MODULE 2: PHARMACOKINETIC MODELLING

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1. INTRODUCTION

Two main factors underpin the pharmacokinetic differences between adults and children requiring dose adjustments: body size and maturation *(1)*.

The effect of body size on drug disposition is well described using the theory of allometric scaling, which predicts a non-linear relationship between drug clearance and body size. Because of this non-linearity, children generally need a larger dose in mg/kg than adults.

In addition, the pharmacokinetics for children younger than two years and neonates can differ considerably from that for older children because of developmental differences in the physiological processes underlying drug absorption, distribution, metabolism and excretion *(2)*. In particular, since metabolic pathways are immature, the values of drug clearance tend to be smaller than body size alone would predict.

Although the effect of body size is similar for all drugs and quite predictable *(3)*, the effects of maturation depend on the drug and need to be specifically investigated. Thus, before any antiretroviral (ARV) drug can be used among neonates, an appropriate neonatal dosing regimen with an appropriate formulation needs to be studied and neonatal safety assessed *(4)*. Neonates and young infants require ARV medicine for both preventing mother-to-child transmission of HIV and for treating HIV infection. The module on trial design and the module on pregnant and breastfeeding women further discuss issues related to safety and pharmacokinetic studies involving neonates.

When designing a pharmacokinetic trial, one needs to consider the method used for data analysis, since several options are available, each with their own advantages and disadvantages depending on the scenarios.

- Non-compartmental analysis is very easy to implement and summarizes the pharmacokinetic profiles in terms of the area under the concentration–time curve and maximum concentration but can only be applied when an intensively sampled pharmacokinetic profile is available for each subject *(5)*.
- Population pharmacokinetic analysis is often the preferred analysis when performing intensive blood sampling is not feasible, for example, in young children, including neonates *(6)*. Population pharmacokinetic analysis involves a mathematical model-based approach suitable with sparse or opportunistically sampled drug concentration data. Population pharmacokinetic analysis estimates primary pharmacokinetic parameters such as clearance and volume of distribution, possibly including in the model the effect of individual covariates (such as body weight and age) on these pharmacokinetic parameters.
- Physiologically-based pharmacokinetics is a complex predictive tool integrating into an in silico platform information about both human physiology and the chemical and physical characteristics of the drug under study *(7)*. This tool is designed to work with very little or no clinical data but only provides an extrapolated prediction.

2. CHALLENGES

Data on pharmacokinetics, safety and efficacy for adults are needed before drugs can be studied among children. Pharmacokinetic studies among children are further delayed when dose-finding studies are performed in sequential age cohorts (see the module on trial design).

2.1 Establishing initial drug doses

Establishing initial drug doses for neonates and other children is especially challenging, since the effects of both body size and the maturation of metabolic pathways on a drug's pharmacokinetic properties need to be considered. Moreover, specific considerations are required when designing pharmacokinetic studies among children, including identifying the optimal drug exposure targets, calculating the number of children needed in each age group or weight band and ensuring that ethically appropriate blood sampling and volumes are drawn.

2.2 Fixed-dose combinations

ARV drugs are now commonly co-formulated in fixed-dose combinations, which simplifies dosing and enhances adherence to treatment. Creating fixed-dose combination tablets for children is also desirable but presents several challenges. For example, the effect of body size and even more so that of maturation on each drug within a novel fixed-dose combination often differ, and thus the optimal ratio between the drugs in the fixed-dose combinations may not be equivalent across all weight bands.

2.3 Influences on drug bioavailability

Factors unique to infants and other young children may influence drug bioavailability. These factors include feeding mode and schedule, differences in fed and fasted states and modifications to formulations to facilitate drug intake, such as splitting or crushing tablets intended to be swallowed whole. Strategies that avoid having to break tablets across dosing weight bands are advocated. Drug–drug interactions among children living with HIV are common, but data cannot be directly extrapolated from adult studies since the extent of the interaction can differ in children.

2.4 Palatability and changes in drug doses

Poor palatability of ARV drug formulations can be a particular challenge for treating children, and frequent changes in drug doses are confusing for caregivers and children. Nevertheless, frequent dose changes may be unavoidable for drugs, especially for neonates and other young children, which are metabolized or eliminated through pathways with rapid maturation.

It is critical to minimize delays in generating pharmacokinetic and safety data for novel ARV drugs and/or formulations involving neonates and other children.

3. SOLUTIONS

Below are some considerations and solutions to the common challenges encountered when designing pharmacokinetic trials assessing ARV drugs for children and adolescents.

3.1 Identifying ARV drug exposure targets

Maintaining ARV drug exposure within therapeutic limits is critical. If ARV drug concentrations are too low, they may fail to achieve viral suppression, whereas if they are too high, they may be associated with drug toxicity. The pharmacokinetic targets for efficacy and safety for children are usually extrapolated from studies performed among adults.

In general, ARV drugs are licensed and used for children based on studies of relatively small numbers of children whose primary outcomes are drug safety and pharmacokinetics. Dosing in these studies is designed with the goal of achieving plasma drug concentration targets equivalent to those established for adults, although the assessment of viral outcomes among the participating children will provide some evidence that the drug concentration targets remain appropriate for children.

3.2 Optimal design of pharmacokinetic studies involving children

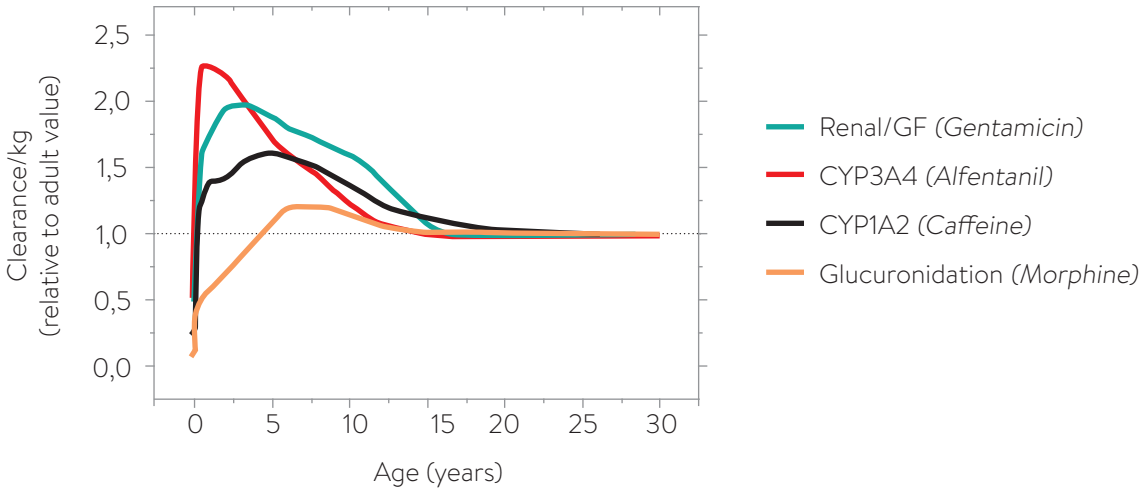
Unless a drug is intended solely or primarily for children, studies involving children cannot be done until data are available on pharmacokinetics, safety and efficacy for adults. The aim of a dose-finding pharmacokinetic study involving children is to determine with sufficient precision the pharmacokinetics for children of different ages, consistent with guidelines provided by regulatory authorities *(8)*. Adolescents are sometimes included as part of initial adult studies, followed by studies among children, starting with the oldest age group and progressing to younger cohorts once reassuring pharmacokinetic and safety data are available for older cohorts.

The choices specific to a pharmacokinetic study of children include the number of children in each age or weight group and the number of blood samples to draw per subject for each pharmacokinetic profile. The number of children in each age or weight group will determine the precision with which typical values of clearance and volume of distribution parameters in each group can be estimated. For example, age bands are generally smaller for smaller ages (such as <3 months, 3–6 months, 6–12 months, 12–24 months, 2–6 years and 6–12 years), to account for the fact that the greatest developmental changes happen in the first months and years of life. Similarly, since the effect of maturation is stronger for younger children (Fig. 2.1), a larger sample size will be required in the youngest age or weight bands.

For the same reason, the lowest degree of variability would be expected among adolescents, with the main effect being body weight, and the variability would then be comparable to that observed for adults. The total number of subjects in each weight and age band will depend on the specific drug and its reported between-subject variability. An online tool is available to calculate this sample size, based on information about the pharmacokinetics of the drug for adults, the information about its main metabolic pathways and the level of variability observed *(9)*.

The number of blood samples drawn in each pharmacokinetic profile will affect the precision with which the individual pharmacokinetic parameters are estimated for each subject in the study. Further, ethical constraints limit the total volume of blood that can be collected from a child *(11)*, so sensitive drug assays are needed that require minimal plasma volumes (10–50 µL). The

Fig. 2.1. Effect of age on drug clearance



Created based on data from: Edginton et al. *(10)*. The lines represent the clearance of drugs through different pathways normalized to body weight and relative to adult reference values.

blood-sampling schedule depends on how the data will be interpreted. If non-compartmental analysis *(5)* is planned, a more intensively sampled profile and strict adherence to the sampling schedule are necessary.

In addition, the entire dosing interval should be covered to accurately calculate the drug exposure (such as area under the concentration–time curve) at steady state. If a population pharmacokinetic approach is to be used, the sampling can be more sparse and less rigid, as long as accurate information is kept about the timing of all samples and doses (even on the days before the blood-sampling visit). Model-based approaches may also have stronger power to determine estimates of pharmacokinetic parameters, because the data from all age bands can be pooled together and analysed jointly.

To optimize the timing of the samples within the schedule, a state-of-the-art approach is to apply optimal design theory *(12)*. Briefly, using a model-based approach, software tools are available that can provide an optimal sampling schedule expected to maximize the information collected in the study. Alternatively, a general rule of thumb comprises drawing a pre-dose sample one around the expected time of maximum concentration and then cover the rest of the curve, aiming to have at least 2–3 samples in the expected terminal phase of the profile. Ideally, the last sample should be drawn as late after the dose as logistically feasible, but avoiding a time range with a high chance of observing values below the lower limit of quantification of the assay.

Interim analysis is advised to assess the exposure and determine as soon as possible whether the observed exposure with the selected dose is in accordance with the predicted values.

3.3 Model-based approaches to establish dosing for initial pharmacokinetics and safety studies among children

Body size and maturation are the two main factors causing the difference in pharmacokinetics between adults and children *(1)mg/kg*. These factors are best accounted for using model-based approaches such as population pharmacokinetics or physiologically based pharmacokinetics. The effect of body size can be predicted well using allometric scaling theory *(13)*, which affects all drugs in the same way. The volume of distribution is scaled linearly with body weight, whereas

clearance (CL) has a non-linear relationship with body weight (WT) (with an exponent of 3/4), as outlined in the following equations:

$$V_i = V_{std} \cdot \left(\frac{WT_i}{WT_{std}}\right)^1 \qquad CL_i = CL_{std} \cdot \left(\frac{WT_i}{WT_{std}}\right)^{\frac{3}{4}}$$

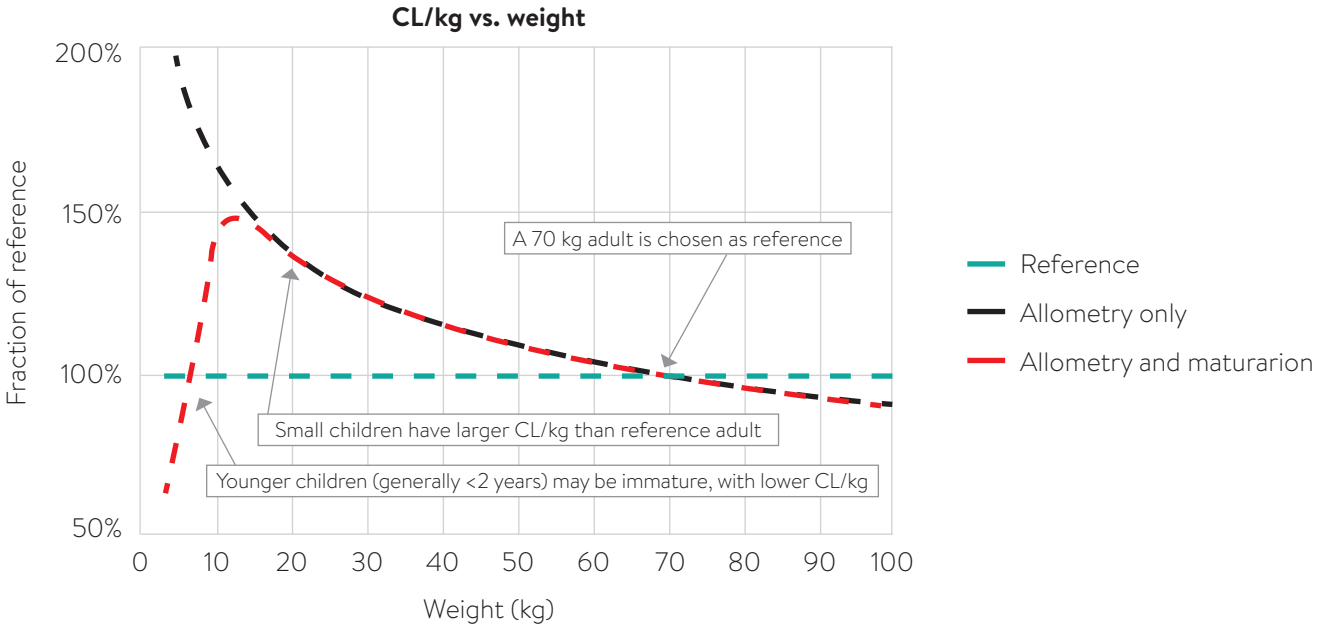
Given the reference adult values of CL_{std} and V_{std}, which relate to an adult of reference body weight WT_{std} (such as 70 kg), the expected values of CL_i and V_i for a person of weight WT_i are calculated according to the formulas above. With the estimate of clearance for a particular weight, the dose can be calculated to achieve a target drug exposure for adults (such as the area under the curve using the classic formula area under the curve = dose/clearance).

Because of this nonlinear relationship between body weight (a surrogate for size) and drug elimination, children generally need a higher mg/kg dose than adults, as shown in Fig. 2.2. Thus, if a dose for children is extrapolated from adults to children using a constant mg/kg, this will generally cause underexposure in children. In addition, a drug's half-life ($T_{1/2}$) tends to be shorter for children, as the ratio between clearance and the volume of distribution will be larger with smaller body size. This may require, for example, splitting what is a single daily dose in adults into two separate doses for children.

The effects of body size on clearance and the volume of distribution, respectively, are expected to affect all drugs similarly. Allometric scaling of these parameters is crucial in predicting the suitable dose for children older than two years. For this reason, the use of allometric scaling as a best-guess reasonable assumption has been advocated *(3)*. Allometric scaling can be applied to simple tools to provide predictions of ARV drug exposure across the weight range of children, such as with the WHO dosing tool to explore optimal drug ratios for fixed-dose combination tablets for children *(14)*.

For children younger than two years, metabolic pathways are generally not yet mature and therefore not operating at full capacity compared with those of adults. Because of this maturation effect, clearance values for infants tend to

Fig. 2.2. Changes in clearance (CL/kg) versus body weight



The green horizontal line represents the reference clearance/kg for a 70-kg adult. The black dashed line shows the effect of allometric scaling alone, without maturation. The pink line shows the combined effect of allometric scaling and maturation.

be smaller than body size alone would predict (Fig. 2.2). The maturation profile may vary greatly between drugs (Fig. 2.1), but if the drug elimination pathways are known, one can use literature information about their maturation and use population pharmacokinetics or physiologically based pharmacokinetics to predict a starting dose *(15)*. However, the prediction of a starting dose will still need to be validated, especially in children younger than one year. Since metabolic pathways mature during fetal development, a more accurate description can be obtained using conception age and not postnatal age, to account for the effect of prematurity.

When determining the optimal dose to use for young children, other factors need to be considered besides the maturation of clearance. The volume of distribution may also be different among very young children since body composition changes during the first months of life, and the speed and extent of absorption (bioavailability) may also change because of differences in the size and motility of the gastrointestinal tract and changes in gastric pH *(16,17)*

3.4 Washout studies in neonates to inform dose selection

Studies in neonates are often performed only after data are available from studies of young infants. Washout studies of the elimination of a drug in neonates that was acquired across the placenta following administration of the drug during pregnancy provides an assessment of the rate of drug elimination in the first days of life, informing dose size selection for initial studies with direct neonatal dosing in the first days of life (see the module on pregnant and breastfeeding women). In vitro studies of the effect of the drug on bilirubin binding may also be conducted before studies of dosing in neonates to ensure that administering the drug to neonates will not result in an increased incidence of kernicterus resulting from the displacement of bilirubin from albumin *(18–20)*.

3.5 Effect of fed and fasted states on drug bioavailability among neonates and other young children

Generating pharmacokinetic data for novel ARV formulations for children in the fed state by using healthy adults is standard practice. For neonates and other young children, consideration should be given to investigating the impact of regional and age-related infant feeding practices, especially in highly endemic countries. Pharmacokinetic data in the fasted state are also equally important to understand the potential impact on drug exposure if no or only a little food was provided. Population pharmacokinetics or physiologically based pharmacokinetic modelling may aid in assessing how food affects drug concentrations, including issues of malnutrition, among neonates and other infants.

3.6 Bioavailability studies of ARV drugs among children

Bioequivalence of novel formulations to be used in children must be assessed. Such studies are often performed initially among adults but should also be assessed among children, since adult bioequivalence studies of some ARV formulations for children did not predict bioavailability problems that were revealed when these formulations were administered to children *(21,22)*.

3.7 Investigating modifications of novel formulations for adults and children is critical

The shift from individual liquid formulations to small dispersible and chewable fixed-dose combination tablets has been a major achievement and has greatly helped families in low- and middle-income countries in administering complex drug combinations to their children daily. However, it is critical to carefully consider how drugs will be administered in a real-life setting across children's age continuum, and efforts to collect pharmacokinetic data

following different modes of administration would be beneficial. Although less common today, modifying the mode of administering fixed-dose combination tablets for adults or children has been necessary to facilitate administration to children, such as splitting or crushing tablets for adults or children that should be swallowed whole *(21)*. Such manipulation of a formulation can significantly affect bioavailability *(23)*. The possible interactions with excipients should also be considered in the formulations of co-administered drugs *(24)*. In this context, proactively performing pharmacokinetic studies of new drug formulations for adults and children among healthy volunteers would be beneficial in helping to clarify how the formulations can be safely modified, if at all, in the clinic and home settings.

3.8 Palatability of ARV formulations for children is paramount

Developing solid formulations is favoured over developing liquid formulations. For example, the recent introduction of a pellet formulation of lopinavir/ritonavir has helped to simplify dosing, although taste issues remain *(25,26)*. In general, flavoured or taste-masked formulations are preferred, and pharmacokinetic and acceptability studies of these formulations in children must be undertaken.

3.9 Dosing strategies should be simplified when possible

Simplifying drug-dosing strategies to achieve target drug exposure is of critical importance in successfully administering drugs to children. WHO weight-band dosing guidelines have helped to simplify dosing, and pharmacokinetic studies among children living with HIV should be undertaken to assess drug exposure and safety with dosing regimens that use these standard weight bands. For example, the IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) P1083 study assessed the WHO weight-band dosing of lopinavir/ritonavir for children *(27)*. Nevertheless, frequent dose changes may be unavoidable for drugs that are metabolized or eliminated through pathways with rapid maturation, such as raltegravir among neonates (see the section on case studies).

3.10 Giving priority to fixed-dose combination formulations for children

The WHO paediatric dosing tool *(14)* enables the joint display of the exposure of several drugs within a fixed-dose combination across weight bands and allows for graphical comparison. A more sophisticated computer optimization method selecting both optimal tablet size and ratio between the ingredients has recently been proposed for tuberculosis *(28)*. A model-based analysis was recently used to determine the optimal drug ratio for a fixed-dose combination abacavir + lamivudine + efavirenz tablet for children and is discussed in the section on case studies *(29)*.

3.11 Drug–drug interactions may differ for children versus adults

Pharmacokinetic data on drug–drug interactions for adults may be used to inform which drugs should not be co-administered to children because of a risk of too high or too low drug exposure. However, drug–drug interactions between ARV drugs and commonly prescribed non-ARV drugs that are expected to interact (for example, because of a common metabolic pathway or substrates for the same drug transporters) should be assessed among children as well. Since such interactions may differ between adults and children, dosing adjustments must be investigated among children. One example of such a difference was observed with the reduction in lopinavir exposure with the co-administration of rifampicin as part of tuberculosis treatment. Doubling lopinavir/ritonavir doses when co-administered with rifampicin resulted in therapeutic lopinavir exposure for adults, but not for children *(30,31)* (see section 2.1 of the module on coinfections).

4. CASE STUDIES

The following section describes two case studies highlighting the pharmacokinetic challenges often encountered when designing clinical trials involving children.

4.1 Raltegravir for neonates

Raltegravir was the first HIV integrase strand transfer inhibitor to be licensed and the first to be available with a formulation suitable for use among neonates. Raltegravir is metabolized by uridine diphosphate-glucuronosyltransferase (UGT) 1A1, which is also the major enzyme responsible for metabolizing bilirubin. Bilirubin glucuronidation is very slow immediately after birth but accelerates dramatically over the first days and weeks of life, and raltegravir metabolism is expected to follow the same developmental pattern.

Studies were conducted to safely and efficiently investigate the pharmacokinetics of raltegravir among neonates and establish an appropriate neonatal dose. An in vitro study of the effect of raltegravir on bilirubin binding showed that raltegravir would have no clinically significant effect on bilirubin binding at typical therapeutic concentrations but could cause potentially harmful effects at concentrations 50–100 fold higher than typical therapeutic concentrations *(18)*. A study of washout pharmacokinetics of raltegravir among neonates following maternal dosing during pregnancy demonstrated that raltegravir elimination was highly variable and extremely prolonged in the first days of life *(32)*. An initial dosing study of two single raltegravir doses during the first week of life, one during the first 48 hours of life and a second at around seven days of life, confirmed that raltegravir elimination was extremely slow immediately after birth but accelerated during the first week of life. These data were combined with pharmacokinetic data for raltegravir from infants older than one month, and a raltegravir population pharmacokinetic model was developed. Simulations were performed evaluating raltegravir exposure with different dosing regimens during the first six weeks of life, with a goal of selecting a regimen that would provide therapeutic plasma target concentrations while avoiding potential toxicity throughout the first month of life *(33)*. The suggested regimen (1.5 mg/kg once a day for the first week of life, 3 mg/kg twice a day for weeks 2–4 and 6 mg/kg twice daily during weeks 5–6) was then evaluated in a study of daily raltegravir dosing among neonates. This study demonstrated that this dosing regimen met the raltegravir target concentrations *(34)* and led to United States Food and Drug Administration (FDA) licensing of raltegravir for neonates in November 2017.

Raltegravir was the first ARV drug to be licensed for neonates since emtricitabine was licensed in 2005. A study of the pharmacokinetics of raltegravir among low-birth-weight infants is now being planned.

4.2 Determining the optimal strength of a novel abacavir + lamivudine + efavirenz formulation for children

The 2016 WHO consolidated ARV drug guidelines *(35)* recommend a combination of abacavir (ABC), lamivudine (3TC) and efavirenz (EFV) as the preferred first-line ARV regimen for children weighing 10–35 kg (about 3–10 years old). So far, no fixed-dose combination tablet of ABC + 3TC + EFV for children is available; however, several generic manufactures have said that they intend to develop this formulation. The first step in developing this fixed-dose combination for children was to determine the

optimal dose of each drug within the fixed-dose combination tablet to provide appropriate dosing of each component across all WHO weight bands through simple dose increments. However, the individual dosing recommendations for ABC, 3TC and EFV do not have equal incremental increases in dosing by weight, leading to different drug ratios across the WHO weight bands. These differences in dosing are a consequence of the different rates of maturation of the elimination pathways for the individual drug components.

Pharmacokinetic data supporting the optimal strength of an ABC + 3TC + EFV fixed-dose combination tablet for children are needed.

Recently, population pharmacokinetic analysis was performed using data pooled from multiple clinical trials and therapeutic drug monitoring datasets from countries around the world *(29)*. Simulations revealed that a fixed-dose combination of ABC + 3TC + EFV for children of 150 + 75 + 150 mg provides the most effective and safe concentrations across the WHO weight bands.

Manufacturers can now move forward to develop this strength tablet, but subsequent pharmacokinetic studies are needed to confirm that optimal drug exposure of each component is achieved in the target population of children.

5. SUMMARY

- Although efficacy for children can generally be extrapolated from that of adults, pharmacokinetic and safety studies are necessary to establish appropriate dosing for children.
- Initial doses in trials for children require understanding the (non-linear) effect of body size and maturation. Modelling and simulation tools are increasingly used to inform initial dose selection.

6. KEY CONSIDERATIONS

- Model-based approaches should be used to help inform dosing in young children. Such data will be critical to support performing pharmacokinetic dose-finding studies in children simultaneously across weight and age bands rather than using the standard 'staggered' or 'step-down' approach.
- Model prediction for infants younger than four weeks are less precise due to the rapid maturation of metabolic pathways during the first month of life. For newly approved ARVs, performing washout studies in neonates will provide key data to inform dose selection and in turn accelerate dosing-finding studies in this vulnerable population.
- Developing robust population pharmacokinetic models using available data in children living with HIV should be prioritized to help determine which strength and/or ratios of novel fixed-dose combination tablets for children manufactures should develop.
- Pharmacokinetic studies in children should be undertaken to assess drug exposure and safety with dosing regimens that use standard WHO weight bands.

7. ACKNOWLEDGEMENTS

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