Abacavir (ABC)

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Formulations

Pediatric Oral Solution: 20 mg/mL

Tablet: 300 mg (scored)

Generic Formulations

- 300 mg tablet
- 20 mg/mL pediatric oral solution

Fixed-Dose Combination (FDC) Tablets

- [Generic] Abacavir 600 mg/lamivudine 300 mg
- [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg
- [Triumeq PD] Abacavir 60 mg/dolutegravir 5 mg/lamivudine 30 mg

When using FDC tablets, refer to other sections of Appendix A: Pediatric Antiretroviral Drug Information for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Neonate (Aged Birth Through <1 Month) Dose

Oral Solution

- Abacavir (ABC) is not approved by the U.S. Food and Drug Administration (FDA) for use in infants aged <3 months.
- However, the Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV (the Panel) recommends ABC 2 mg/kg twice daily for full-term infants from birth through <1 month of age. This recommendation is based on data from pharmacokinetic (PK) modeling of neonatal ABC dosing to target adult plasma ABC exposures and observational data supporting safety of ABC in neonates. The World Health Organization Optimal Antiretroviral Dosing Guidance provides weight-band dosing recommendations for full-term neonates based on the same data. See the Approval, Pharmacokinetics in Neonates and Infants, and Safety in Neonates and Infants sections below.

Infant (Aged ≥1 Month to <3 Months) Dose

Oral Solution

- ABC is not approved by the FDA for use in infants aged <3 months.

Selected Adverse Events

- Hypersensitivity reactions (HSRs) can be fatal. HSRs usually occur during the first few weeks of therapy. Symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, and respiratory symptoms (e.g., cough, shortness of breath).

Special Instructions

- To predict the risk of HSRs, test patients for the HLA-B*5701 allele before starting therapy. Patients who test positive for the HLA-B*5701 allele should not be given ABC. Patients with no prior HLA-B*5701 testing who are tolerating ABC do not need to be tested.
- Warn patients and caregivers about the risk of serious, potentially fatal HSRs. Occurrence of an HSR requires **immediate and permanent discontinuation of ABC. Do not rechallenge.**
- ABC and coformulated tablets can be given with or without food. The oral solution does not require refrigeration.

- The Panel recommends ABC 4 mg/kg twice daily in full-term infants aged ≥1 month to <3 months. This recommendation is based on modeling data of the ABC 4 mg/kg twice-daily dose using PK simulation for full-term infants aged ≥1 month to <3 months. The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1106 study and two observational cohorts provided reassuring data on the safety of ABC in infants with HIV aged <3 months. See the Approval, Pharmacokinetics in Neonates and Infants, and Safety in Neonates and Infants sections below.

Infant and Child (Aged ≥3 Months) Dose

Oral Solution

- ABC 8 mg/kg twice daily (maximum 300 mg per dose) or ABC 16 mg/kg once daily (maximum 600 mg per dose)
- In infants and young children who are being treated with liquid formulations of ABC, initiation with once-daily ABC generally is not recommended. The ABC dose can be changed from twice daily to once daily with the liquid formulation to harmonize with other antiretroviral drugs administered once daily.

Weight-Band Dosing of ABC Tablets for Children and Adolescents Weighing ≥14 kg and <25 kg

Weight	Scored 300-mg ABC Tablet		
	Twice-Daily Dose, AM	Twice-Daily Dose, PM	Once-Daily Dose
14 kg to <20 kg	½ tablet (150 mg)	½ tablet (150 mg)	1 tablet (300 mg)
≥20 kg to <25 kg	½ tablet (150 mg)	1 tablet (300 mg)	1½ tablets (450 mg)

Child and Adolescent (Weighing ≥25 kg) and Adult Dose

- ABC 300 mg twice daily or ABC 600 mg once daily

Abacavir/Lamivudine

Child and Adolescent (Weighing ≥25 kg) and Adult Dose

- One tablet once daily

[Triumeq PD] Abacavir/Dolutegravir (DTG)/Lamivudine (3TC)

Child Weighing ≥3 kg to <25 kg and Aged ≥1 Month

- Dispersible Triumeq PD tablets are FDA approved for children aged ≥3 months and weighing ≥6 kg to <25 kg. They are not recommended for children weighing ≥25 kg.
- Administer the appropriate number of tablets once daily, dispersed in 15–20 mL of water. See Special Instructions below. Triumeq PD tablets should not be swallowed whole, chewed, cut, or crushed.
- For ABC/DTG/3TC dispersible tablets, fully disperse them in 15–20 mL of drinking water in the supplied cup and swirl the suspension so that no lumps remain. After full dispersion and within 30 minutes of mixing, administer the oral suspension. Rinse the dosing cup with a small amount of water and give this additional water to the child to ensure that the child takes the full dose and that no medication remains in the dosing cup. ABC/DTG/3TC dispersible tablets should not be swallowed whole, chewed, cut, or crushed.
- Screen patients for hepatitis B virus (HBV) infection before using ABC FDC tablets that contain 3TC. Severe acute exacerbation of HBV infection can occur when 3TC is discontinued (see Lamivudine).

Metabolism/Elimination

- ABC is systemically metabolized by alcohol dehydrogenase and glucuronyl transferase.
- The majority of ABC is excreted as metabolites in urine.

Abacavir Dosing in Patients With Hepatic Impairment

- ABC requires dose adjustment in patients with mild hepatic insufficiency and is contraindicated with moderate or severe hepatic insufficiency.
- **Do not use** ABC/3TC, Triumeq PD, or Triumeq (or the generic equivalents of these FDC tablets) in patients with impaired hepatic function because the dose of ABC cannot be adjusted.

Abacavir Dosing in Patients With Renal Impairment

- ABC does not require dose adjustment in patients with renal impairment.
- **Do not use** FDC tablets containing 3TC (ABC/3TC, Triumeq PD, Triumeq, or the generic equivalents of these FDC tablets) in patients with creatinine clearance (CrCl) <30 mL/min or patients on dialysis, because the doses of 3TC cannot be adjusted. Data from FDC DTG/3TC (Dovato) suggest that patients with a sustained CrCl of 30–49 mL/min may experience a higher 3TC exposure and should be monitored for hematologic toxicities and potential FDC discontinuation and subsequent adjustment

- Population PK modeling supports the use of a single Triumeq PD tablet once daily in infants weighing ≥3 kg to <6 kg and aged ≥4 weeks.

Weight-Band Dosing of Triumeq PD Tablets for Children Aged ≥1 Month and Weighing ≥3 kg

Weight	Recommended Daily Dose	Number of Triumeq PD Tablets	Volume of Water
3 kg to <6 kg[a]	ABC 60 mg DTG 5 mg 3TC 30 mg	1	5 mL
6 kg to <10 kg	ABC 180 mg DTG 15 mg 3TC 90 mg	3	15 mL
10 kg to <14 kg	ABC 240 mg DTG 20 mg 3TC 120 mg	4	20 mL
14 kg to <20 kg	ABC 300 mg DTG 25 mg 3TC 150 mg	5	20 mL
20 kg to <25 kg	ABC 360 mg DTG 30 mg 3TC 180 mg	6	20 mL

[a] This dosing is not currently approved by the FDA. ABC/DTG/3TC dispersible tablet dosing has only been approved for those weighing ≥6 kg and aged ≥3 months. However, this dosing is recommended by the Panel based on available PK modeling and simulation data.

- Use in children who are antiretroviral (ARV) naive or ARV experienced (but integrase strand transfer inhibitor [INSTI]–naive) and who are not being treated with uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) or cytochrome P450 (CYP) 3A inducers.

[Triumeq] Abacavir/Dolutegravir/Lamivudine

Child and Adolescent (Weighing ≥25 kg) and Adult Dose

- One tablet once daily
- This FDC tablet can be used in patients who are ARV naive or ARV experienced (but INSTI-naive) and who are not being treated with other drugs that act as UGT1A1 or CYP3A inducers.

of the treatment regimen. See package inserts for additional information.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- Abacavir (ABC) neither inhibits nor is metabolized by hepatic cytochrome P450 enzymes. Therefore, it does not cause significant changes in the clearance of agents, such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), that are metabolized through these pathways.
- ABC plasma concentrations can decrease when ABC is used concurrently with the ritonavir-boosted PIs atazanavir/ritonavir, lopinavir/ritonavir (LPV/r), and darunavir/ritonavir.[1-3] The mechanism and the clinical significance of the drug interactions with these PIs are unknown. Currently, no recommendations exist for dose adjustments when ABC is coadministered with one of these boosted PIs.
- In a pooled analysis of 230 African children with HIV with a median age of 2.1 years (range 0.1–12.8 years) and a median weight of 9.8 kg (range 2.5–30.0 kg), the population pharmacokinetics (PK) of ABC showed that children on boosted PI LPV/r or NNRTI efavirenz had similar ABC exposures, while concomitant tuberculosis treatment and use of superboosting with LPV significantly reduced ABC concentrations.[4]
- Alcohol exposure (0.7 g per kg ethanol, which is equivalent to five alcoholic drinks) interferes with ABC metabolism; it affects the activity of alcohol dehydrogenase and glucuronyl transferase. This interference increased ABC area under the curve plasma exposure by 41% in adult men with HIV who received ABC 600 mg daily.[5]
- ABC oral solution contains sorbitol, which decreased the exposure of lamivudine (3TC) oral solution in adults when the drugs were administered concurrently.[6] The clinical significance of this interaction is unknown.

Major Toxicities

- *More common:* Nausea, vomiting, fever, headache, diarrhea, rash, anorexia
- *Less common (more severe):* Serious and sometimes fatal hypersensitivity reactions (HSRs) have been observed in approximately 5% of adults and children (rate varies by race/ethnicity) receiving ABC. HSRs generally occur during the first 6 weeks of therapy, but they have also been reported after a single dose of ABC. The risk of an ABC HSR is associated with the presence of the HLA-B*5701 allele; the risk is greatly reduced by not using ABC in those who test positive for the HLA-B*5701 allele. The HSR to ABC is a multiorgan clinical syndrome usually characterized by rash, or signs or symptoms in two or more of the following groups:
    - Fever
    - Constitutional symptoms, including malaise, fatigue, or achiness
    - Gastrointestinal signs and symptoms, including nausea, vomiting, diarrhea, or abdominal pain
    - Respiratory signs and symptoms, including dyspnea, cough, or pharyngitis
    - Laboratory and radiologic abnormalities, including elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, lymphopenia, and pulmonary infiltrates. Lactic acidosis and severe hepatomegaly with steatosis—including fatal cases—also have been reported. Pancreatitis with laboratory abnormalities can occur.

    If an HSR is suspected, ABC **should be stopped immediately and not restarted because hypotension and death may occur upon rechallenge.**
- *Rare:* Increased levels of liver enzymes, elevated blood glucose levels, and elevated triglycerides (see information on cardiovascular risk under Safety in Children and Adolescents below). Pancreatitis, lactic acidosis, and severe hepatomegaly with steatosis—including fatal cases—have been reported.

- *Rare*: Drug reaction (or rash) with eosinophilia and systemic symptoms, or DRESS, syndrome.

Resistance

The International Antiviral Society–USA maintains a list of updated HIV drug resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

ABC is approved by the U.S. Food and Drug Administration (FDA) for use in children with HIV aged ≥3 months as part of the nucleoside reverse transcriptase inhibitor (NRTI) component of antiretroviral therapy (ART). The World Health Organization (WHO), however, provides dosing guidance for ABC as a component of the NRTI backbone for full-term neonates starting at birth and weighing ≥2 kg (see the WHO Optimal Antiretroviral Dosing Guidance). The WHO guidance for ABC dosing in neonates increases the choices of antiretroviral (ARV) agents for the management of newborns in special situations in which stock-outs of nevirapine or zidovudine (ZDV) may affect the ability to effectively provide postnatal prophylaxis or treatment of neonatal HIV. The WHO recommendation of ABC dosing for infants starting at 1 month of age is based on the inclusion of ABC as a preferred NRTI component of the first- and second-line ARV regimens for children in the WHO guidance. This recommendation also takes into account the availability of pediatric generic ABC formulations tentatively approved in the President's Emergency Plan for AIDS Relief (or PEPFAR)—including coformulations that include 3TC—and the cost of ARV drugs in resource-limited settings.

Efficacy

Both the once-daily and twice-daily doses of ABC have demonstrated durable antiviral efficacy in pediatric clinical trials, comparable to the efficacy observed for other NRTIs in children.[7-11] In an observational study of nine cohorts from the International epidemiology Databases to Evaluate AIDS Southern Africa (IeDEA-SA) collaboration, 6- and 12-month viral suppression rates (<400 copies/mL) were evaluated among infants who initiated ART at age <3 months and compared with viral suppression rates among infants aged <28 days and ≥28 days and weighing <3 kg and ≥3 kg at the time of ART initiation. Viral suppression at 12 months did not differ by age or weight at the time of ART initiation and was slightly lower in infants on ABC (174/329 [53%]) than in infants on ZDV (77/138 [56%]) (adjusted odds ratio 1.8; 95% confidence interval (CI), 1.0–3.2).[12] In the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) 2019 clinical trial of dispersible and immediate-release ABC/dolutegravir (DTG)/3TC tablets in children with HIV, 54 of 55 participants aged <12 years and weighing 6 kg to <40 kg who remained on the study drug through Week 48 had viral loads of <200 copies/mL; 45 of 55 participants (83%), including 2 of the 3 treatment-naive participants, had viral loads ≤50 copies/mL,.[13]

Pharmacokinetics

Pharmacokinetics in Neonates and Infants

The IMPAACT P1106 trial reported PK data in 25 infants aged <3 months with HIV who were initiated on a median ABC dose of 10 mg/kg (range 6–13 mg/kg) twice daily in combination with 3TC and LPV/r after 1 month of life. Median age was 6 weeks (range 1.5–11 weeks), median weight was 2,250 g (range 1,360–3,320 g), and median gestational age was 36 weeks (range 27–39 weeks). Sparse and pre-dose PK ABC samples were obtained repeatedly over the 24 weeks of study follow-

up. ABC plasma exposures were high compared with published data on infants aged >3 months and decreased rapidly between 2 and 8 months of age as the infants matured and ABC clearance increased.[14] In the Tygerberg cohort study from South Africa, 10 healthy term neonates at the median postnatal age of 10 days (range 6–15 days) who were administered a single ABC dose of 8 mg/kg before 15 days of life had substantially higher exposures than those observed in infants and children and no reported adverse events.[15] The higher ABC exposure levels in neonates compared with infants and children are likely due to slower drug clearance through immature enzyme pathways.

PK modeling of ABC starting at birth has been conducted using pooled data from 308 ABC concentration measurements obtained from three studies administering ABC liquid to 45 young infants (including 21 full-term neonates <15 days of age with intensive PK).[15] Two of these studies, the Pediatric AIDS Clinical Trials Group (PACTG) 321 study and the Tygerberg cohort, performed intensive PK sampling in full-term neonates receiving ABC for HIV prophylaxis. The third study, IMPAACT P1106, described above, performed sparse PK sampling on full-term and low birth weight (LBW; <2,500 g) infants with HIV. LBW infants were older at the first PK assessment, with a median postnatal age of 73 days (range 41–190 days) and weight of 3.8 kg (range 2.4–5.8 kg). ABC PK parameters in neonates were estimated using PK simulations to achieve plasma ABC exposures (area under the curve from time zero to 12 hours after drug administration; $AUC_{0–12}$) within the expected adult range (3.2–25.2 mcg•hr/mL). The PK model predicted a slow ABC clearance of 2.51 mL/min per kg at birth, which doubled by 4 weeks of age. Simulations predicted that an ABC dose of 2 mg/kg twice daily in full-term neonates from birth to <4 weeks and an ABC dose of 4 mg/kg twice daily in infants aged 4 to 12 weeks would achieve target $AUC_{0–12}$; however, data in LBW infants are lacking.[15] Based on these data, the weight-band dosing of ABC for neonates has been developed for neonates from birth to age <1 month and is included in the WHO Optimal Antiretroviral Dosing Guidance.[16] This weight-band dosing for neonates approximates the ABC dosing per kg based on the postnatal age (see Table 1 below).

Table 1. Simplified Weight-Band Dosing for Full-Term Neonates From Birth to <1 Month of Age (WHO Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery, and Monitoring, Annex 1: Table A1.4)

Birth to <1 Month of Age		
Weight	**Volume of ABC Oral Solution 20 mg/mL Twice Daily[a,b]**	**ABC Dose in mg Twice Daily** (ranges mg/kg, from lowest to highest weight within the weight band)[a,b]
2 kg to <3 kg	0.4 mL	8 mg (4.0–2.8 mg/kg)
3 kg to <4 kg	0.5 mL	10 mg (3.3–2.6 mg/kg)
4 kg to <5 kg	0.6 mL	12 mg (3.0–2.4 mg/kg)

[a] Simplified weight-band dosing exceeds recommended mg/kg ABC dosing in neonates and infants.

[b] Neonatal ABC dose is based on birth weight and does not require weight-based adjustment during the first month of life.

Key: ABC = abacavir

The PETITE trial, a recent open-label, two-stage, single-arm, Phase 1/2 PK and safety study, evaluated the generic fixed-dose combination (FDC) of ABC/3TC (120/60 mg) double-scored dispersible tablets and LPV/r (40/10 mg) granules in 24 neonates with HIV exposure (≥37 weeks' gestational age; birth weight 2,000–4,000 g) in South Africa.[17] Following a dose-finding cohort of 8 neonates, 16 neonates received an ABC/3TC dose of 30/15 mg once daily starting between 9 and 59 hours of life and continuing through 28 days of life. No PK data were collected among neonates younger than 6 days of age. As anticipated, geometric mean ABC and 3TC exposures (area under the curve from time zero to 24 hours after drug administration) were higher at 6 to 14 days (51.7 mg•h/L for ABC and 17.2 mg•h/L for 3TC) than at 19 to 24 days of age (25.0 mg•h/L for ABC and 11.3 mg•h/L for 3TC). High ABC and 3TC exposures during the first 2 weeks of life are likely due to the relatively high dose imposed by the currently available generic pediatric FDC (i.e., 10 mg/kg ABC and 5 mg/kg 3TC for a neonate weighing 3 kg). However, due to the rapid maturation of enzymes involved in ABC metabolism, exposures rapidly decreased to within target ranges without a safety signal.[18]

For infants aged ≥1 month with weight 3 kg to <6 kg, the WHO Optimal Antiretroviral Dosing Guidance currently recommend a twice-daily dose of 3 mL (60 mg) of ABC 20 mg/mL solution (range 10–20 mg/kg/dose). The weight-band dosing for infants with weight 3 kg to <6 kg within the WHO pediatric HIV guidelines is higher than the modeled weight-based dosing and is based on the practical considerations of the generic fixed-dose pediatric formulations available in resource-limited settings.[19] As new generic pediatric formulations of ABC become available in resource-limited settings, there is potential for the revision of the WHO guidelines for weight-band dosing of ABC for young infants.

Based on PK modeling from three infant studies[15] and neonatal and infant safety data from the IMPAACT 1106 study and two observational cohort studies (see Safety in Neonates and Infants below), the Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV recommends an ABC dose of 2 mg/kg twice daily for neonates from birth to <1 month of age and an ABC dose of 4 mg/kg twice daily for full-term infants aged ≥1 month and <3 months.

Pharmacokinetics in Children

PK studies of ABC in children aged <12 years have demonstrated that metabolic clearance of ABC in adolescents and young adults (aged 13–25 years) is slower than that observed in younger children and approximates clearance seen in older adults.[20]

The PKs of ABC administered once daily in children with HIV aged 3 months through 12 years were evaluated in three crossover open-label PK trials of twice-daily versus once-daily dosing of ABC and 3TC (PENTA 13 [n = 14], PENTA 15 [n = 18], and ARROW [n = 36]).[5,21-24] The data from these three pediatric trials were used to develop a model for ABC PKs. This model predicted that systemic plasma ABC exposure after once-daily dosing would be equivalent to the exposure seen after twice-daily dosing in infants and children aged ≤12 years.[21-25] Both the trials and PK modeling have demonstrated that once-daily dosing with either the tablet or the liquid formulation of ABC produces plasma exposures comparable to those seen with a twice-daily dosing schedule that uses the same total daily dose of ABC.[5]

Dosing

Dosing and Formulations

A total daily dose of ABC 600 mg can be used safely in a person weighing 25 kg.[5] Doses of the liquid ABC formulation are similar to those used for weight-band dosing with tablet formulations and should be considered for use in younger children who are unable to swallow a pill.[26]

In the three ABC dosing pediatric trials described above,[21-24] only children who had low viral loads and who were clinically stable on the twice-daily dose of ABC were eligible to change to once-daily ABC dosing. Efficacy data from a 48-week follow-up in the ARROW trial demonstrated clinical non-inferiority of once-daily ABC (n = 336) versus twice-daily ABC (n = 333) in tablet form combined with a once-daily or twice-daily 3TC-based ARV regimen.[11] To date, no clinical trials have been conducted involving children who initiated therapy with once-daily dosing of the ABC liquid formulation. In children who can be treated with pill formulations, initiating therapy with once-daily dosing of ABC at a dose of 16 mg/kg (with a maximum dose of ABC 600 mg) is recommended. However, twice-daily dosing is recommended for infants and young children who initiate therapy with the liquid formulation of ABC. Switching to once-daily dosing with the liquid formulation could be considered when harmonizing with other antiretroviral drugs administered once daily, such as 3TC and dolutegravir (DTG).

Recent data from the IMPAACT 2019 clinical trial of dispersible and immediate-release ABC/DTG/3TC tablets in children with HIV have validated the FDA-approved dosing in infants and children weighing 10 kg to <25 kg and have led to a newly proposed dosing of this FDC—three tablets once daily of ABC 60 mg, DTG 5 mg, and 3TC 30 mg dispersed in 15 to 20 mL of water—in infants aged ≥3 months weighing 6 kg to <10 kg.[5,13,27,28] ABC/DTG/3TC dispersible FDC dosing was developed based on PK and safety data in each weight band at the originally selected dosing, which aligned with WHO weight-band dosing for the individual ARV agents. In a population PK (popPK) model based on the IMPAACT 2019 results, ABC, DTG, and 3TC PK exposures following once-daily ABC/DTG/3TC (60 mg/5 mg/30 mg) dispersible tablet dosing were comparable to those observed in pediatrics and adults with single entities, supporting the extrapolation of adult efficacy data.[28] Follow-up through 24 and 48 weeks confirmed the overall safety, tolerability, and virological efficacy of both formulations.[13,29]

PopPK models of ABC, DTG, and 3TC were then further extended to evaluate whether a single ABC/DTG/3TC (60 mg/5 mg/30 mg) tablet in infants aged ≥4 weeks and weighing ≥3 kg to <6 kg could achieve drug exposures comparable to those observed in older children and adults based on

dosing simulations, thus providing comparable safety and efficacy. These models applied maturation functions to the DTG, ABC, and 3TC models and used data from young children across weight bands from the IMPAACT 2019 (≥6 kg), P1093 (≥3 kg), and ODYSSEY (≥3 kg) clinical trials for DTG and the PETITE clinical trial for ABC and 3TC.[28] ABC/3TC data from the PETITE study in neonates[15,18] and available ABC, 3TC, and DTG safety data in infants <3 months (see Safety in Neonates and Infants below) were used to interpolate safety for infants aged ≥4 weeks to <3 months and suggested no safety concerns for coadministration of ABC/3TC/DTG in young infants. Notably, doses in the safety evaluation mostly aligned with WHO weight-band dose recommendations for fixed-dose formulations of ABC/3TC 120 mg/60 mg, which were higher than the weight bands under evaluation in this modeling and simulation. Panel members agree that, based on these findings, the fixed-dose formulation of the single ABC/3TC/DTG dispersible tablet may be considered as an alternative to separate formulations of ABC, 3TC, and DTG in infants weighing ≥3 kg to <6 kg and aged ≥4 weeks to facilitate treatment adherence.

Toxicity

Safety in Neonates and Infants

Data from the PACTG 321, the IMPAACT P1106 trial, and two observational European and African cohorts provided reassuring data on the safety of ABC in infants when initiated at <3 months of age, including infants with weight <3 kg.[12,14,30] The IMPAACT P1106 trial reported 24 weeks of safety data in 27 infants in whom repeated dosing of ABC was initiated at the median age of 60 days. Fifteen infants (55.6%; 90% CI, 38.3–72.0) met the safety endpoint of death or a Grade 3 or higher adverse event (AE). None of the AEs were related to ABC, and none led to interruptions or adjustments of ABC dosing. No hypersensitivity reactions were reported with the multi-dose treatment.[14] In two cohorts of neonates (<1 month of age) who received a single ABC dose, ABC was well tolerated; all reported AEs in the PACTG 321 study were unrelated to ABC, and no AEs were reported in the Tygerberg cohort.[15]

The PETITE trial of generic FDC of ABC/3TC (120/60 mg) double-scored dispersible tablets and LPV/r (40/10 mg) granules in 24 neonates from South Africa reported no Grade 2 or worse AEs related to study drugs. One neonate had a Grade 1 prolonged corrected QT interval that spontaneously resolved.[18]

The European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) reported safety outcomes among 139 children from 13 cohorts in 11 countries in Europe who initiated ABC at age <3 months. By 12 months on ABC, 3.6% (n = 4) had discontinued ABC because of an ART safety concern, and 11.8% (n = 15) discontinued ABC for any reason.[30] Another observational study of nine cohorts from the IeDEA-SA collaboration compared safety outcomes (measured as ABC discontinuations and their reasons) between infants who started ABC aged <28 days (n = 232) and those aged ≥28 days (n = 605), and between infants who started ABC with weight <3 kg (n = 53) and those with weight ≥3 kg (n = 784) at the time of ABC initiation.[12] ABC discontinuations at 6 and 12 months were not significantly different in infants who started ART aged <28 days versus ≥28 days or in infants who weighed <3 kg versus ≥3 kg. ABC discontinuations were less frequent than ZDV discontinuations (adjusted hazard ratio 0.14, 95% CI, 0.10–0.20).[12]

Safety in Children and Adolescents

ABC has less of an effect on mitochondrial function than the NRTI ZDV[7,8] and less bone and renal toxicity than tenofovir disoproxil fumarate.[31,32]

A systematic review and meta-analysis of 54 full-text articles reporting on observational and experimental studies that were conducted in infants, children, and adolescents with HIV aged 10 to

19 years, included data on safety, efficacy, or both, and were published in 2009–2022 in English or French concluded that toxic effects due to ABC use in infants, children, and adolescents remain rare and manageable.[33] In the IMPAACT 2019 clinical trial of dispersible and immediate-release ABC/DTG/3TC tablets in children with HIV aged <12 years and weighing 6 kg to <40 kg, out of 57 participants, 2 participants withdrew due to poor drug tolerability. All participants were HLA-B*5701 genotype negative. One participant discontinued the study drug because of the Grade 4 drug-induced liver injury attributed to ABC and DTG at Week 36; this participant's drug exposures for ABC, 3TC, and DTG were comparable to other participants on the same dose.[13]

Several observational cohort studies, including contemporary cohort analyses, suggest that an increased risk of cardiovascular disease (CVD) events—such as myocardial infarction, stroke, and invasive cardiovascular procedure—exists in adults who are currently using ABC or who have recently used ABC (see Cardiovascular Risk in Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Therapy in the Adult and Adolescent Guidelines); however, other studies have not substantiated this finding. Limited data are available on the CVD risks associated with ABC use in children. One cohort study of South African adolescents (385 participants with HIV and 63 participants as HIV-negative controls) with a median age of 12 years reported an association between ABC exposure and insulin resistance, which was evaluated using homeostatic model assessment. These findings suggested that ABC use may be a CVD risk factor for young people with perinatally acquired HIV.[34] In a recent prospective study of 101 virally suppressed (≤400 copies/mL) youth aged 10 to 18 years with HIV and 97 uninfected controls from Uganda, the baseline common carotid artery intima-media thickness (IMT) was slightly higher in participants with HIV than in controls ($P < 0.01$), and pulse wave velocity (PWV) did not differ between groups. In longitudinal analyses, the longer ART duration was associated with lower PWV in youth with HIV (β = 0.008 [95% CI, -0.008 to 0.003]), while ABC use was associated with greater IMT in youth with HIV (β = 0.043 [95% CI, 0.012–0.074]). These findings suggest that in adolescents with HIV, early prolonged ART may prevent progression of subclinical vascular disease, while prolonged ABC use may increase it.[35]

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