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Viewpoint

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Doctopic: Review and Opinion

# What babies need: accelerating access to current and novel antiretroviral drugs in neonates through pharmacokinetic studies

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**Although 23 antiretroviral drugs are approved for use in adults, only six are approved by regulatory authorities for use in term neonates born to women with HIV, with even fewer options for preterm neonates. A major hurdle for approvals is the delay in the generation of pharmacokinetic and safety data for antiretrovirals in neonates. The median time between the year of approval from the US Food and Drug Administration of an antiretroviral agent for adults and the first publication date for pharmacokinetic data in neonates less than 4 weeks old is 8 years (range 2–23 years). In this Viewpoint, we address pharmacokinetic research gaps and priorities for current and novel antiretroviral use in neonates. We also consider the challenges and provide guidance on neonatal clinical pharmacology research on antiretroviral agents with the goal of stimulating research and expediting the availability of safe medications for the prevention and treatment of HIV in this vulnerable population.**

## Introduction

Antiretroviral agents are not just essential components of HIV treatment for those who have acquired HIV, but also an important prevention measure provided to neonates (younger than 28 days) who were perinatally exposed to HIV and who are consequently at risk of being vertically infected. International guidelines recommend antiretroviral postnatal prophylaxis to prevent vertical transmission to all neonates born to women living with HIV.[1,2] Every year about 1·3 million neonates need postnatal prophylaxis.[1] Effective maternal antiretroviral therapy during pregnancy and breastfeeding, together with postnatal prophylaxis, greatly reduces the risk of perinatal transmission of HIV.[3] Despite this, 150 000 children were estimated to have acquired HIV in 2020.[4] There is global consensus on starting antiretroviral agents as soon as possible in infants (younger than 2 years) with confirmed HIV infection, which considerably reduces the risk of mortality and limits the size of the HIV reservoir.[5–7] Increased early detection of HIV infection in neonates and infants soon after birth has enabled more neonates to initiate HIV treatment.[8]

Many highly effective antiretroviral agents with excellent safety profiles and high barriers to resistance are available for adults and adolescents, but dosing advice for neonates is scarce because of the absence of pharmacokinetic and safety data.[9,10] This absent dosing advice, coupled with the general challenges of administering antiretroviral agents to neonates, results in delayed treatment initiation and consequently can contribute to low treatment coverage in children compared with adults.[4] Additionally, treatment success of antiretroviral agents is consistently lower in children than in adults, especially for infants and neonates.[11,12]

Dose selection is particularly challenging for neonates due to the rapid maturation of organs and drug-metabolising enzymes during the first month of life.[13] Efficacy of antiretrovirals for neonates and infants is commonly extrapolated from the relationship between pharmacokinetics and pharmacodynamics reported in adults, and is supported by multiple regulatory agencies.[14] In this context, only small sample size pharmacokinetic studies are required to approve dosing in neonates and infants. To enable access to better medicines for this vulnerable population, we must clarify research gaps and target research efforts to address the questions with greatest possible effect in this population.

## Antiretroviral treatment options and evidence gaps for neonates

Among the 23 antiretroviral agents approved for adults, only six are approved by regulatory authorities for HIV treatment or postnatal prophylaxis in term neonates. In order of registration date, these agents are zidovudine, nevirapine, ritonavir-boosted lopinavir (from 2 weeks postnatal age and 42 weeks post gestation), emtricitabine, raltegravir, and maraviroc. In addition, despite an absence of formal regulatory approval, lamivudine is supported for neonates by both international and local HIV treatment guidelines,[1,15–18] and dosing information for abacavir (liquid formulation) was added for neonates in the 2021 WHO guidelines.[1,15] Data are missing for the pharmacokinetics of paediatric solid fixed-dose combinations in this age group. Data on abacavir and lamivudine fixed-dose combinations in neonates are pending.[19] Of note, none of these drugs, except lamivudine and abacavir, are currently recommended as HIV first-line treatments for adults or individuals older than 4 weeks, and three of them have a low barrier to viral resistance (raltegravir, lamivudine, and nevirapine).[1]

Even fewer antiretroviral agents are available for preterm neonates and none are specifically approved for preterm neonates by regulatory authorities. Despite no

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antiretroviral agents being approved for use in preterm neonates, several international HIV treatment guidelines include dose recommendations for preterm neonates for zidovudine for all gestational ages, nevirapine from 34 weeks gestational age, and lamivudine from 32 weeks gestational age.[1,2] The paucity of evidence informing dosing for antiretroviral agents for preterm infants is of great concern as both HIV infection and antiretroviral agent treatment during pregnancy are associated with an increased likelihood of preterm (32–37 weeks after gestation) and highly preterm birth (28–32 weeks after gestation).[20,21] Because of this likelihood, there is a pressing need to develop and investigate innovative approaches and dosing adapted to preterm neonates and infants to reduce the risk of vertical transmission.

Even when data are gathered, the median time between the year of US Food and Drug Administration (FDA) approval of an antiretroviral agent for adults and publication date of first pharmacokinetic data in neonates younger than 4 weeks is 8 years (range 2–23 years; figure), with information absent for most new agents (appendix p 4).

See Online for appendix

As for all children, formulations for neonates should ideally allow for dosing flexibility; meet quality standards; be compatible with feeding practices; be easy to prescribe, administer, store, and transport; and be affordable in all settings.[22] The development of dispersible oral tablets, when possible in fixed-dose combinations, has improved acceptability by caretakers, health-care workers, and programmes, therefore, these formulations are preferred by WHO.[23] However, dispersible tablets might not always be appropriate for neonatal use as most do not disperse evenly, which means that administering only part of the dispersion is not possible and some formulations cannot be dispersed in expressed breastmilk. Development of lower-dose tablets might be limited by compounding issues. It is often challenging to meet requirements around variations in exact drug content of the tablets.

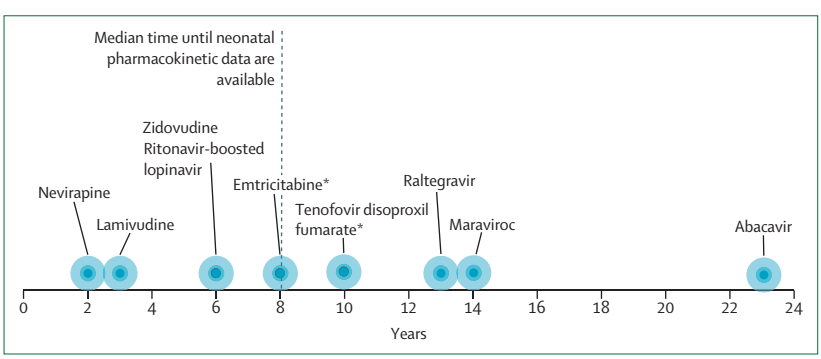


*Figure:* **Time between year of US Food and Drug Administration approval for adult formulation and first pharmacokinetic data for neonates published in a peer-reviewed journal by 2021**
*Only studied as a single dose at birth. No data for cabotegravir (≥1 year); fostemsavir (≥2 years); doravirine (≥3 years); ibalizumab (≥4 years); bictegravir (≥4 years); tenofovir alafenamide (≥7 years); dolutegravir (≥9 years); cobicistat-boosted elvitegravir (≥10 years); rilpivirine (≥11 years); etravirine (≥14 years); ritonavir-boosted darunavir (≥16 years); ritonavir-boosted atazanavir (≥19 years); enfuvirtide (≥19 years); and efavirenz (≥24 years). References used to develop this figure are available in the appendix (p 4).

Addressing all these gaps requires a targeted and concerted effort that needs to start from clarifying research priorities and related implementation considerations for optimal and accelerated action.

## Prioritising research and development for neonates

The Paediatric Antiretroviral Drug Optimization (PADO)-HIV 5 meeting was convened by WHO in September, 2021 to review medium-term and long-term priorities for paediatric antiretroviral agent research and development.[24] Many of the described challenges and limitations were examined to identify research priorities for oral antiretroviral agents for neonates that have US FDA approval for adults (table 1). The group also agreed that studies on drugs that are anticipated to be highly efficacious and convenient for use in low-income and middle-income countries (ie, a dosing interval of once per day or longer, favourable toxicity profile, and high genetic barrier) should be prioritised across the full age and weight spectrum, including both term and preterm neonates (table 2). Long-acting antiretroviral agents are being increasingly considered for neonates as they require less frequent administration (ie, weekly or monthly) than for the current oral daily standard. Parenteral and transdermal formulations, including subcutaneous formulations or microarray patches, could be particularly beneficial for preterm neonates who have feeding intolerances and in whom gastrointestinal developmental changes influence drug absorption.[25,26] However, caution is needed, particularly for preterm neonates, as their skin is very permeable during the first days of life, which puts them at risk for chemical damage and infections.[27] Also, the development of long-acting formulations for neonatal use could be challenged by the rapid changes in drug metabolism, clearance, and body growth through this age period.[28] Other points of concern are that intramuscular injections are difficult to deliver to neonates because it is difficult to accurately estimate their low muscle mass and depot release rate due to variable muscular vascularisation and blood flow.[26,29] Finally, as the time required to attain therapeutic concentrations with an intramuscular injection (ie, cabotegravir) might be too slow when protective systemic concentrations need to be rapidly achieved after birth, an oral lead-in phase or loading dose could be necessary for treatment to be efficacious. Broadly neutralising antibodies (bNAbs) give an alternative for oral postnatal prophylaxis. VRC01 (a bNAb) was studied in neonates and infants exposed to HIV in addition to regular oral postnatal prophylaxis.[30] VRC01 was shown to be safe and the target for pharmacokinetic plasma concentration was reached at day 28 after a single subcutaneous dose.[30] VRC01LS—a modified form of VRC01—and VRC07-523LS, have prolonged half-lives and were studied in neonates. These bNAbs were safe and reached pharmacokinetic targets; because they require less frequent dose administrations than VRC01, they might provide better options for infants requiring long-term

| | Research gap | Priority | Methodology | Comments |
|---|---|---|---|---|
| Lamivudine | Lamivudine in extreme preterm neonates (before 32 weeks of gestation) | High to moderate | Predictive pharmacokinetic modelling | Lamivudine exposure in this population could be predicted by modelling existing pharmacokinetic data from term neonates |
| Abacavir | | | | |
| Priority one | Multidose abacavir in term neonates | High | Multidose prospective pharmacokinetic study | Although a neonatal dose of liquid abacavir twice daily has been recommended, more pharmacokinetic data on solid formulations and once-daily dosing is needed, along with long-term safety data for neonates |
| Priority two | Abacavir in preterm neonates | Low | .. | Abacavir is metabolised largely through UGT2B7; as UGT2B7 activity is extremely low in preterm neonates, dosing with the current paediatric solid formulation is not feasible as it could lead to very high abacavir exposures |
| Dolutegravir | | | | |
| Priority one | Dolutegravir in term neonates | High | Multidose prospective pharmacokinetic study | Dolutegravir is only available as 5 mg dispersible tablets, which does not disperse evenly to allow for dosing at lower dosages; initial neonatal dosing could involve dosing 5 mg every 48–72 h until the metabolism is appropriate for daily dosing |
| Priority two | Dolutegravir in preterm neonates | Low | .. | As UGT1A1 activity is extremely low in preterm neonates, dolutegravir dosing with the 5 mg dispersible tablet will be complex; the increased risk of hyperbilirubinaemia makes this drug class in its current formulation not ideal for preterm neonates |
| Ritonavir-boosted lopinavir | Ritonavir-boosted lopinavir solid formulations in term neonates younger than 2 weeks | Low | Multidose prospective pharmacokinetic study | Due to potential safety concerns seen with the liquid formulation, solid formulations of ritonavir-boosted lopinavir should be studied in a large population to assess its safety in neonates younger than 2 weeks |
| Nevirapine | Nevirapine treatment dose for highly preterm neonates (before 34 weeks of gestation) | High | Predictive pharmacokinetic modelling | There is sufficient knowledge about CYP3A4 activity in very preterm neonates, which makes it feasible to predict nevirapine exposure in this population by modelling pharmacokinetic data from previous studies in preterm neonates |
| Raltegravir | Raltegravir in preterm neonates | Low | .. | Raltegravir is metabolised through UGT1A1; as UGT1A1 activity is extremely low in preterm neonates, dosing is complex and there is increased risk of hyperbilirubinaemia |
| Zidovudine | None | .. | .. | Zidovudine is the only compound for which sufficient research has been done to confidently dose zidovudine in the preterm neonatal period |

Recommendations from the fifth Paediatric Antiretroviral Drug Optimization (PADO HIV-5) meeting.[24] This table includes only antiretroviral agents that are already recommended for neonatal use and those that are expected to be used in the near future. CYP=cytochrome P450. UGT=UDP-glucuronosyltransferase.

***Table 1:*** **Research priorities for different antiretroviral agents to optimise neonatal therapy**

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| | Advantages | Disadvantages |
|---|---|---|
| Cabotegravir | Ideal agent for postnatal prophylaxis, because of its once or twice monthly dose interval that aligns with infant clinic and immunisation visits; favourable safety profile | Depending on the dosage volume, the pain at injection site irritation may be prohibitive; challenges with preterm neonates as cabotegravir is primarily metabolised through UGT1A1; viral breakthrough could result in viral resistance for other integrase inhibitors, complicating future HIV treatment; for postnatal prophylaxis, oral lead-in is required to rapidly achieve therapeutic cabotegravir concentrations after birth, but only if maternal antiretroviral agents do not readily cross the placenta |
| Lenacapavir | Ideal agent for postnatal prophylaxis during breastfeeding because of its 6-month dosing interval | Frequent lenacapavir dose adjustments might be needed during the neonatal and infant period as it is primarily metabolised by UGT1A1, complicated by rapid weight gain in the first months of life; a second agent with a similar dose interval is required for treatment of HIV |
| Islatravir | Ideal agent for postnatal prophylaxis, because of its monthly dose interval for oral dosing, and an even longer interval for parenteral formulations, metabolism of islatravir is independent of drug-metabolising enzymes and is therefore not affected by enzyme maturation during the neonatal period, which simplifies neonatal dosing | Current clinical development has been put on hold and future development is uncertain because decreases in total lymphocyte and CD4 T-cell counts have been observed in some adult participants receiving islatravir in clinical studies; formulating a neonatal oral dose might be challenging as the required dose would be very small; a second agent with a similar dose interval is required for treatment of HIV; the relationship between pharmacokinetics and pharmacodynamics is based on intracellular islatravir concentrations instead of plasma concentrations and is therefore difficult to determine in neonates |
| bNAbs | Preliminary pharmacokinetic data are already available for bNABs in neonates and infants; bNAbs have a favourable safety profile so can be studied in neonates in parallel with adult studies; possibility of dosing once every 3 months via subcutaneous injection | Prices are expected to be high due to high production costs, which poses challenges for global access to bNAbs; a combination of bNAbs is needed to be efficacious, with potentially different combinations required against specific clades; however, these combinations have not yet been evaluated |

Recommendations from the fifth Paediatric Antiretroviral Drug Optimization (PADO-HIV 5) meeting.[24] bNABs=broadly neutralising antibodies. UGT=UDP-glucuronosyltransferase.

***Table 2:*** **Potential antiretroviral agents for neonatal use and their main advantages and disadvantages**

therapy (ie, prevention during breastfeeding or HIV treatment).[31,32] The efficacy of these bNAbs for HIV treatment and prevention has not been established and current bNAbs do not effectively neutralise HIV-1 subtype C viruses; therefore, a combination of bNAbs might be required.[33] The approach for bNAbs, for which neonatal pharmacokinetic studies are done shortly after the first adult clinical studies, should be an example for

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***Panel:*** **Neonatal pharmacokinetic study methods and their main advantages and disadvantages**

**Neonatal wash-out pharmacokinetic studies**

- A few neonatal blood samples (at least two timepoints) after in-utero exposure to maternal antiretroviral agents can assist with the studying of drug clearance; in addition, the simultaneous sampling of cord blood and maternal plasma can help with the understanding of placental transfer
- Advantage: clinical pharmacokinetic data can be obtained without administering a drug to the neonate after birth
- Disadvantage: this method does not allow for the quantification of drug absorption

**Predictive neonatal pharmacokinetic modelling studies**

- Use of pharmacokinetic data from older children, adults, or neonatal wash-out studies to simulate the pharmacokinetics in neonates with physiologically based pharmacokinetic modelling or allometrically scaled population pharmacokinetic models to predict an initial dose for neonates
- Advantage: no clinical data are needed to predict pharmacokinetics for a range of drug dosages in various study populations
- Disadvantage: currently neonatal population pharmacokinetics and physiologically based pharmacokinetic models are not sophisticated enough to adequately estimate drug exposure in neonates without the validation of the model with clinical data

**Single-dose pharmacokinetic studies**

- Administration of a single dose of a drug to a neonate, usually in addition to regular postnatal prophylaxis or HIV treatment
- Advantage: few concerns with regards to safety and efficacy as it is a single dose given on top of regular treatment or prophylaxis
- Disadvantage: developmental pharmacokinetics and long-term safety cannot be assessed by this method

**Multidose prospective pharmacokinetic studies**

- Administration of multiple doses of an experimental drug as part of postnatal prophylaxis or HIV treatment to obtain pharmacokinetic samples at various timepoints during treatment (either by sparse or intensive sampling)
- Advantage: possibility to assess safety, efficacy, and development of pharmacokinetics over time
- Disadvantage: this method can only be applied when the preliminary safety and efficacy of the drug has already been established as the experimental drug has to be administered as part of postnatal prophylaxis or HIV treatment

doing neonatal research in the context of other clinical development programmes.

Addressing the research priorities identified by PADO-HIV 5 requires careful consideration of the lessons learned from the optimisation of pharmacokinetic research for neonates and infants and will allow the rapid, safe, and effective generation of data required for evidence-based dose recommendations in this population. Effective and safe pharmacotherapy in neonates requires an understanding of the pharmacokinetic and pharmacodynamic properties of the drug, and the physiological characteristics of the population (panel).[28]

## Pharmacokinetic target exposures

Well established pharmacokinetic–pharmacodynamic relationships exist for some antiretroviral agents in adults. It is important to consider that plasma target concentrations are a surrogate for the concentrations in cellular and tissue compartments where antiretroviral agents are pharmacologically active and distribution might differ in neonates. However, drug concentrations in these compartments are challenging to study and interpret.[34] Regulatory authorities generally accept pharmacokinetic target plasma concentrations derived from these adult studies to be directly extrapolated to neonates and children.[14,35] Target concentrations for most antiretroviral agents are similar for neonatal HIV treatment and prophylaxis. Compared with standard HIV treatment, only nevirapine is administered at a lower dose when used for postnatal prophylaxis in neonates at low risk of vertical transmission. This dosage is given as a lower plasma concentration target is set for postnatal prophylaxis (0·1 mg/L instead of 3·0 mg/L).[36,37] To simplify the use of antiretroviral agents in neonates and prevent underdosing, use of the same dosing and pharmacokinetic targets for both neonatal HIV treatment and postnatal prophylaxis might be preferable. This strategy is generally applied for HIV prevention in post-exposure prophylaxis of HIV and other infections in adults and children.[38]

## Establishing initial drug doses

Currently, neonatal antiretroviral drug dosages are selected on the basis of whether the pharmacokinetic target concentrations (ie, those reached in adults for treatment) are met. Establishing an initial drug dose for neonates is complex as drug absorption, distribution, metabolism, and excretion change rapidly during the first 4 weeks of life due to the maturation of organs, body composition, and metabolic activity.[28] Therefore, safety and pharmacokinetic data in neonates are needed before dosing guidance can be developed. Drug doses for preterm neonates often vary from term neonates because their renal function and drug-metabolising enzyme activity are lower and develop differently. Preterm neonates also absorb medications poorly compared with term neonates.[28]

Drug wash-out studies (from maternal antiretroviral agents) after birth give the foundation for initial neonatal pharmacokinetic variables such as the elimination half-life.[39,40] For drugs that cross the placenta, these data inform pharmacokinetic models to support initial neonatal dose recommendations to be used in clinical trials. Neonatal wash-out pharmacokinetic data are known for various antiretroviral agents (appendix p 2). For example, dolutegravir clearance is substantially prolonged in neonates (time for half-life of dolutegravir 32 h in neonates *vs* 13 h in adults) after in-utero dolutegravir exposure.[39] Therefore, initial dolutegravir doses in neonates will probably need to be lower than that for children older than 4 weeks or given less frequently (eg, every other day).

Single-dose pharmacokinetic studies also inform initial drug doses in neonates without exposing them to

potentially toxic or subtherapeutic drug concentrations for a long period (appendix p 2). The investigational drug is given in addition to active therapy, preferably with various doses. For neonates exposed to HIV and infants younger than 3 months living with HIV, the use of abacavir was studied in a single-dose pharmacokinetic study.[41] The authors reported substantially higher exposure of abacavir in neonates after a single dose of 8 mg/kg than in children, although no safety concerns were reported. Subsequent population pharmacokinetic modelling found that abacavir should be dosed at 2 mg/kg twice daily for the first month of life, 4 mg/kg twice daily from age 1 month, and 8 mg/kg for those older than 3 months.[42] These findings should be confirmed by a therapeutic drug monitoring study in clinical practice.

Pharmacokinetic modelling and simulations are important methods for the prediction of drug exposure in neonates (appendix p 2). Population pharmacokinetic modelling is characterised by its ability to make use of sparse sampling at carefully selected timepoints. This approach requires less frequent sampling and less blood volume to be drawn per participant than in intensive pharmacokinetic studies.[43,44] For raltegravir, simulations on the basis of population pharmacokinetic modelling effectively predicted a safe daily dosing regimen for term neonates that was subsequently confirmed with real-life data.[45] Approaches, such as physiologically based pharmacokinetic modelling, that mechanistically describe the pharmacokinetics of drugs without initially exposing neonates to medications and blood drawings are also being used to predict initial neonatal drug doses.[43] This approach could be particularly beneficial for premature infants for whom it is even more challenging to collect clinical pharmacokinetic data. However, uncertainty in the physiological variables of neonates poses challenges for adequate mechanistic description of a drug's pharmacokinetics.[46,47] This issue was shown by a neonatal dose-finding physiological pharmacokinetic study of dolutegravir in which predictions about most of its metabolism had to be scaled allometrically due to an absence of data about the ontogeny of metabolic pathways.[48] The incorporation of elements from physiological pharmacokinetic approaches in population pharmacokinetic models with knowledge about the behaviour of other compounds with similar clearance mechanisms could optimise neonatal modelling.

## Effect of age on drug exposure in neonates

Weight-band dosing has been developed for paediatric antiretroviral agents to simplify and ease implementation. However, weight-based dosing strategies might not be entirely applicable for neonates because the pharmacokinetics of antiretroviral agents are affected by both age and weight.[13] Differences in the maturation speed of various enzymes further complicate weight-based dosing for neonates. For example, uridine glucuronosyltransferase 1A1 (UGT1A1) activity is very low at birth and increases substantially in the first weeks of life. Raltegravir, which is predominantly metabolised by UGT1A1, therefore requires a very low dose of 1·5 mg/kg once daily during the first week of life to reach adequate plasma exposures, but this dose increases to 3 mg/kg during weeks 2–4, and 6 mg/kg twice daily after 4 weeks.[45] By contrast, the ontogeny of cytochrome P450 3A4 (CYP3A4) is much slower, which means that antiretroviral agents that are metabolised through CYP3A4, such as nevirapine, require fewer dose adjustments in neonates.[49] Therefore, selection of the most appropriate antiretroviral agents for neonates could also depend on the enzyme systems that change the least in the first 4 weeks of life. As described previously, gestational age also effects drug bioavailability and clearance. In preterm babies, zidovudine clearance was approximately half of that observed for term babies due to the reduced activity of enzymes responsible for the glucuronidation of zidovudine and slower maturation.[50,51] Therefore, gestational age at birth establishes when the zidovudine dose should be increased to the full dose; this factor should also be considered for other antiretroviral agents in neonatal pharmacokinetic studies.

## Exposure to maternal antiretroviral agents

When establishing initial drug doses, transplacental transfer should be considered. If a mother receives raltegravir between 2 h and 24 h before delivery, initiation of raltegravir-based postnatal prophylaxis should be delayed for 24–48 h after birth.[45] Direct initiation of raltegravir within the first 24–48 h of life could result in high plasma concentration due to low UGT1A1 activity. A high raltegravir concentration in plasma could result in bilirubin-induced toxicity because of the competition for metabolism through UGT1A1 and the displacement of bilirubin from the albumin by raltegravir.[52] This approach also appears to be appropriate for the initiation of raltegravir in term neonates after in-utero exposure to other antiretroviral agents that are metabolised through UGT1A1 and readily cross the placenta, such as dolutegravir, bictegravir, or cabotegravir.[53,54]

Neonates can also be exposed to maternal antiretroviral agents through breastmilk.[39,55] Of the antiretroviral agents most used by breastfeeding women living with HIV (ie, dolutegravir, tenofovir disoproxil fumarate, lamivudine, and efavirenz), only lamivudine readily transfers into breastmilk.[55] The amount of lamivudine ingested over the course of a full day equals about 12% of the dose for a neonate weighing 3 kg, which is corrected for the volume of breastmilk ingested by a neonate. Exposure through breastmilk is minimal so no dose adjustments are needed for neonates on postnatal prophylaxis, who are breastfed while the mother is on antiretroviral agents. Importantly, drug exposure through breastmilk is also too low to serve as neonatal postnatal prophylaxis. However, there are

concerns that low concentrations of antiretroviral agents in breastmilk might hinder early infant diagnosis of HIV infection during the breastfeeding period.[56]

## Drug safety assessment

The existing severity tables developed for the grading of paediatric adverse events, which are typically used for safety reporting in clinical trials, are not tailored for use in neonates. Neonatal conditions (including apnoea of prematurity, respiratory distress syndrome, and necrotising enterocolitis), are not included in the latest version of the *Division of AIDS Table for Grading of Severity of Adverse Events* (version 2.1), which hinders the accurate collection of adverse event data in neonates.[57] When assigning a grade to a biochemical adverse event, the absence of established normal reference ranges for this population adds further complexity. Furthermore, it is difficult to assess the causality of a study drug to an adverse event, because critically ill neonates are generally exposed to multiple medications. Recently, the International Neonatal Consortium has described a consensus process that led to the development of standard severity criteria for neonatal adverse events.[58] This tool has the potential to address this research gap but has yet to be validated in resource-constraint settings. There is an urgent need for a standardised way to assess and grade the safety of use of antiretroviral agents in neonates so that we can compare across studies and improve safety assessments.

## Fixed-dose combinations

Dose ratios for paediatric fixed-dose combinations are generally based on adult dosages. Physiological differences between adults and infants complicate the extrapolation of these ratios to young children and neonates particularly as some medications require lower mg/kg dosages for neonates compared with older children and adults, whereas others require increased mg/kg dosages. Two single-tablet fixed-dose combinations have been developed for children, consisting of nevirapine, lamivudine, and zidovudine; and abacavir, lamivudine and ritonavir-boosted lopinavir; but neither of the dose ratios match the WHO recommended dosages for neonates for all compounds. The combination tablet of abacavir, lamivudine, and ritonavir-boosted lopinavir has been tested in neonates within the PETITE study and was found to be unsuitable as the concentration of lopinavir was too low and the concentrations of abacavir and lamivudine were towards the upper ranges reported in other studies.[19] For the combination tablet of nevirapine, lamivudine, and zidovudine, the dosage ratio is developed for children older than 4 weeks; the required dosage of nevirapine relative to the dosage of lamivudine and zidovudine is about 2-fold higher in neonates than in children older than 4 weeks and this tablet is therefore not suitable for neonatal use. Future paediatric dolutegravir-based fixed-dose combinations are not expected to be suitable for neonates as dolutegravir exposure will probably be very high when aiming for therapeutic exposure of the other antiretroviral agents due to a neonates' immature UGT1A1 metabolism. This discrepancy in exposure is even more problematic for preterm neonates. At this point, use of single-tablet fixed-dose combinations for term and preterm neonates does not seem feasible for the antiretroviral agents that are currently available.

## Recommendations to accelerate pharmacokinetic antiretroviral agent studies for neonates

Effective and timely implementation and completion of pharmacokinetic research in neonates and infants depends on various stakeholders, including pharmaceutical companies with low commercial interest due to the continually-evolving HIV epidemic and decreasing rates of vertical transmission; global research networks that are leading the investigations of neonatal and infant pharmacokinetics and pharmacodynamics for antiretroviral agents; regulatory authorities and their different requirements (eg, timely access to medications and incentives for the development of neonatal drug formulations); funding agencies that too often forget this small but extremely vulnerable population; and international organisations that are essential to ensure timely neonatal access to antiretroviral agents. All these stakeholders could join forces and develop a more effective response for timelier neonatal pharmacokinetic research and prompt availability of crucial evidence on the effect and safety of new antiretroviral agents in neonates in need of HIV treatment or prevention.

Increased research support is needed to facilitate the study of high-priority antiretroviral agents for neonatal use and to improve state-of-the-art research methodologies for neonatal studies, such as physiologically based pharmacokinetic and neonatal population pharmacokinetic modelling and simulations. Further development of novel study methodologies could improve future dose-finding studies by predicting drug exposure more accurately without the need to expose neonates to the drug, thereby minimising the volume of blood needed to be drawn from neonates in pharmacokinetic studies.

The collaboration of key stakeholders will help the neonatal HIV treatment agenda to progress. The IMPAACT P1093 and ODYSSEY trials are successful examples of such collaborations that resulted in the rapid (within 1 year after presentation of the paediatric pharmacokinetic and safety results) registration of dolutegravir paediatric dispersible tablets and accelerated access to these medications in infants older than 4 weeks.[59]

For the evaluation of new drugs for use in neonates, increased efficiency in research trial design is needed so that the time until the first clinical studies in neonates are done is reduced. With the ongoing shift towards

simultaneous enrolment of different age groups based on weight, the study of new medications in neonates should be done in parallel with, or at least close to, other age groups, unless there are specific concerns for safety in neonates.

In premarketing trials, the inclusion of pregnant women is important not only for their benefit but also as a means to obtain neonatal wash-out pharmacokinetic data early in the drug development phase through opportunistic sampling after delivery, and to acquire preliminary safety data. In the past, pregnant women and neonates have often been excluded from research protocols to protect them from new drugs with potentially harmful effects. In fact, this exclusion has had the opposite effect, as pregnant women and neonates have been exposed to the same treatments, but without regulation, and have not benefited from research interventions and learning. Currently, the inclusion of pregnant women in clinical trials for antiretroviral agents is insufficient.[60]

The development of best practices for neonatal pharmacokinetic studies with extensive safety monitoring are essential to create a foundation for researchers who are planning to study antiretroviral agents in neonates (panel). Wash-out pharmacokinetic studies in neonates after in-utero exposure to new antiretroviral agents provide initial pharmacokinetic variables to estimate the clearance of the drug in neonates. These data should be collected in all maternal trials. Initial dosages for neonates can be predicted by subsequent physiologically based pharmacokinetic modelling or population pharmacokinetic simulation on the basis of neonatal wash-out data, allometric scaling of data from older children and adults, and knowledge from other compounds with similar clearance mechanisms. A single-dose pharmacokinetic study in neonates can confirm the adequacy of the predicted dose and should be followed by population pharmacokinetic modelling to establish a potential dose and to extrapolate the efficacy from older children and adult studies. Finally, in larger cohorts of neonates receiving an antiretroviral agent as part of their treatment, opportunistic pharmacokinetic sampling and safety studies are preferable to confirm dosing and safety for the broader population.

It is important that new antiretroviral agents and drug formulations are considered for use in neonates earlier in the drug development cycle so that plans can be made for the development of neonate-appropriate formulations. Many new formulations and antiretroviral agents are being developed, but few end up being used in neonates. The inclusion of neonates in early studies of bNAbs before US FDA registration for adults will set a precedent for the development of other neonatal antiretroviral agents. Research priorities as defined by PADO-HIV 5 facilitate the decision making around which antiretroviral agents and formulations should be developed for neonatal use.

In conclusion, treatment options for prevention or treatment of HIV in neonates are not addressing the specific needs of this population and, as a result, neonates are being left behind in research. Despite substantial efforts to increase awareness, the time between market authorisation in adults and the first published pharmacokinetic data in neonates has increased recently and the future does not look promising unless urgent action is taken to change this trajectory. As the WHO-hosted GAPf network[61] creates a renewed momentum to spark collaborations and address the needs of all children irrespective of their age, neonates must be an urgent focus of attention for shared commitment and action. As the Nurturing Care for Early Childhood Development community says: "if you change the beginning of the story you change the whole story".[62]

#### Contributors

TGJ, SS, and AC conceptualised the manuscript. TGJ, SS, AB, and AC developed the initial draft. All authors made substantial contributions to the paper and approved the final version.

#### Declaration of interests

AB has received honoraria from Sandoz, and trial grants from National Institute of Health and UNITAID. AC has received honoraria from Merck Sharp and Dohme, paid to her institution, and trial grants from ViiV Healthcare, Gilead, and Merck, paid to her institution. All other authors declare no competing interests.

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