 2023.

The principal reasons for requesting this inclusion are as follows:

- Darunavir (DRV) as a representative of the protease inhibitor (PI) class of antiretroviral drugs (ARVs), given with ritonavir (RTV, /r) as a pharmacokinetic booster, has demonstrated effectiveness in multiple patient populations, has a favorable safety profile, and has a higher barrier to resistance than other PIs, making it an excellent candidate for use in a public health approach to HIV treatment.
- According to the most recent WHO Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations For A Public Health Approach (June 2021), a regimen containing DRV/r plus other ARVs is recommended as a preferred regimen for pediatric patients older than 3 years of age and weighing at least 10 kg who have failed prior ARV treatment.[1]

2. Consultation with WHO technical departments

Consultation with WHO technical department: Department of Global HIV, Hepatitis and STI Programmes
Focal points: Nandita Sugandhi and Marco Vitoria
Initial consultation: July 8, 2024
This submission is being made at the request of the WHO pediatric HIV focal point with whom CHAI works closely on issues related to pediatric drug development and global access.

In addition, the application is supported by Martina Penazzato, Technical Lead, Global Accelerator for Paediatric Formulations (GAP-f), WHO.

3. Name of organization(s) consulted and/or supporting the application.

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4. Key information summary for the proposed medicine(s)

Table 1: Product attributes

INN	darunavir and ritonavir
ATC code	J05AR26 (for DRV/r), J05AE10 (for DRV)
Indication	Treatment of HIV-1 infection in pediatric patients aged at least 3 years and weighing at least 10 kg

ICD-11 code	IC62 - Human immunodeficiency virus disease without mention of tuberculosis or malaria		
Dosage form	**Strength**	**EML**	**EMLc**
Low-dose tablet	DRV 120 mg/r 20 mg	No	Yes

An assessment of the age-appropriateness of the pDRV/r tablet according to the WHO paediatric quality product profile assessment tool (PQPPAT) was conducted and the results are shown in Annex 1. Based on a PQPPAT assessment (all attributes assessed as either "low risk" or "moderate risk"), this formulation was determined to be appropriate for the ages and weights indicated (greater than 3 years and greater than 10 kg). In addition, this formulation was identified and prioritized as this FDC by the WHO convened Paediatric Antiviral Drug Optimization (PADO) working group in the PADO-2 meeting[2] and the component ratio and strength was published in the PADO-3 meeting report.[3]

5. Listing as an individual medicine or representative of a pharmacological class/therapeutic group

We request inclusion of pDRV/r in the EMLc as an individual medicinal product but as an FDC. This FDC contains single products already listed in the EMLc. We propose pDRV/r be listed in category 6.4.2 "Antiretrovirals," in the sub-category 6.4.2.5 "Fixed-dose combinations of antiretroviral medicines," without a square box. There are other FDCs of antiretroviral drugs, but they are not considered therapeutic equivalents of pDRV/r which represents a superior pediatric boosted PI product for children living with HIV (CLHIV) who have failed a previous HIV therapeutic regimen.

6. Information supporting the public health relevance

In its 2024 Global AIDS Update, UNAIDS reported there were almost 40 million people living with HIV/AIDS globally, with estimated 1.3 million new HIV-1 infections in 2023, a decrease of 39% since 2010, and 630,000 HIV-related deaths. Over 95% of infected people live in low- and middle-income countries (LMIC) but for the first time, more new infections are occurring outside sub-Saharan Africa than inside sub-Saharan Africa. Progress in reducing new HIV infections has been highly variable, with rising rates of infection in Eastern Europe and Central Asia, Latin America, and the Middle East and North Africa. Overall, approximately 30.7 million people were receiving antiretroviral therapy (ART) in 2023, an estimated 77% of HIV infected people.[4]

Early and effective ART not only significantly improves the health of those living with HIV, but also reduces transmission of the disease as shown in the START study.[5] For this reason, beginning in 2015, the WHO called for treatment for all people living with HIV. Easy to administer, highly effective, safe treatment options remain desperately needed in many areas of the world. While efforts are ongoing to develop a cure for HIV, currently lifelong treatment with combinations of ARVs is required and many HIV-infected individuals, including children, will receive multiple different regimens during their lifetime.

However, the numbers of new infections, deaths, and number of patients on treatment missed the UNAIDS 90-90-90 targets, which called for 90 percent of people living with HIV to know their status, 90 percent of those with known infection to be on ART, and 90 percent of those on ART to be virally suppressed by the year 2020[6] and we appear in danger of missing the both the updated 95-95-95 Targets by 2025 and the 2030 target to eliminate HIV as a public health threat.[7] UNAIDS estimates that in 2023 1.4 million children 0 through 14 years of age are living with HIV

infection, 86% of whom live in sub-Saharan Africa. Despite an impressive reduction in mother to child transmission of HIV in recent years, 120,000 new pediatric infections occurred in 2023, and 76,000 children died from AIDS-related causes.[4] Evidence shows that in the absence of ART, over 50% of HIV-infected infants progress to AIDS or death by the age of 2 years,[8] but the introduction of effective pediatric ART has changed HIV infection in children from a life-threatening illness to a chronic-but-manageable infection, albeit highly dependent on good adherence and sustained access to ART. Despite recognition of the advantages of early treatment, pediatric treatment coverage still reached only 57% of children eligible for treatment in 2023 and only 48% of all CLHIV are virally suppressed, substantially fewer than the 78% of adults living with HIV.[4] This lack of successful suppression among CLHIV on treatment ultimately leads to uncontrolled viral replication, development of resistance, and progression of HIV disease.

The WHO's Report on HIV Drug Resistance published in 2021 described national surveys of pretreatment HIV drug resistance among adults initiating or reinitiating first-line ART with results reported and analyzed from 35 of 56 countries implementing the surveys between 2014 and 2020. The report is representative of countries from all geographic regions. In 21 surveys reported to WHO, pretreatment HIV drug resistance to nevirapine (NVP) or efavirenz (EFV) in populations initiating first-line ART reached levels above 10%, with some countries in sub-Saharan Africa, the Americas, and the Caribbean reporting greater than 20% resistance to these widely used non-nucleoside reverse transcriptase inhibitors (NNRTIs). Rates of NNRTI resistance were significantly higher in individuals with known prior exposure to ARVs. The rates of resistance to other classes of ARVs have also increased since earlier reports but less dramatically than for NNRTIs as shown in the table below. As noted in the WHO report, resistance to DTG has been reported in some regions but remained low at the time of report publication.[9]

Table 2: Prevalence of pretreatment HIV drug resistance among adults initiating ART, 2014–2020

	Africa %, 95% CI[a]	The Americas %, 95% CI[a]	South-East Asia %, 95% CI[a]	Western Pacific %, 95% CI[a]	Overall %, 95% CI[a]
All ART initiators					
NRTI	6.1, 2.7–9.5	6.4, 3.9–9.0	3.1, 1.5–4.6	4.0, 2.9–5.1	5.4, 2.6–8.1
EFV or NVP	15.4, 13.9–17.0	16.7, 10.3–23.2	5.3, 3.3–7.3	6.9, 0.0–14.9	12.9, 9.0–16.9
ATV/r, DRV/r or LPV/r	0.3, 0.0–0.7	0.8, 0.2–1.5	0.4, 0.0–1.0	0.0, 0.0–0.6	0.4, 0.0–0.7
INSTI	0.1, 0.0–0.3	2.7, 0.0–10.2	ND	ND	0.6, 0.0–2.0

Source: WHO Report on HIV Drug Resistance, 2021

NNRTI-based ART has been widely used in pediatric patients for both prevention of transmission and treatment, a previous survey of newly diagnosed children in five sub-Saharan African countries published in 2017 indicated resistance to one or more NNRTIs was identified in up to 53% of the cohort.[10] These high rates of resistance to the previously recommended first-line ARV prompted WHO to recommend rapid transition to dolutegravir (DTG)-based treatment as child-friendly formulations became available. The 2021 WHO Report on HIV Drug Resistance includes data from 10 countries that reported the results of surveys between 2012 and 2020 of pretreatment HIV drug resistance among ART-naive infants younger than 18 months. Unfortunately, the WHO report confirms high rates of NNRTI resistance among newly diagnosed infants with a pooled prevalence of 45.5%, with a range from 34% to 68%. In addition, pretreatment resistance to abacavir (ABC) and 3TC (the preferred NRTIs for infants) was also high and had exceeded 10% in five and four of the 10 reporting countries, respectively.[9]

While resistance to DTG remains relatively low, multiple reports suggest that resistance mutations do emerge and may be more common than previously suspected based on results of clinical trials. Not surprisingly, isolated case reports have been described in many geographic settings, including France,[11] Haiti,[12] and KwaZulu-Natal.[13] However, additional reports suggest higher rates of resistance may develop in some circumstances. For example, the original DTG cohort studied in the IMPAACT 1093 pediatric clinical trial reported in 2022 the emergence of DTG resistance in 8 of 142 study participants (5.6%).[14] In a cross-sectional survey of CLHIV < 15 years of age in Malawi conducted in 2022-2023, 128 of 297 (43%) remained unsuppressed; 15.5% of unsuppressed children were reported to have high-level DTG resistance while 41% had NRTI resistance and 65% had NNRTI resistance, but relatively few (5.2%) demonstrated PI resistance.[15]

Due to this increase in drug resistance, and potential for drug intolerances, treatment-experienced patients of all ages will continue to need access to highly effective PI-based regimens for the foreseeable future. DRV in combination with RTV represents a best-in-class boosted PI that has proven to be an effective ART in both treatment-naïve and treatment-experienced HIV-infected people with multiple drug resistance mutations. Superior clinical efficacy, a favorable tolerability and toxicity profile, along with a high genetic barrier to the development of resistance makes DRV an optimal second-line ARV drug for adults, adolescents, and pediatric patients ≥3 years old.[16]

Currently, the only PI widely available to children in low- and middle-income countries (LMIC) is coformulated lopinavir/ritonavir (LPV/r), which is available in oral solution, pellet, granule, and low-dose tablet formulations. There are significant issues with LPV/r formulations. The LPV/r oral solution requires refrigeration, is unpalatable, contains high levels of alcohol and propylene glycol, and causes significant rates of gastrointestinal adverse reactions that lead to poor adherence and substantial levels of drug resistance. The LPV/r pellets also cause significant rates of gastrointestinal adverse reactions that lead to poor adherence and substantial levels of drug resistance and are difficult to administer. The LPV/r granules likely have similar issues as the pellets, but have been in use for a relatively short time. Clinicians in many settings have urged access to another boosted PI because of the difficulties associated with administering LPV/r to pediatric patients.

Pediatric formulations have been available of the innovator product Prezista (Janssen) as suspension (100 mg/mL) and low-dose tablets (75 mg and 150 mg), none of which are widely available in LMIC but have been widely used in the high income countries since its approval for use in older children and adolescents in 2008. Thus, the most recent WHO recommendations for pediatric use of pDRV/r in an LMIC public health setting are based on modeling the DRV concentrations expected to be provided with the pDRV/r tablets to match adult pharmacokinetic (PK) targets shown to be safe and effective. The 120 mg/20 mg strength and ratio were identified as the optimal FDC by the WHO's Paediatric Antiretroviral Working Group (PAWG) to achieve appropriate concentrations across all the relevant weight bands from 10 kg to <35 kg and reported by PADO.[3]

7. Treatment details

Dosage regimen and duration of treatment

The 2021 WHO recommendations for treatment of HIV in infants and children identify DRV/r as an alternative regimen for use in CLHIV (3 years of age and weighing at least 10 kg) who have failed prior therapy. pDRV/r must be administered in combination with an optimized backbone to construct a potent second- or third-line regimen for children in whom DTG-based or NNRTI-based regimens are failing.[1] U.S. pediatric HIV treatment guidelines also recommend a regimen consisting of boosted DRV in combination with other ARVs for CLHIV experiencing

treatment failure.[17] Treatment for HIV is lifelong and the dose must be adjusted as children grow. Dosing recommendations for pDRV/r for both once and twice daily use are shown in the table below based on current dose recommendations for Prezista (Janssen) and modeling and simulation.[18] These dose recommendation have been endorsed by the WHO PAWG.

Table 3: DRV/r dosing for the DRV/r 120/20 mg tablet in children twice daily per WHO weight bands

Weight Band	DRV/r 120/20 mg tablets	DRV/r Dose	Freq	DRV/r ratio
10 to < 14 kg	2 tablets	240/40 mg	BID	6:1
14 to <20 kg	3 tablets	360/60 mg	BID	6:1
20 to <25 kg	3 tablets	360/60 mg	BID	6:1
25 to <35 kg	4 tablets	480/80 mg	BID	6:1

Table 4: DRV/r dosing for the DRV/r 120/20 mg tablet in children once daily per WHO weight bands

Weight Band	DRV/r 120/20 mg tablets	DRV/r Dose	Freq	DRV/r ratio
10 to < 14 kg	4 tablets	480/80 mg	OD	6:1
14 to <20 kg	5 tablets	600/100 mg	OD	6:1
20 to <25 kg	5 tablets	600/100 mg	OD	6:1
25 to <35 kg	5 tablets	600/100 mg	OD	6:1

Requirements to ensure appropriate use of the medicine(s)

HIV infection can be diagnosed with relatively simple, point-of-care, rapid testing kits or in clinic or hospital laboratories. The WHO recommends treatment for all patients diagnosed with HIV infection regardless of age, clinical stage, or laboratory parameters. While receiving pDRV/r as part of an antiretroviral therapy (ART) regimen, patients should be monitored for treatment failure according to national guidelines. However, specialized testing is not required for patient diagnosis or management while receiving pDRV/r therapy. HIV requires life-long treatment. Administration of pDRV/r requires no specialized treatment facility or healthcare provider training other than routine pediatric HIV treatment guidelines training.

DRV absorption is increased by concomitant food intake. For this reason, it is recommended that pDRV/r always be taken with food to achieve optimal drug concentrations.[19]

8. Review of evidence for benefits and harms

Summary of available evidence for comparative effectiveness and comparative safety

DRV was first approved by the U.S. Food and Drug Administration for use in CLHIV in 2008 and was included in the 2015 WHO pediatric treatment guidelines; DRV/r was included in the WHO 2015 treatment guidelines as an alternative to existing second-line regimens (LPV/r and ATV/r) for adults and adolescents. All of the boosted PIs are taken in combination with other ARVs, either two NRTIs (either ABC, zidovudine (AZT), or tenofovir disoproxil fumarate (TDF) plus lamivudine (3TC) or emtricitabine (FTC) usually administered as an FDC) or DRV/r can be

given with DTG. The WHO also recommends DRV/r as a third-line regimen for adults and adolescents, as well as for pediatric patients over the age of 3 years after failure on LPV/r, ATV/r, integrase strand transfer inhibitor (INSTI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) based second-line regimens.[1] Because of adverse findings in a nonclinical juvenile toxicology study, DRV (either boosted or unboosted) is not recommended for use in CLHIV younger than 3 years of age.[19] Because RTV is being used at low dose as a pharmacokinetic booster of the DRV and is not being used in therapeutic doses, this efficacy and safety review will focus on the DRV active component. Other than the first innovator studies conducted in adults, all studies evaluating DRV used a RTV-boosted DRV regimen.

The data supporting inclusion of DRV/r in the WHO treatment guidelines come from clinical trials conducted in diverse patient populations. As with most pediatric ARVs, the controlled clinical trial data supporting antiviral efficacy is primarily derived from the larger, comparative adult studies. In a multi-national, Phase 3 trial of first-line treatment in adults (Study TMC 114-C211, ARTEMIS), 70% of patients receiving DRV/r (800 mg/100 mg once daily) in combination with FTC/TDF achieved and maintained viral suppression through 192 weeks compared to only 61% of those receiving LPV/r (800 mg/200 mg once daily) plus FTC/TDF according to the FDA analysis.[19] Only 5% of the DRV/r patients discontinued ARVs due to an adverse reaction or death compared to 13% of those receiving LPV/r.[20] In addition, among adult patients failing other ARVs (Study TMC114-C214, TITAN), 58% randomized to DRV/r (600 mg/100 mg twice daily) combined with optimized background NRTIs achieved viral suppression compared to 52% randomized to LPV/r (400 mg/100 mg twice daily) with optimized background after 96 weeks. When given in the twice daily regimen, the safety profiles of the two boosted PI regimens was similar.[21] Finally, an open label comparison of the once daily and twice daily DRV/r regimens given with optimized background in treatment experieinced adults (TMC114-C229, ODIN) demonstrated similar efficacy of the regimens through 48 weeks. In the ODIN trial the once daily regimen was associated with slightly lower incidence of abnormal triglycerides among participants.[22]

Regulatory and normative bodies including the WHO (and its pediatric working groups), the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the International Council on Harmonization (ICH) have all accepted the concept of extrapolation of efficacy and safety of ARVs in pediatric patients based on bridging PK data.[23] Dosing for Prezista (Janssen) in pediatric patients was based on matching critical pharmacokinetic parameters and extrapolating efficacy from the larger, more diverse, comparative adult studies. The U.S. FDA package insert notes that dosing for once daily DRV/r was based on data collected in 12 to <18 year old adolescents and on population pharmacokinetic modeling and simulation for children 3 to < 12 years of age and was predicted to achieve similar darunavir exposures to the approved adult 800 mg/100 mg daily regimen.[19] Dosing for treatment-experienced children receiving second- or third-line ART was based on matching the approved adult 600 mg/100 mg twice daily regimen.

Clinical trials in pediatric patients are small but generally reflect the findings of the larger adult trials. The pediatric data used to support approval of the innovator product Prezista (Janssen) is comprised of three clinical trials enrolling both treatment experienced and treatment naïve CLHIV from 3 to 18 years of age and designed to demonstrate that pharmacokinetic targets were achieved. DRV plus RTV twice-daily was studied in two trials of treatment-experienced children: Study TMC114-C212 (DELPHI)[24] in children 6 to <18 years of age (N=80) and Study TMC114-C228 (ARIEL)[25] (N=21) in children 3 to <6 years of age (and 10 kg to 20 kg). Among the 6 to <18 year olds, 77 out of 80 children (96%) completed the 24-week study period and only one patient discontinued treatment due to an adverse event. The proportion of children with HIV ribonucleic acid (RNA) <400 copies/mL and <50 copies/mL was 64% and 50%, respectively and the mean increase in CD4+ cell count from baseline was 117 cells/mm^3. The study description for TMC114-C212 notes that of the 44 children who initially received RTV oral solution as part of their DRV/r regimen, 23 switched to the 100 mg capsule formulation, often exceeding the recommended weight-based

RTV dose without observed safety issues. Among 3 to <6 year olds, 20 out of 21 children (95%) completed the 48-week study period and only one subject prematurely discontinued treatment due to vomiting assessed as related to RTV. The proportion of subjects with HIV RNA <50 copies/mL at Week 48 was 71%, the mean increase in CD4+ percentage was 4%, and the mean change in CD4+ cell count was 187 cells/mm^3. Another pediatric trial (TMC114-C230, DIONE),[26] conducted in treatment naïve adolescents 12 to 18 years of age weighing at least 40 kg, evaluated the adult once-daily (QD) dose (800/100 mg DRV/r) with excellent results; 83% achieved HIV RNA <50 copies/mL at 48 weeks with none of the 12 patients discontinuing treatment.[19, 26]

In the twice-daily dosing studies among CLHIV 3 to less than 18 years of age and weighing at least 10 kg, the adverse event profile was similar to that observed in adults. Frequency, type, and severity of adverse drug reactions in CLHIV receiving once daily DRV/r were comparable to those observed in the analogous adult population. The most common adverse events observed were diarrhea, abdominal pain, and nausea. Laboratory abnormalities included elevated cholesterol, triglycerides, and liver transaminases.[19] As described in the U.S. FDA package insert for Prezista, darunavir is not indicated for children younger than 3 years of age. The label notes the following: "In a juvenile toxicity study where rats were directly dosed with darunavir (up to 1000 mg/kg), deaths occurred from post-natal day 5 at plasma exposure levels ranging from 0.1 to 1.0 of the human exposure levels. In a 4-week rat toxicology study, when dosing was initiated on post-natal day 23 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) 2 times the human plasma exposure levels."[19]

In addition to the Janssen-sponsored innovator pediatric trials described above, a number of other publications highlight the importance and feasibility of using DRV/r in CLHIV in LMIC. Among the largest and most impactful has been the New Horizon Collaborative, sponsored by Janssen and coordinated by Elizabeth Glaser Pediatric AIDS Foundation (EGPAF). New Horizons supports care and treatment of children and young adults who have drug-resistant HIV and provides donated DRV and etravirine (an NNRTI also used in some treatment-experienced patients) in 11 countries across sub-Saharan Africa. To date, New Horizons has enrolled over 1400 children, adolescents and young adults to receive optimized second- and third-line ART with 78% of those on donated third-line therapy achieving viral suppression.[27] Tukei et al published follow-up outcomes data on a cohort of 871 of these New Horizons patients receiving DRV-based third line ART from nine sub-Saharan African countries (0.2 to 24.7 years of age, median 14.8 years). Of the 809 participants who had a final outcome reported, 711 were alive and still in care at the end of the study follow-up, 30 transferred to another facility, 29 had died, and 39 were lost to follow-up, and 81% of those with viral load results at the end of study had viral suppression.[28] The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) Study Group reported on the safety of DRV and atazanavir (ATZ) in their cohort of CLHIV in Europe and Thailand. In this cohort 431 children received DRV and 372 received ATZ. Rates of Grade 3 or higher laboratory abnormalities were very low in both groups ($\leq$ 3/100 person years) except for elevated bilirubin in the ATZ group. Of interest, 18% of the cohort received their ARV at an age not approved for the drug and 9% received a dose not approved. Three of the children receiving DRV had serious-drug related clinical adverse events that led to discontinuation. At the time of last follow-up, 89% of those receiving DRV remained on the drug.[29] A slightly different approach was evaluated in the Penta SMILE study conducted internationally, enrolling virologically suppressed children 6 to 18 years of age to either continue their standard of care 3-drug regimen or switch to a regimen of once daily INSTI plus DRV/r, almost all DRT plus DRV/r. At the 48 week primary endpoint, 8 participants in the INSTI/DRV/r arm had confirmed HIV RNA > 50 copies/mL compared to 12 in the SOC arm leading the authors to conclude that the NRTI-sparing INSTI/DRV/r regimen was non-inferior to SOC.[30]

Published descriptions of multiple other smaller retrospective or cohort studies attest to the safety and efficacy of DRV/r-containing regimens, mostly as third-line ART or in CLHIV with known or suspected multi-drug resistance.[31, 32, 33, 34] even in the absence of appropriate formulations.[35] Some publications describe an improvement in serum lipids when CLHIV were switched from LPV/r or other older PIs to a DRV/r-based regimen.[36, 37] Overall, DRV/r-based

regimens appear to be well-tolerated and effective in pediatric populations who have failed NNRTI (efavirenz or nevirapine) or PI (LPV/r) based regimens and are expected to be effective in those who may fail INSTI (DTG or raltegravir) based regimens.

Search strategy and selection criteria

Clinical evidence of effectiveness in children is based on information gathered from literature search, review of WHO treatment guidelines and briefing documents, and additionally supported by review of the U.S. FDA package insert for Prezista suspension and tablets for oral use (Janssen Pharmaceuticals).

PubMed search criteria "(darunavir) AND (children)" and "(darunavir) AND (review) AND (children)" were used to identify additional relevant information, including meta-analyses or systematic reviews of darunavir use in CLHIV. No self-described "meta-analysis" or "systematic review" publications were found. However, the WHO commissioned a "scoping review" published in 2017 to inform their revision of guidelines for second- and third-line ART for children failing therapy. This scoping review is described in Section 9 below. Similar Google search criteria gave similar results.

Assessment of applicability of the available evidence across diverse populations and settings

Both the adult and pediatric clinical trials of boosted DRV have been conducted in international settings. No concerns regarding safety or efficacy in any subgroup or population have been identified. There is no evidence suggesting that the FDC is less effective or less safe in any identifiable sub-group or population than the two individual products.

9. Summary of recommendations in current clinical guidelines

Recommendations in existing WHO guidelines

In 2017, a comprehensive systematic search and scoping review commissioned by the WHO was published. This review found only 18 studies involving 1063 children and adolescents that provided virologic and safety outcome data of various ART regimens used in children receiving second- or third-line treatment. None of the studies identified were randomized, controlled trials comparing the then-recommended second- and third-line ART regimens to newer regimens WHO considered potentially useful; five of the 18 studies reported on use of DRV. The authors of this review considered the quality of evidence to support second- and third-line ART recommendations low but noted that there are many factors that might decrease the likelihood of high quality studies being conducted in the pediatric population.[38]

The 2nd Paediatric Antiretroviral Drug Optimization (PADO-2) meeting was the first to recommend the use of DRV/r as second- or third-line ART to the WHO guidelines group in its report in 2015[2] and subsequent PADO reports have continued to prioritize the pDRV/r 120 mg/20 mg tablet. As of the most recent WHO consolidated HIV treatment guidelines published in 2021, DRV/r was noted to be an alternative drug for second-line ART and a preferred drug for third-line ART in children (older than 3 years of age) and adolescents, as noted in Tables 5 and 6 below.[1]

Table 5: Preferred and alternative second-line ART regimens for adults, adolescents, children and infants

Population	Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimens
Adults and adolescents[a]	TDF[b] + 3TC (or FTC) + DTG[c]	AZT+ 3TC + ATV/r (or LPV/r)	AZT + 3TC + DRV/r[d]
	TDF + 3TC (or FTC) + EFV (or NVP)	AZT +3TC + DTG[c]	AZT + 3TC + ATV/r (or LPV/r or DRV/r)[d]
	AZT + 3TC +EFV (or NVP)	TDF[b] + 3TC (or FTC) + DTG[c]	TDF[b] + 3TC (or FTC) + ATV/r (or LPV/r or DRV/r)[d]
Children and infants	ABC + 3TC + DTG[e]	AZT+ 3TC + LPV/r (or ATV/ rf)	AZT +3TC + DRV/r[g]
	ABC (or AZT) +3TC + LPV/r	AZT (or ABC) + 3TC + DTG[e]	AZT (or ABC) +3TC + RAL
	ABC (or AZT) + 3TC + EFV	AZT (or ABC) + 3TC + DTG[e]	AZT (or ABC) +3TC + LPV/r (or ATV/r[f])
	AZT + 3TC + NVP	ABC + 3TC + DTG[e]	ABC + 3TC + LPV/r (or ATV/r[f])

[a] Sequencing if a PI is used in first-line ART: TDF + 3TC (or FTC) + ATV/r (or LPV/r, or DRV/r, depending on programmatic considerations) in first-line ART should be sequenced to AZT + 3TC + DTG in second-line ART.

[b] See Box 4.3.

[c] TAF can be used as an alternative NRTI for children and in special situations for adults (see section on TAF in first-line ART).

[d] RAL + LPV/r can be used as an alternative second-line regimen for adults and adolescents.

[e] As of July 2021, the United States Food and Drug Administration and the European Medicines Agency have approved DTG for infants and children older than four weeks and weighing at least 3 kg.

[f] ATV/r can be used as an alternative to LPV/r for children older than three months, but the limited availability of suitable formulations for children younger than six years, the lack of a fixed-dose formulation and the need for separate administration of the RTV booster should be considered when choosing this regimen.

[g] DRV/r should not be used for children younger than three years and should be combined with appropriate dosing of RTV (see the annexes).

Source: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. 2021.

Table 6: Summary of sequencing options for first-line, second-line and third-line ART regimens and preferred and alternative first-line regimens for adults, adolescents and children

Populations	First-line regimen	Second-line regimen	Third-line regimen
Adults and adolescents	Two NRTIs + DTG	Two NRTIs + ATV/r (or LPV/r)	DRV/r[a] + 1–2 NRTIs ± DTG[b] Optimize the regimen using a genotype profile (if LPV is used in second-line ART)
		Two NRTIs + DRV/r	Optimize the regimen using a genotype profile
	Two NRTIs + EFV	Two NRTIs + DTG	Two NRTIs + (ATV/r, DRV/r or LPV/r) ± DTG[b]
Children	Two NRTIs + DTG	Two NRTIs + LPV/r (or ATV/r[c])	DRV/r[a,d] + 1–2 NRTIs ± DTG[b,e] Optimize the regimen using a genotype profile for children younger than three years
	Two NRTIs + LPV/r	Two NRTIs + DTG	DRV/r[a,d] + 1–2 NRTIs ± DTG[b,e] Optimize the regimen using a genotype profile for children younger than three years
	Two NRTIs + NNRTI	Two NRTIs + DTG	Two NRTIs + (ATV/r, LPV/r or DRV/r[d]) ± DTG[e]

[a] 600/100 mg twice daily.
[b] 50 mg twice daily.
[c] Boosted PI.
[d] DRV cannot be used for children younger than three years.
[e] For age and weight groups with approved DTG dosing (<20 kg).

Source: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. 2021.

Recommendations in other current clinical guidelines

Current U.S. DHHS treatment guidelines recommend the use of genotype-directed optimized ART following confirmed virologic failure with resistance, but generally recommend use of potent boosted PI-based regimens, such as DRV/r, as preferred or alternative second-line therapy, depending on what ARVs were used initially.[17]

10. Summary of available data on comparative cost and cost-effectiveness

The new, fixed-dose combination of pDRV/r 120/20mg does not yet have a public price as it is currently under review by the U.S. FDA under the PEPFAR program (see Section 11).[39] However, CHAI and Unitaid are working to negotiate a price with Laurus Labs as part of a drug development incentive program.[40]

There is no generic license for darunavir, but the innovator Janssen has announced that they will not enforce patents on darunavir for sale in sub-Saharan Africa and Least-Developed Countries.[41] Janssen, with implementer EGPAF, runs an access program which currently provides donated pediatric DRV 75mg and 150mg tablets to 10 countries in sub-Saharan Africa. However, this access program has limited reach and a relatively narrow eligibility criteria for patients (only second- and third-line) and is scheduled to end in 2025.

Pricing per pack for existing separate pediatric DRV and RTV formulations, as well as LPV/r, can be found in the below table. Total annual treatment costs vary by weight band, prior protease inhibitor (PI) exposure, and potential resistance. It is anticipated that the fixed-dose combination of pDRV/r from Laurus Labs will be less expensive than the separate DRV and RTV products, in addition to the added benefits that a fixed-dose combination will bring (e.g., simplification of supply chain and administration, potentially improved adherence).

Table 7: Per Pack Cost of Pediatric LPV/r, DRV, and RTV Products (USD, EXW)

Products	Per Pack Price	Est. PPPY Price (14-19.9kg)
DRV 75mg tablets – 480-count packs	$65.00[1]	$455.00
DRV 150mg tablets – 240-count packs	$54.54[2]	$382.00
RTV 25mg tablets – 30-count packs	$3.00[1]	Depends on PI
RTV 100mg tablets – 30-count packs	$7.00[1]	Depends on PI
LPV/r 100/25mg tablets – 60-count packs	$5.50[1]	$132.00
LPV/r 40/10mg granules – 120-count packs	$16.90[1]	$507.00
LPV/r 40/10mg pellets – 120-count packs	$17.25[1]	$517.50

1. Global Fund PPM Reference Price List, August 2024
2. GHSC-PSM e-Catalog, May 2024

Potentially eligible users include all children living with HIV within sub-Saharan Africa and Least Developed Countries (per Janssen's patent requirements). It is anticipated that pDRV/r 120/20mg tablets can be used in children who are PI-naïve as well as those with some prior PI experience and/or resistance. The ultimate indications and dosing recommendations, as well as eligible ages and weight bands, will be available after U.S. FDA tentative approval is completed. It is also expected that many countries will procure pDRV/r for treatment-experienced CLHIV. As of early 2024, 22 LMICs were procuring or planning to procure DRV/r 400mg/50 mg for their adult and adolescent patients failing first- or second-line ART.[39]

Cost Effectiveness Analyses

DRV use in LMICs, especially among children, has been extremely limited to date and largely only used in third-line salvage therapy or via the New Horizon's donation program. A literature search of Google Scholar ("darunavir" AND "child" AND "cost") found no cost-effectiveness studies done for darunavir in children in LMICs. There are some that have been done in high-income countries, but the findings don't translate given the vast differences in drug costs between settings.

11. Regulatory status, market availability and pharmacopoeial standards

Regulatory status of the proposed medicine(s)

Janssen Therapeutics is the innovator for darunavir (Prezista®), acquiring the drug after Tibotec, Inc. first received U.S. FDA approval in 2006 for DRV tablets of various strengths, and then approval in 2011 for DRV oral suspension for children. Janssen has also received WHO prequalification (PQ) for DRV 75 mg, 150 mg, and 600 mg tablets, and received a positive opinion from the European Medicines Agency in 2006.

Multiple generic manufacturers have also received U.S. FDA tentative or full approval and WHO PQ for DRV tablets of various strengths. Suppliers with U.S. FDA full or tentative approval for DRV 75 mg include Mylan/Viatris, Cipla Limited, and Zydus Lifesciences. Suppliers with U.S. FDA full or tentative approval for DRV 150 mg include Micro Labs, Hetero Labs, Teva Pharms, Mylan/Viatris, Cipla Limited, and Zydus Lifesciences. DRV 75 mg and 150 mg are generally considered "pediatric" strengths, whereas 400 mg, 600 mg, and 800 mg are generally considered "adult" strengths.

Abbvie/Abbott is the innovator of RTV (Norvir®), which is a PI and CYP3A4 boosting agent for use with other PIs such as DRV. RTV was first approved in 1996 by the U.S. FDA in 100 mg capsule and 80 mg/ml oral solution formulations. The most common presentation of RTV is in 100 mg tablets or capsules (manufacturers with U.S. FDA approval or tentative approval: Abbvie, Cipla, Mylan, Hetero, Hikma, Aurobindo, and Amneal; manufacturers with WHO PQ: Abbvie, Cipla, Mylan, Hetero, Shanghai Desano). However, lower dose RTV versions are preferred for pediatric patients to expand dosing down to lower weight bands. Cipla has U.S. FDA tentative approval for RTV 25 mg and 50 mg tablets, and WHO PQ for 25 mg tablets. Mylan has WHO PQ for RTV 25mg tablets. There is also a Norvir 100 mg powder available from Abbvie (U.S. FDA approval), but uptake has been very limited given a high price and complex administration process.

Market availability of the proposed medicine(s)

Despite multiple generic manufacturers with U.S. FDA tentative approval and/or WHO PQ, none are currently supplying DRV 75 mg or DRV 150 mg (the more common pediatric formulations) to public sector buyers in LMICs. Country programs must purchase DRV 75 mg or 150 mg from Janssen unless they receive donated product as part of the EGPAF-led New Horizons Collaborative (limited to second- or third-line use in 11 countries in sub-Saharan Africa). The innovator products can be expensive to procure and occasionally difficult to source, and the restrictions placed on donations via the New Horizons Program limit the general availability of darunavir-based products for children in LMIC.

There is no generic license for DRV, but the innovator Janssen has indicated that they will not enforce patents on DRV for sale in sub-Saharan Africa and Least-Developed Countries. RTV is off-patent at this time.

As noted above, CHAI and Unitaid have led an incentive program with Laurus Labs to accelerate the development, commercialization, and registration of DRV/r 120/20mg tablets. Laurus Labs filed their product dossier with the U.S. FDA in June 2024 and the product was granted a priority review. If approved, Laurus Labs will work to register the product in priority, high-burden countries. Further information regarding review status of this product is expected in December 2024, and this application will be updated with any relevant new data as soon as possible following the review decision. It is anticipated that approval of this product will dramatically increase access to DRV-based treatment for children living with HIV in LMIC.

RTV is largely available in LMICs, both as a single product and co-formulated with PIs. However, at present, the only PI/r co-formulated products for children are LPV/r.

Pharmacopoeial standards

Darunavir is not yet listed in any of the widely used pharmacopoeias. However, there are currently draft proposals for inclusion for The International Pharmacopoeia for darunavir tablets, suspension, and active ingredient in the public comment phase of development prior to presentation to the Expert Committee on Specifications for Pharmaceutical Preparations (planned in October, 2024).

Ritonavir is listed in multiple pharmacopoeial standards, including the International Pharmacopoiea and the U.S. Pharmacopoeia.

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Annex 1: PQPPAT assessment for pDRV/r

Product Name: Darunavir/ritonavir 120 mg/20 mg (pDRV/r)				
EMLc Section(s): Antiretroviral drugs, fixed-dose combinations - 6.4.2.5				
Route of Administration: Oral				
Dosage Form: Tablet (immediate release)				
Evaluation for WHO EMLc paediatric population, 3 to 12 years.				
Attribute	**Result**	**Comparison to Target and Risk Assessment**	**Score**	**Additional considerations/information**
Target population (age)	2 - Suitable for most of the API indicated paediatric population	DRV is indicated for children older than 3 years of age who have failed previous ARV treatment. It is limited to those older than 3 years due to identified risk in juvenile animals (see product label for Prezista) and this formulation is intended only for children 3 years and older who can	2	
Dose and dose flexibility	3 - Able to easily measure and administer the required doses to all patients.	The strength and ratio of this formulation of pDRV/r were developed as part of a PAWG/PADO assessment and intended to cover age/weight bands from 3 to 12 years and 10 to 25 kg. The dose recommendations were developed in collaboration with PAWG/PADO and supported by modeling/simulation work completed by Penta clinical pharmacologists. Tablets do not need to be split to provide appropriate dosing.	3	
Patient acceptability: 0-5 years	2 - Some concerns re: acceptability in this age range, e.g., children 3-5 years of age must swallow tablets whole and will need to take 2-5 tablets depending on weight and treatment regimen.	This product is intended for children who have failed initial ARV therapy and therefore are expected to be somewhat older than those beginning therapy. Additionally, DRV is not recommended for children younger than 3 years of age. It is likely that some children between 3 years and 5	2	
Patient acceptability: 6-12 years	3 - Acceptable for this age range.	In general, it is anticipated that children 6 years of age and older should be able to swallow tablets, although it is possible that some may not be able to or may only be able to swallow very small tablets.	3	
Excipients safety	3 - Contains excipients which generally have an acceptable safety profile.	There are no novel excipients and none of known concern in the intended pediatric population.	3	
Administration considerations	3 - No manipulation or measurement required, children are dosed with 2-5 whole tablets once or twice daily depending on weight and treatmet history (domiciliary use).	These are standard oral tablets that are dosed according to weight bands. Tablets should not be split, chewed or crushed and no dispersing in liquid is required.	3	
Stability, storage conditions and primary packaging material	3 - May be stored under room temperature conditions. Minimum 2-year shelf life. Light packaging with low bulk footprint. Simple packaging design.	These are standard oral tablets that are stored at room temperature in standard pill bottles.	3	
Registration status	2 - Approval by Stringent Regulatory Authority anticipated. pDRV/r has been submitted to the U.S. FDA for review and is currently being considered for tentative approval under the PEPFAR program.	The FDA goal date for completion of this review is December 2024.	2	
Overall Conclusions				
It is our conclusion that the pDRV/r product is acceptable for use in the intended population (3-12 years of age and at least 10 kg), carries a low-risk and meets the target for a formulation to be deployed for this age/weight group and indication. While it is possible that some children 3-5 years of age may not be able to swallow the tablet, most children older than 5 years are expected to be able to swallow it. Given the poor palatability of RTV oral solution and granules/pellets in the same age groups, the tablet formulation is considered appropriate for this product.				

Risk Scores	**No or insufficient information**	0
	High risk/issues; does not meet target	1
	Moderate risk/issues; partially meets target	2
	Low risk/no issues; meets target	3
Date of review: 26 August 2024		
Prepared by: Linda L. Lewis, M.D., Clinton Health Access Initiative		

SUMMARY
pDRV/r 120 mg/20 mg has been prioritized by the WHO Paediatric Antiretroviral Drug Optimization (PADO) group since 2015 and this strength and ratio of darunavir (DRV) and ritonavir (/r, RTV) have been recommended by the WHO Paediatric Antiviral Working Group (PAWG) and included in the WHO consolidated HIV treatment guidelines. Because it is intended for children experiencing antiretroviral treatment failure and because DRV is not recommended in children younger than 3 years of age, the tablet formulation is considered appropriate and can be dosed across all relevant weight bands. Of note, RTV is extremely unpalateble and because of its chemical properties can not be formulated as a dispersible tablet formulation.