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MEDECINS SANS FRONTIERES

A.1 Abacavir/dolutegravir/lamivudine 60 mg/5 mg/30 mg, fixed-dose combination pediatric dispersible tablet

MSF strongly supports the proposal of the Clinton Health Access Initiative and the WHO Department of Global HIV, Viral Hepatitis and Sexually Transmitted Infections Programme for the inclusion of abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) 60 mg/5 mg/30 mg, fixed-dose combination (FDC) pediatric dispersible tablet on the Core List of the WHO Model List of Essential Medicines for Children for the treatment of HIV infection among children living with HIV/AIDS, aged at least 1 month and weighing at least 6 kg.

Currently, the dual FDC abacavir/lamivudine (120mg/60mg scored dispersible tablets), single products lamivudine (50mg/5ml solution) and dolutegravir (10 mg scored dispersible tablets) are included in both the WHO Model List of Essential Medicines (EML) and the WHO Model List of Essential Medicines for Children (EMLc).

In "The urgency of now: AIDS at a crossroads, 2024"(1), UNAIDS states that in 2023, an estimated 120 000 children acquired HIV, bringing the total number of children aged 0–14 years living with HIV globally to 1.4 million, with 43% (over 580,000) unable to access life-saving antiretroviral therapy (ART), far below the UNAIDS 95-95-95 target seeking to ensure that by 2030: 95% of people living with HIV know their status, 95% of diagnosed individuals receive sustained antiretroviral therapy, and 95% of patients on ART achieve viral suppression. Sub-Saharan Africa bears the greatest burden, home to 86% of children under 15 living with HIV. Without timely treatment, one-third of HIV-positive infants die before their first birthday, and half die by the age of two**,** highlighting the urgent need for early diagnosis and ART. While 67% of HIV-exposed infants received diagnostic testing within two months of birth in 2023, only 29% of children on ART were under five years old, reflecting delays between diagnosis and treatment. This fact contrasts with international guidelines recommending immediate ART initiation for all children under five years old upon diagnosis. Treatment coverage disparities between adults and children remain important, with 57% of children receiving ART compared to 77% of adults in 2023. Although pediatric ART coverage tripled from 2010 to 2020 (16% to 54%), progress stalled post-2015, with AIDS-related child deaths declining at slower rates after 2015 "Treat All" WHO policies took effect. The consequences of these gaps are evident in mortality trends: children account for 12% of AIDS-related deaths despite comprising just 3% of people living with HIV**.** In 2023, 76 000 children aged 0–14 years died due to AIDS.

In 2017, MSF strongly supported the application from the WHO HIV/AIDS department for the inclusion of dolutegravir 50 mg tablet in the EML and the inclusion of the fixed-dose combination abacavir/lamivudine, dispersible, scored tablet (120 mg/60 mg) in both the EML and EMLc.
In 2019, MSF strongly supported the application from the WHO HIV/AIDS department for the inclusion of dolutegravir 50 mg tablet in the EMLc.

In 2021 MSF strongly supported the application from the WHO Department of Global HIV, Viral Hepatitis and Sexually Transmitted Infections Programmes for the inclusion of dolutegravir 10 mg scored dispersible tablet in the EMLc.

According to 2021 WHO "Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach" (2), "since 2015, WHO has recommended initiating ART for all children with HIV. As ART is expanded to all children regardless of clinical and immune status, all children younger than five years are considered to have advanced HIV disease and should be given priority for treatment because of their higher risk of death and rapid disease progression".

Dolutegravir, an integrase strand transfer inhibitor (INSTI) combined with abacavir and lamivudine, two nucleoside reverse transcriptase inhibitors (NRTIs) as dual nucleoside backbone, is recommended as the preferred first-line regimen for people living with HIV initiating ART, for infants and children with approved DTG dosing.

DTG in combination with 2NRTIs is also the preferred second-line regimen for all children for whom an approved DTG dosing is available. As of July 2021, the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) have approved DTG for infants and children older than four weeks and weighing at least 3 kg.

During the Paediatric Antiretroviral Drug Optimization (PADO) Meeting 4, in December 2018 (3), ABC/DTG/3TC 60 mg/5 mg/30 mg was identified to be the most needed FDC formulation for children for the medium term, with darunavir/ritonavir 120/20 mg identified as the most important boosted protease inhibitor formulation and they were both included in the PADO 4 medium-term priority list (3–5 years).

In March 2022, the US FDA approved ViiV Healthcare's ABC/DTG/3TC 60 mg/5 mg/30 mg, pediatric FDC dispersible tablet for children living with HIV, weighing 10 kg to < 25 kg.
In June 2023, the US FDA extended the indication to infants aged at least 3 months and weighing at least 6 kg. However, it was expected that separate pediatric abacavir/lamivudine and pediatric dolutegravir will still be used for children in the 3 to 5.9 kg weight band. Generic formulations of ABC/DTG/3TC dispersible tablet obtained US tentative approval in August 2023.

MSF would like to draw the attention of the Expert Committee to the following points:

- ABC/DTG/3TC 60 mg/5 mg/30 mg FDC will be the only one in the EML representing an age-appropriate FDC combining one INSTI and two NRTIS allowing a complete first-line ART regimen.
- The inclusion of this pediatric dispersible FDC incorporating the entire regimen in a child-friendly, easy-to-administer, palatable, dispersible tablet will provide oral suspension to children from 1 month of age and weighing at least 6 kg, across all age groups and weight bands. This inclusion will help to implement more widely the DTG-based regimens for all children on first line treatment and will enhance adherence to treatment, in order to improve outcomes and reduce mortality for the infants and children living with HIV.
- The inclusion of this pediatric dispersible FDC will significantly simplify supply chain management for country programs (reduced storage, easier transportation and

distribution) and reduce overall cost of shipping and storage. Countries should be encouraged to make the transition from the two separate products to the FDC as a first-line paediatric-friendly ARV treatment.

- The inclusion of this pediatric dispersible FDC will serve as a basis for National Essential Medicines lists and therefore will facilitate importations, alert manufacturers about the need for local registrations, and will increase interest for pediatrics formulations.
- The efforts of the Medicines Patent Pool in negotiating with pharmaceutical companies to make generic formulations widely available have ensured that millions of people in low- and middle-income countries have access to affordable HIV treatment, with generic DTG-based treatments having been rolled out in 128 countries so far.
- Recently, the WHO Paediatric Antiretroviral Working Group have endorsed dose recommendations for all children aged at least 4 weeks and weighing at least 3 kg, based on a 2023 modeling data concluding that "predicted exposures with single FDC ABC/DTG/3TC in infants weighing ≥3 to <6 kg (aged ≥4 weeks) were above the targets and expected to provide comparable efficacy observed in pediatrics and adults and the available safety data suggest a positive benefit-risk balance for use of single ABC/DTG/3TC FDC dispersible tablet in the ≥3 to <6 kg weight band, and from 4 weeks of age." Clinical trials in the future will provide critical data to confirm these pharmacokinetic modeling predictions.
- Previously, all products listed in the EMLc were also listed in the EML: if this logic is maintained, ABC/DTG/3TC 60 mg/5 mg/30 mg FDC pediatric dispersible tablet should also be included in the EML.

MSF has included dolutegravir 50 mg as a standard medicine in its list in 2016, dolutegravir 10 mg for children in 2021, abacavir/lamivudine (120 mg / 60 mg) for children in 2010 and abacavir/dolutegravir/lamivudine 60 mg/5 mg/30 mg, pediatric dispersible tablet as soon as it has been available (2024).

At the end of 2023, in collaboration with Health Authorities in 16 countries, MSF treated 45,000 people living with HIV/AIDS, with antiretroviral treatment.

Considering all these elements, MSF urges the 25th Expert Committee on the Selection and Use of Essential Medicines to include abacavir/dolutegravir/lamivudine 60 mg/5 mg/30 mg, fixed-dose combination pediatric dispersible tablet in the WHO Model List of Essential Medicines for Children and therefore in the WHO Model List of Essential Medicines, for the treatment of HIV infection among children living with HIV/AIDS.

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2.Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach.World Health Organization (2021). https://www.who.int/publications/i/item/9789240031593

3.WHO Paediatric Antiretroviral Drug Optimization (PADO) Meeting 4, 10–12 December 2018, Geneva, Switzerland, Meeting report.