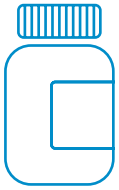
Abacavir (ABC)

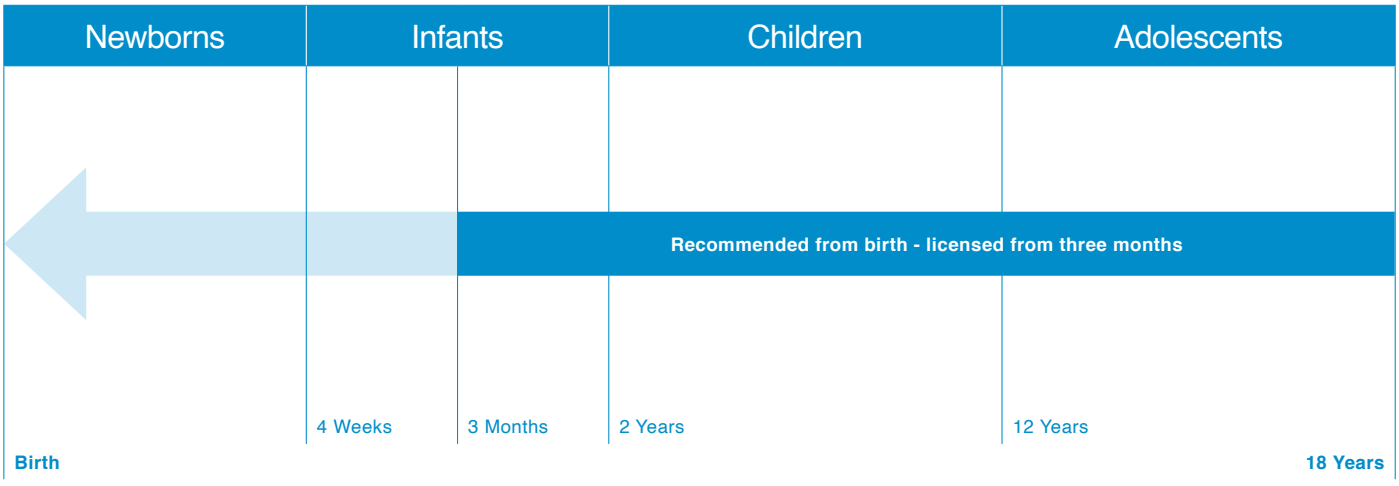
Available Formulations

Single drug formulations	Fixed-dose combinations	
		
Liquid formulation/oral solution	Dispersible tablet (scored)	Dispersible tablet (scored)
ABC 20 mg/mL	ABC 60 mg	ABC + 3TC 60/30 mg ABC + 3TC 120/60 mg

Formulations for adults
ABC 300 mg
ABC + 3TC + AZT 300/150/300 mg
ABC + 3TC 600/300 mg
DTG + ABC + 3TC 50/600/300 mg

WHO dose recommendation - age

WHO recommends using ABC from birth, based on recent data on ABC pharmacokinetics among newborns (Bekker et al.). In contrast, the United States Food and Drug Administration and European Medicines Agency license ABC for children three months and older, and the United States guidelines recommend ABC from three months onward.



World Health Organization

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WHO dose recommendation – weight bands

Oral liquid from birth to four weeks of age [a]

Drug	Strength of paediatric tablets	2 – <3 kg		3 – <4 kg		4 – <5 kg	
		AM	PM	AM	PM	AM	PM
ABC	20 mg/mL	0.4 mL	0.4 mL	0.5 mL	0.5 mL	0.6 mL	0.6 mL

[a] To avoid dose changes over a short period of time and to minimize the likelihood of errors, all ARV drugs except for RAL should be dosed based on weight when treatment starts and maintained until four weeks of age (weight gain is limited during the first four weeks of life).

Child-friendly fixed-dose solid formulations for twice-daily dosing for infants and children four weeks and older

Drug	Strength of paediatric tablets	Number of tablets or capsules by weight band once daily										Strength of adult tablet	Number of tablets or capsules by weight band once daily	
		3 – <6 kg		6 – <10 kg		10 – <14 kg		14 – <20 kg		20 – <25 kg			25 – <35 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
ABC	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300mg	1	1
ABC	20 mg/mL oral liquid	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	–	–	–	–	–	–	–
ABC/3TC [a]	Tablet (dispersible) 60/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	600/300 mg	0.5	0.5
ABC/3TC	Tablet (dispersible) 120/60 mg	0.5	0.5	0.5	1	1	1	1	1.5	1.5	1.5			

[a] This formulation will be phased out over time, and programmes should transition to using the 120 mg/60 mg dispersible scored tablets.

Simplified dosing of child-friendly solid formulations for once-daily dosing for infants and children four weeks and older

Drug	Strength of paediatric tablets	Number of tablets or capsules by weight band once daily					Strength of adult tablet	Number of tablets by weight band once daily
		3 – <6 kg	6 – <10 kg	10 – <14 kg	14 – <20 kg	20 – <25 kg		25 – <35 kg
ABC/3TC	Tablet (dispersible) 60/30 mg [a]	2	3	4	5	6	600 mg / 300 mg	1
	Tablet (dispersible) 120/60 mg	1	1.5	2	2.5	3		

[a] This formulation will be phased out over time, and programmes should transition to using the 120 mg/60 mg dispersible scored tablets.

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Rationale WHO dose selection

The United States Food and Drug Administration and European Medicines Agency recommend screening for carriage of the HLA-B*5701 allele before initiating treatment with ABC, to prevent hypersensitivity reaction. ABC should not be used for people known to carry the HLA-B*5701 allele. However, in sub-Saharan Africa, the frequency of the HLA-B*5701 allele is low (<2%) and hypersensitivity reactions in children are rare (Jesson et al. and Musiime et al.). The prevalence of HLA-B*5701 varies from 1% to 4% in Asian countries, but HLA-B*5701 screening is not performed in accordance with the standard of care in these countries. Because of the low prevalence of the HLA-B*5701 allele in sub-Saharan Africa and the fact that hypersensitivity reactions among children in this region are rare, ABC can be started without screening for the allele. However, close clinical monitoring to detect hypersensitivity reaction remains important.

Although the United States Food and Drug Administration and European Medicines Agency license ABC from three months of age onwards, WHO recommends using solid formulations for children older than four weeks of age and weighing at least 3 kg. This decision was based on ABC pharmacokinetic and safety data from the ARROW and PENTA-13 trials and a population pharmacokinetic modelling article based on 15 studies showing that the disposition of ABC among children appears to be affected only by differences in weight, regardless of the child's age (Zhao et al.). Another study reporting therapeutic drug monitoring of children from age one month to 16 years reported that plasma clearance was proportional to body weight and supported the 8-mg/kg twice-daily ABC dosage regimen for treating children living with HIV (Jullien et al.).

Initial ABC weight-band dosing was developed using this mg/kg dose as guidance. However, pharmacokinetic data for children three months and younger were not available when the initial guidance was published. Using the available generic solid formulations for children, experts recommended 60 mg twice daily or 120 mg once daily for children at least four weeks old and weighing 3.0–5.9 kg. The dose per kg of body weight in the 3.0–5.9 kg weight band ranges from 10 to 20 mg/kg twice daily, which is higher than the proposed 8 mg/kg twice-daily dose. However, because of the apparent absence of a clear relationship between ABC exposure and the side-effects (especially hypersensitivity, which depends on genetic factors and not on exposure) of ABC treatment, the expected higher plasma ABC exposure in the lowest weight band was thought to be acceptable in the absence of data. Preliminary data on ABC pharmacokinetics among newborns are available (see below), and further ABC pharmacokinetic data for newborns and young infants are being generated and will help to inform future dosing in this age group.

Once-daily versus twice-daily dosing: once-daily ABC + lamivudine (3TC) was non-inferior to twice-daily ABC + 3TC in viral load suppression, with similar resistance, adherence, clinical, immune and safety outcomes (Musiime et al.). ABC + 3TC provides the first once-daily nucleoside backbone across childhood that can be used to simplify ART.

Newborns and Premature Infants

A recent study described single-dose ABC pharmacokinetics for newborns 6–15 days old and showed significantly reduced oral clearance compared with infants older than three months (Bekker et al.). For children 1–3 months old, the exposure for ABC 8 mg/kg twice-daily dosing also seems to be higher than that for older children. Another study of malnourished children found high exposure: threefold higher than adults (Archary et al.). Bekker et al. performed pharmacokinetic analysis using ABC plasma concentrations from newborns using the oral liquid formulation to determine ABC mg/kg dosing guidelines for newborns. Data from three studies were pooled (PACTG321, Tygerberg cohort and IMPAACT P1106), and 308 samples from 45 newborns were used. ABC elimination was low at birth but rapidly increased over the first weeks of life. The optimal dose of 2 mg/kg twice daily for newborns (0–4 weeks old) achieved exposure within the expected range for older children, using a population pharmacokinetic approach. Modelling of the weight bands for newborns younger than four weeks resulted in an optimal dosing schedule of 8 mg twice daily for newborns 2.0–2.9kg; 10 mg twice daily for newborns 3.0–3.9 kg and 12 mg twice daily for newborns 4.0–4.9 kg. WHO adopted these doses; although ABC oral liquid is not widely available, this facilitates dosing with ABC in newborns. De Waal et al. presented safety data of 96 newborns starting ABC oral liquid between birth and four weeks old. The results suggest that ABC may be safe and effective for infants younger than four weeks.

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Important information

Toxicity

Serious and sometimes fatal hypersensitivity reactions have been found for about 5% of adults and children (the rate varies by race or ethnicity) receiving ABC. The hypersensitivity reaction 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, diarrhoea or abdominal pain; respiratory signs and symptoms, including dyspnoea, cough or pharyngitis; and laboratory and radiological abnormalities, including elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, lymphopaenia and pulmonary infiltrates. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases (on rechallenge), have also been reported. Pancreatitis can occur. Hypersensitivity reactions generally occur during the first six weeks of therapy, but they have also been reported after a single dose of ABC. If an hypersensitivity reaction is suspected, ABC should be stopped immediately and not restarted—hypotension and death may occur upon rechallenge. The risk of an ABC hypersensitivity reaction is associated with the presence of the HLA-B*5701 allele. For people with the allele, the risk of hypersensitivity reaction is greatly reduced when using ART that does not contain ABC (Clinicalinfo.hiv guideline).

Current ongoing trials involving children

Clinical trials on ClinicalTrials.gov

Knowledge gaps

Solid ABC formulations from birth need to be investigated.

Research priorities according to PADO4

ABC + 3TC + LPV/r granules as well as ABC + 3TC + EFV and ABC + 3TC + DTG 10-mg scored dispersible tablets will be developed, and data on these formulations in newborns and young children are a high priority.

Drug–drug interactions

No relevant drug–drug interactions with TB medication.

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