PK and safety of ZDV, 3TC, and LPV/r in children with HIV and severe acute malnutrition (SAM) were studied in International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) P1092.[19] Steady-state PK, safety, and tolerability were compared in children with HIV with and without SAM. Overall safety and tolerability did not differ between the two cohorts, and similar area-under-the-curve values for ZDV, 3TC, and LPV/r were observed in these children who were dosed according to World Health Organization weight-band dosing recommendations.[19]

Zidovudine clearance is decreased in patients with impaired renal function. A dose reduction of 50% is recommended for adolescents and adults with renal failure (creatinine clearance [CrCl] <15 mL/min) or on hemodialysis or peritoneal dialysis (see the manufacturer's prescribing information). Although no neonate-specific data exist, based on expert opinion, a similar dose reduction of 50% is recommended in neonates with renal failure (CrCl < 10 mL/min).

The PK of intravenous ZDV in a premature neonate with gestational age of 32 weeks on extra corporal membrane oxygenation (ECMO) has been reported in a single case report. Based on measurements of ZDV plasma concentrations during and after ECMO, the authors concluded that ECMO did not have an impact on ZDV PK and that standard intravenous dosing of ZDV can be used in preterm neonates.[20]

Toxicity

Several studies suggest that the adverse hematologic effects of ZDV may be concentration-dependent, with a higher risk of anemia and neutropenia in patients who have higher mean plasma area-under-the-curve values for ZDV.[6,7,21] A significant reduction in the incidence of hematologic toxicity was observed during a retrospective analysis of infants who received a short course of ZDV (2 weeks) to prevent perinatal HIV transmission.[22] In this study, 137 infants received ZDV for 2 weeks and 184 infants received ZDV for >2 weeks; of these infants, 168 (91.3%) received 4 weeks of ZDV prophylaxis. The risk of anemia (defined as a Division of AIDS severity grade of mild or higher) was significantly lower in the short-course group at both age 1 month ($P < 0.001$) and age 3 months ($P < 0.001$).[22] For infants who develop significant anemia while receiving ZDV for prevention of perinatal HIV transmission, early discontinuation may be considered for infants who are determined to be at a low risk of transmission after expert consultation. A prospective cohort study conducted in Thailand evaluated the safety of triple ARV neonatal presumptive therapy with ZDV/3TC/NVP for 6 weeks in infants at high risk of acquisition of HIV compared with 4 weeks of monotherapy with ZDV in infants considered at low risk. No significant differences were observed in the incidence of neutropenia, hepatoxicity, or severe anemia between the triple ARV and the ZDV monotherapy groups.[23]

Incidence of hematological toxicity was investigated in the ARROW study, which randomized ART-naive Ugandan and Zimbabwean children to receive either ZDV-containing regimens or ABC-containing regimens. The incidence of severe anemia was similar regardless of ZDV use; this finding suggests that advanced HIV disease contributed to low hemoglobin values. ZDV use was associated with severe neutropenia in a small number of children.[24] In a retrospective study conducted in Ethiopia, an evaluation of predictors of anemia among children on ART[25] was conducted from 2007 to 2017. Study participants receiving ZDV-containing regimens were four times more likely to develop anemia than children receiving ABC-containing regimens. Other predictors of anemia in addition to ZDV in this patient population included tuberculosis, severe immunosuppression, and undernutrition.