Table 248.3. Doses of ritonavir and recommended protease inhibitors in children.

Atazanavir[a] (> 10 kg or 3 months)

Daily dosing

	Ritonavir	Atazanavir powder
10–15 kg	80 mg	200 mg
15–25 kg	80 mg	250 mg

Children 6–18 years, > 15kg

	Ritonavir	Atazanavir capsule
15–20 kg	100 mg	150 mg
20–40 kg	100 mg	200 mg
> 40 kg	100 mg	300 mg

Darunavir[b] (> 3 years)

Twice daily dosing

	Ritonavir	Darunavir
10–11 kg	32 mg	200 mg
11–12 kg	32 mg	220 mg
12–13 kg	40 mg	240 mg
13–14 kg	40 mg	260 mg
14–15 kg	48 mg	280 mg
15–30 kg	48 mg	375 mg
30–40 kg	100 mg	450 mg
> 40 kg	100 mg	600 mg

Ritonavir–lopinavir (> 14 days)

Twice daily dosing

All patients: 75/300 mg/m^2 (maximum of 100/400 mg per dose in those > 1 year)

Alternative for treatment-naive patient > 1 year: 57.5/230 mg/m^2

Number of 25/100 mg tablets (given twice daily)

	300 mg	230 mg
15–20 kg	2	2
20–25 kg	3	2
25–30 kg	3	3
30–35 kg	4[c]	3
35–45 kg	4	4
> 45 kg	4	4

[a]Atazanavir powder is not equivalent or interchangeable with atazanavir capsules.

[b]Over 12 years or 40 kg, the dose of ritonavir is 100 mg. The dose is variable based on treatment experience and resistance.

[c]Or two 50/200 mg tablets. Once daily dosing is *not* recommended in those < 18 years.

ited. Co-formulated lopinavir–ritonavir or ritonavir-boosted atazanavir are the recommended protease inhibitors in children, and ritonavir-boosted darunavir is an alternative. The dose of ritonavir depends on the child's weight or body surface area, antiretroviral treatment experience, and the particular protease inhibitor used. A summary is in Table 248.3 (see also the relevant chapter on each protease inhibitor).

COBICISTAT

Cobicistat is not approved for use in children under 18 years, as its safety and efficacy have not been established.

Pediatric formulations are being investigated to establish bioequivalence (Custodio *et al.*, 2014a). In addition, the current US Dept of Health and Human Services guidelines for use of antiretrovirals in pediatric HIV infection mention a small study (14 participants) of the fixed-dose combination tablet containing elvitegravir–cobicistat–emtricitabine–tenofovir in treatment-naive children and adolescents, aged 12–17 years. This study reported pharmacokinetic (PK), tolerability, and virologic efficacy at 24 weeks. The therapy was well tolerated, and all subjects taking the combined antiretroviral treatment (cART) at 24 weeks had viral loads < 400 copies/ml; 11 had viral loads < 50 copies/ml. Steady-state exposure was similar to that observed in adults, as were small increases in serum creatinine without evidence of nephrotoxicity. These data suggest that the fixed-dose combination elvitegravir–cobicistat–emtricitabine–tenofovir is efficacious in children and adolescents aged 12 to 18–years, but evidence is insufficient for this regimen to be recommended as initial therapy for treatment-naive children and adolescents in this age group (Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children, 2015).

4c. Pregnant and lactating mothers

RITONAVIR

Ritonavir is a category B drug.

Low (boosting) doses of ritonavir are used in pregnancy; for some years lopinavir–ritonavir was the therapy of choice, however, boosted darunavir and atazanavir are now the preferred regimens (Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children, 2015).

Pharmacokinetic data suggest that with standard adult dosing, plasma concentrations of lopinavir–ritonavir, atazanavir, and darunavir are reduced during the second and/or third trimesters (see the chapters on specific protease inhibitors). The need for a dose adjustment depends on the protease inhibitor, an individual patient's treatment experience, and use (if any) of concomitant medications with potential for drug interactions. The ritonavir component of the therapy remains at the low boosting dose, should any adjustment occur.

A systematic review of pharmacokinetic studies of HIV-positive women taking antiretrovirals that measured drugs in breast milk found that overall penetration of protease inhibitors into breast milk was low (< 40%) relative to mother's plasma. One study from Malawi was able to detect lopinavir and ritonavir in the plasma of breastfed infants, at ~ 2% of mother's plasma levels (Waitt *et al.*, 2015). An open-label pharmacokinetic study in a subset of HIV-infected mothers and their uninfected infants enrolled in the Breastfeeding, Antiretroviral, and Nutrition study described drug exposure at multiple time points (Corbett *et al.*, 2014). Among 30 mother–infant pairs, ritonavir breast milk concentrations were 80% lower than maternal concentrations and there were no detectable infant concentrations of ritonavir. Ritonavir's