Considerations for the use of Long-acting and Extended-release Agents During Pregnancy and Lactation

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Abstract

Long-acting agents hold significant promise for treating and preventing common illnesses, including infections. Pharmacokinetic and safety data during pregnancy and lactation are often unavailable for new drugs; these data are vital to facilitate optimal drug use by pregnant and lactating women and women who may conceive. In this commentary, we summarize the circumstances in which pregnant and lactating women are likely to use and benefit from long-acting agents. We focus on long-acting formulations of small molecules (rather than biologics such as monoclonal antibodies) and on several infections of global importance (HIV, tuberculosis, malaria, and hepatitis C). We discuss pregnancy pharmacokinetic/pharmacodynamic and potential safety and efficacy considerations pertaining to the use of long-acting agents in pregnancy and lactation. Finally, we summarize existing pre-clinical and pregnancy pharmacokinetic data that are available (or expected in the near future) for several agents that are under development or approved, and how key research gaps may be addressed.

Introduction

Twenty million women are living with HIV, approximately 1.3 million pregnancies occur annually in women with HIV, and half of new HIV infections occur in women [1]. Antiretroviral treatment (ART) is recommended for all persons living with HIV, including throughout pregnancy, and pre-exposure prophylaxis (PrEP) is recommended for persons at high risk for HIV to reduce their risk of acquiring the virus (with pregnancy a potentially higher-risk period for HIV acquisition) [2, 3]. More than 3 million women are estimated to have active tuberculosis each year [4] (more than 200,000 during pregnancy) [5] and one in four individuals is believed to be living with latent tuberculosis infection (LTBI), many of whom qualify for LTBI treatment [6]. Pregnant women are also particularly susceptible to malaria and to severe malaria disease [7], and malaria in pregnancy is a major cause of maternal morbidity and mortality and of adverse pregnancy outcomes [8]. Pregnant women can transmit hepatitis B or C to their fetus/newborn, if untreated. These are among the many common infectious diseases that often warrant treatment or prevention during pregnancy.

Long-acting (LA) agents for treatment and prevention hold significant promise for patients, providers, and programs. They may help overcome barriers related to adherence and stigma [9, 10]. In most studies, the majority of individuals express preference for LA agents (including injectables) over daily oral pills when used for HIV antiretroviral treatment (ART) and pre-exposure prophylaxis (PrEP) (e.g., 91% of participants in a trial of LA cabotegravir/rilpivirine injections for HIV treatment preferred the LA therapy) [11-14]. An example of demonstrated patient and program preference for LA agents (when a mixture of different formulations is available) is the greater increase over time in the number of women who are using LA injectable reversible contraception with a compared with daily oral hormonal contraception

globally [15]. LA agents may be particularly attractive to women during pregnancy and postpartum, periods that can be associated with greater adherence challenges [16-18] (particularly postpartum, when women may be breastfeeding).

We must also anticipate that substantial numbers of women will conceive while taking LA agents. Therapeutic levels of LA agents often persist for months after the last dose; hence, even if women were to stop a LA drug as soon as pregnancy is diagnosed, mother and fetus will experience prolonged exposure to the agent. The absence of pregnancy and lactation PK and safety data may deter patients, providers and programs from offering potent and preferred LA agents to women of childbearing potential and to pregnant/lactating women. Women who are pregnant or breastfeeding (or who may conceive) should not be denied the opportunity to take the optimal prevention and treatment agents, including promising LA agents. They deserve access to timely, high-quality quality pregnancy data to inform their medical care decisions. It is thus important that we understand the PK/PD and safety of LA drugs during pregnancy.

Key Pharmacokinetic Considerations for LA Formulations Use in Pregnancy

Measures of drug exposure derived from adequate characterization of pharmacokinetics often form the basis for decisions about safe and effective drug concentration. For drugs with existing oral formulations, LA formulations are usually designed to achieve and maintain systemic exposures already established to be safe and effective throughout the dosing interval. This simplifies the regulatory application process (e.g. through the FDA 505(b)(2) abbreviated approval pathway). Here we highlight three features that are unique to LA

formulations that are also relevant to pregnancy/lactation PK and safey: flip-flop kinetics, burst release and inactive pharmaceutical ingredients.

Flip-flop kinetics and fetal drug exposure

For most immediate-release orally administered drugs, the elimination rate is slower than absorption rate, hence the concentration at steady state is a function of the elimination rate. One of the key attributes of LA formulations is their flip-flop pharmacokinetics, characterized by a slower rate of absorption than elimination. Since a drug cannot be eliminated any faster than it enters into the systemic circulation, drug release and absorption from the site of administration becomes the limiting process for overall disposition. This enables control of payload delivery over an extended period from LA formulations, allowing dosing intervals ranging from monthly to longer [19]. The flip-flop phenomenon has important implications for what to expect when a pregnant or lactating woman is administered a LA drug. For drugs that cross the placenta or excreted into breastmilk, maternal plasma drug concentration is the key driver of fetal or breastfed infant drug exposure; hence the major difference between immediate-release oral and LA formulations will be driven mainly by changes in bioavailability, not by the total amount of drug per dose. Parenterally administered LA formulations avoid first-pass hepatic metabolism, which often increases their bioavailability subject to the influence of drug and formulation properties, patient factors, and injection site vascularity. Interestingly, the reduced peak-to-trough plasma concentration differences and fluctuations resulting from slower absorption rate, often leads to fewer side effects and better tolerability of LA. The implications of this on peak *in utero* fetal or breastfed infant drug exposure has not been explored.

Burst release and maternal/fetal drug exposure

An initial release of a large bolus of drug immediately after injection has been observed with several LA formulations. Depending on formulation characteristics, up to 25% of total administered dose may be involved in this burst release, resulting in significantly higher initial versus subsequent steady state plasma concentration. Possible mechanisms and clinical examples from FDA approved LA formulations have been described elsewhere [20, 21]. Importantly, the pharmacokinetic profiles of the LA injectable antiretroviral drugs cabotegravir [22], rilpivirine [23] and doravirine [24] show the presence of an initial rapid release followed by a prolonged release. Therefore, adequate characterization of the pharmacokinetics of LA drug in the period immediately after administration in non-pregnant adults is crucial to enable proper assessment of likely worst-case maternal and fetal exposure scenarios during pregnancy. Where burst release is significant and uncontrollable, its implications for side effect profile and tail phase pharmacokinetics of the LA drug will require comprehensive assessment to generate the necessary data to guide their use during pregnancy. A major consideration in such assessment will be fetal and neonatal drug elimination capacity, and whether significant initial 'loss' due to burst release may result in subtherapeutic drug concentration before the next dose is due. For example, available evidence indicates immaturity of the hepatic glucuronidation pathway in the prenatal [25] and neonatal [26] periods, hence high-level fetal or neonatal exposure is likely to result in significant accumulation in the absence of efflux transporter role.

Maternal adaptation to pregnancy, pharmacogenetic variability and drug-drug interactions

Maternal adaptation to pregnancy results in physiological changes that alter the pharmacokinetics of several drugs, often through hormonal influence on transcriptional

regulation of disposition genes. For many immediate-release orally administered drugs, plasma concentration remains above the minimum effective concentration and no dosage adjustment is warranted. For example, effective concentration of rilpivirine from daily oral formulation is maintained during pregnancy despite significantly lower exposure versus postpartum [27, 28]. If the disposition pathway of a LA agent has a high propensity for pregnancy-induced changes, there is a need to evaluate the implications for tail-phase pharmacokinetics and, if necessary, review the adequacy of dosing interval established based on data from non-pregnant adults.

A better understanding of the inter-individual variability in LA pharmacokinetics in the general population is desirable to provide the needed foundation for assessment of how these may be further impacted during pregnancy, as well as the consequences for fetal exposure. Previous studies with orally administered drugs showed that pregnancy-induced changes may be accentuated in certain subsets of patients due to polymorphisms in drug disposition genes, e.g. CYP2B6 substrates efavirenz [29] and CYP2D6 substrate paroxetine leading to increased incidence of depressive symptoms during pregnancy [30]. The *CYP2D6* poor metabolizer genotype is associated with higher incidence of side effects in patients receiving LA antipsychotic risperidone [31]. *UGT1A1* polymorphisms were shown to affect steady state cabotegravir pharmacokinetics from oral and LA injectable formulations leading to higher exposure in carriers of reduced-function alleles (*6, *28 and *37) versus non-carriers. The combined influence of pregnancy-induced changes and function-enhancing alleles on daily trough concentration seen with immediate release formulations will be absent in LA formulations. However, evaluation of how these may affect tail-phase pharmacokinetics of LA formulations and the potential clinical implications warrant further investigation,

especially for drugs with significant genetic contribution to observed pharmacokinetic variability.

The disposition pathway of a LA drug will determine its propensity for drug-drug interaction. For example, cabotegravir is metabolized primarily by UGT1A1, and rilpivirine by CYP3A4, hence they are potential victims of drug-drug interaction when co-administered with inhibitors or inducers of these enzymes. The clinical significance of any potential drug-drug interaction with LA depends on certain key factors, including the directionality of impact, duration of treatment with co-administered drug (e.g. 3-day antimalarial therapy versus LA contraceptive), and the magnitude of impact on exposure. A recent review based on Liverpool drug interaction website indicates that 21% of expected drug-drug interactions with LA cabotegravir and rilpivirine are likely to be clinically important, generally mirroring expectations for their oral formulations [32]. As with pharmacogenetic variability, the clinical significance of any drug-drug interaction with LA will depend on how much it confounds pregnancy-induced alterations in tail-phase pharmacokinetics. In both cases, significant changes in trough concentration at tail may necessitate considering adjusting the dosing interval.

Leveraging model-informed approaches to optimize the use of LA drugs in pregnancy

Considering the potential challenges of conducting a dedicated PK study for LA agents in healthy pregnant women volunteers, model-based approaches are required and supported by existing regulatory guidance. The important role of quantitative modelling and simulation approaches (e.g. PK/PD modeling, population PK modeling, physiologically based PK (PBPK) modeling, and exposure-response analysis) in streamlining LA products was recently

extensively reviewed [33]. Using a physiologically based pharmacokinetic modelling approach, co-administration of rifampicin with LA injectable cabotegravir and rilpivirine is predicted to result in sub-therapeutic concentrations of both drugs (41-82% decrease in trough plasma concentration on day 28) in non-pregnant adults [34]. Several applications of PBPK modelling in materno-fetal pharmacology have been published and summarized in a recent review [35]. We believe that materno-fetal PBPK models with acceptable predictive capacity confirmed by real-world data across multiple therapeutics can be used to characterize maternal and fetal drug exposure in relevant unstudied clinical scenarios to support decision-making and facilitate best practice, including:

- Potential implications of burst release on maternal and fetal/infant drug exposure.
- Combined influence of pregnancy-induced changes and pharmacogenetic variability or drug-drug interactions.
- Adequacy of dose in women who become pregnant while enrolled in a phase III trial and agree to continue study drug.
- Assessing the adequacy in pregnancy of doses and dosing intervals not included in clinical trials, without the need for a dedicated phase clinical trial for regulatory approval.
- Model-informed bioequivalence studies in pregnant women for generic LA formulations with adequately characterized release kinetics.

Ongoing work at the University of Liverpool includes qualifying our existing materno-fetal PBPK models [36, 37] for LA formulations to explore some of these scenarios.

Need for Better Preclinical Models of Developmental and Reproductive Toxicity (DART)

Animal models currently used for preclinical assessment of human DART (typically in two species, one rodent and one nonrodent such as rabbit [38, 39]) are inadequate in their representation of human physiology. Significant advances in tissue and biomedical engineering in the last few years have led to the development of models that better recapitulate human physiology [40]. A separate paper in this issue highlights their potential in bridging existing gaps in DART assessment to facilitate early inclusion of pregnant women in clinical trials [41]. Early insight from human-relevant models will be a key strategy for improving preclinical testing of novel LA drug candidates to inform decisions about agents that can safely be advanced to clinical trials in pregnant women.

Safety of LA agents in pregnancy and lactation: general considerations

Duration of fetal/infant exposure to drug

In contrast to short-acting agents, LA or depot agents taken in pregnancy will by definition be detectable in maternal plasma for a prolonged period even after cessation (with the exception of removable delivery systems that elute short-acting drugs). This has several implications. Initiation of a LA agent during pregnancy may result in detectable maternal drug levels throughout the remainder of the pregnancy, for injections that are administered every month or less frequently. Non-pregnant people who are taking LA agents would need to stop the drug many months prior to conception in order to avoid first-trimester drug exposure. Conception while actively taking a LA agent will result in first-trimester exposure and in many cases, detectable drug levels throughout pregnancy, even if the drug is stopped as soon as pregnancy is confirmed. If a LA agent is stopped early in pregnancy and other agents are substituted (in cases when use of a treatment or prevention agent is deemed necessary), the

mother and fetus will be exposed to a greater number of drugs during pregnancy (compared with continuation of the LA agent alone).

Safety of formulation excipients in pregnancy and lactation

A recent review identified more than 60 excipients used in LA formulations to control drug release, stabilize suspensions, buffer pH and control osmolarity, provide mechanical strength and to control other properties [42]. Although excipient-induced toxicities have been observed [43], manufacturers of LA formulations have to choose from any of the following three excipients approval mechanisms: (1) presence on the FDA generally recognized as safe (GRAS) substances list; (2) pre-qualified based on prior safety testing for an approved drug; or (3) qualified as part of preclinical safety and toxicity package. The regulatory requirements for new excipients with no prior safety information will vary depending on the clinical situation, including the expected treatment duration (e.g. acute versus chronic), amount per dose, and route of administration. The GRAS list summarises safety reports of over 370 substances, each one assigned a conclusion type on a scale ranging from 1 (high level of confidence on safety) to 5 (lowest level of confidence due to insufficient data). Therefore, where excipients on the GRAS list with no safety liabilities in similar circumstances are used, there are usually no concerns about their safety during pregnancy, the only exception being where an excipient has been size-reduced to under 1000 nm or incorporated into a nanomaterial as these may alter its biodistribution [44]. Confirmation of safety within a full preclinical toxicology programme is usually required to support the use of novel excipients in LA formulations.

Bioavailability of the drug

As noted earlier, bioavailability differs by drug formulation. The Cmax tends to not be as high with LA agents (with the exception of burst) but declines more slowly. For drugs for which the Cmax is correlated with toxicity (including that related to pregnancy/fetal outcomes), some LA agents may be expected to have lower toxicity than oral agents. However, LA formulations that have greater bioavailability than oral administration could be associated with greater toxicity.

Available and planned pregnancy/lactation PK and safety data for LA agents that are approved or in development for treating/preventing HIV, tuberculosis, and malaria

More than 95% of all drugs approved by the U.S. Food and Drug Administration from 2000-2010 had undetermined teratogenic risk and 70% had no human pregnancy data [45], primarily a result of the routine exclusion of pregnant and lactating women from clinical trials [46]. More pregnancy data exist for drugs used to treat HIV than for most other medical conditions; however, even when available, these data are generally limited (to pregnancy pharmacokinetics [PK] with minimal safety information in a small number of women) and are only available a median of 6 years after drug registration [47] (following collection in "opportunistic" PK studies among pregnant women who are taking approved medications in routine clinical care).

Unfortunately, the absence of pregnancy/lactation PK and safety data is even more stark for LA agents used to treat/prevent HIV, tuberculosis and malaria—almost no human data are available yet. Some of these drugs (such as the HIV antiretroviral rilpivirine and the anti-tuberculosis agents rifapentine and rifabutin) have been administered for years as daily oral

therapy and have accumulated some pregnancy/lactation PK and safety data (Table 1). Others (such as the LA HIV antiretroviral agents cabotegravir, islatravir, and lenacapavir) are first being used in humans in their LA formulations.

Retrospective analysis of safety outcome data in pregnancy registries from opportunistic exposures to LA agents will likely provide the first preliminary insight. Hence, it is critically important to capture as many off-label exposures as possible (e.g. LA cabotegravir and rilpivirine was added to the antiretroviral pregnancy registry shortly after approval [52]).

Closing the research gap: potential approaches to safety and efficacy studies of LA agents in pregnancy and lactation

Numerous stakeholders have articulated the need for and potential ethical and feasible approaches to accelerating the study of new drugs during pregnancy and lactation, including for HIV [60]. Some key principles from this work include: 1) involve women from affected populations throughout research design, recruitment, conduct and results dissemination; 2) perform non-clinical DART studies earlier during drug development; 3) if non-clinical DART studies do not raise concern and after dose is established in non-pregnant adults, permit women who become pregnant in trials to consent to stay on study drug if they wish, and evaluate pregnancy/lactation PK and preliminary safety (alternatively or in addition, enroll pregnant women in small pregnancy PK/preliminary safety studies, considering risk:benefit); 4) investigate adverse pregnancy/birth outcomes through dedicated pregnancy safety studies for priority agents that are expected to be important for young/pregnant/lactating women (to start late in Phase III or shortly after licensure); and 5) expand active post-licensure surveillance of drug safety in pregnancy.

Note that offering women who become pregnant in trials the option to consent to stay on study drug (and studying pregnancy PK/safety in these participants) is an important step towards enhancing timely availability of pregnancy/lactation data and makes particular sense with LA agents, as the mother/fetus will usually be exposed to drug throughout most of the remaining pregnancy even if it is stopped after pregnancy is diagnosed (and switching study drug to alternative treatment will expose the mother and fetus to a larger number of drugs).

Approaches to studying pregnancy PK

It is reasonable to consider a tiered approach to studying LA agents in pregnancy/lactation, incorporating a formulation risk definition that follows the FDA categorization of LA formulations which is based on the predictability of drug release rate and the risk of clinically significant changes in biodistribution with the LA formulation -- e.g. to the placenta -- compared with the free drug [44]:

- **Tier 1**: Drugs with established safety record for the oral formulation in human pregnancy/lactation, but no data on the LA formulation: if the formulation is low risk (per the FDA definition), conduct in silico pregnancy PK studies to assess the expected impact of pregnancy on maternal/fetal exposure. Include pregnant women in clinical trial (using model-informed pregnancy dosing interval where applicable), and assess tail phase pharmacokinetics and newborn exposure at delivery.
- **Tier 2**: Drugs with inadequate data on safety in human pregnancy for oral formulation, and no pregnancy data on LA formulation (but dose established in non-pregnant adults): conduct in silico pregnancy PK study to assess expected impact of pregnancy on maternal/fetal exposure. If drug is not specifically contraindicated in pregnancy (based on

non-clinical data) and formulation is low risk (per FDA definition), permit women who become pregnant in Phase III clinical trials (of oral or LA formulation) to consent to continue study drug, evaluate PK (including maternal tail phase and newborn at delivery) and safety.

- **Tier 3**: Medium to high risk LA formulation of drugs with an oral equivalent that is known to be embryotoxic in preclinical animal models but no information in human pregnancy, or novel drug candidate that is only suitable for LA formulation: consider resolving any DART uncertainties by using adequately qualified novel preclinical *in vitro* models that are relevant to human pregnancy and resolve uncertainties in release kinetics and tissue distribution. If both categories of uncertainties are positively resolved, handle as tier 2. This aligns with current FDA thinking about the use of new alternative methods [61].

Approaches to studying pregnancy/lactation safety of LA agents

For LA agents that have an established human pregnancy/lactation safety record for the oral formulation (and that use a GRAS excipient), it would generally not be necessary to replicate these safety data (unless pregnancy PK studies raise potential concerns, e.g. if greater drug exposure is expected with the LA compared with usual oral formulation). If no pregnancy/lactation safety data are available for the active drug in an LA agent (e.g. from studies of the oral equivalent), then it would be important to gather pregnancy safety data from at least a small number of women (who become pregnant in clinical trials, or who enroll during pregnancy). For drugs, including LA agents, that are likely to be of substantial importance for women of childbearing potential, pregnancy/lactation safety data should ideally be collected in larger interventional studies. High-quality post-marketing surveillance will be essential when LA agents are scaled up post-approval, as the majority of pregnancy

exposures to LA drugs will likely be in women who conceive on them (and it is not feasible to study early first trimester exposure in interventional trials).

Pregnancy/lactation safety studies should focus on outcomes that are uniquely important to mothers and infants. For pregnancy exposure, these includes birth outcomes (preterm/very preterm birth, fetal loss, small/very small for gestational age); congenital anomalies; neonatal mortality; maternal adverse events that can differ between pregnant and non-pregnant women (e.g. gestational diabetes, hypertension, pre-eclampsia, hepatotoxicity, maternal neuropsychiatric concerns, insufficient or excess gestational weight gain); and, where possible, infant growth and fertility. For lactation exposure, where possible, infants should be monitored for adverse effects (with monitoring targeted to the known side effects of the drug) and growth.

Studying efficacy of LA agents in pregnancy

If PK studies of LA agents indicate adequate drug exposure during pregnancy, it will generally not be necessary to specifically test efficacy of these agents in pregnancy.

Conclusion (250 words)

Long-acting agents will almost certainly become increasingly important for treating and preventing illnesses globally, including infections. Pregnant and postpartum women would benefit from being able to access these drugs, and will conceive while taking LA agents once they are offered in clinical settings. Differences in pregnancy PK between LA and daily oral formulations may affect drug dosing and safety in pregnancy. Pregnant and lactating women should have quality pregnancy/lactation PK and safety data to inform their medical care

decisions; these data are almost completely absent to date. Several research approaches during drug development and post-licensure should be implemented, to improve the timely availability of pregnancy/lactation data for LA agents that are likely to be of importance to young and pregnant/lactating women.

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Table 1. Existing/planned pregnancy/lactation PK and safety data for LA agents that are approved or in advanced stages of development, for treating and/or preventing HIV, tuberculosis, and malaria

Long-acting agent[#]	Existing pregnancy/lactation PK data	Existing pregnancy safety data	Ongoing/planned pregnancy PK and safety data collection
HIV			
Cabotegravir (CAB) LAI	-- No human pregnancy PK data available for oral formulation -- In 6 pregnant women stopping CAB/RIL LA, rate of [CAB] decline was similar to rate in non-pregnant adults [48] -- Low placental CAB transfer in *ex vivo* model [49] --No human breast milk PK data	--26 women conceiving on CAB/RIL LA (stopped injections): 8 elective/7 spontaneous abortions, 11 live births [48]: • 10 term, 1 at 36 weeks • 1 baby with growth restriction and congenital ptosis (maternal risks)	--Women who become pregnant in open-label extension of the HPTN 084 trial of CAB LA PrEP (NCT03164564) may consent to stay on study drug and take part in PK/safety assessment --Women who become pregnant in CAB/RPV treatment trials (SOLAR, CARES, LATA) may consent to stay on drug/on

		--29 women conceived on CAB LA PrEP in HPTN 084 (stopped injections): 18 with pregnancy outcome, 13/18 livebirth, 5 fetal losses, no congenital anomalies observed [50]	study, to collect pregnancy and breastmilk PK and pregnancy safety outcomes
Rilpivirine (RPV) LAI	--Studies of daily oral RPV show 30-50% lower RPV exposure in pregnancy [27, 51] -- In 6 pregnant women stopping CAB/RPV LA, rate of [RPV] decline was similar to rate in non-pregnant adults [48]	-- 631 women with 1st trimester RIL exposure; no increase in rate of birth defects over background [52]	--Women who become pregnant in CAB/RPV treatment trials (SOLAR, CARES, LATA) may consent to stay on drug/on study, to collect pregnancy and breastmilk PK and pregnancy safety outcomes

Islatravir LAI	--No human pregnancy/lactation data	--No human pregnancy/lactation data	--Women who become pregnant in PrEP trial (MK-8591-022 IMPOWER 022) and treatment trial (combination of ISL/MK-8507, study MK-8591-013) may consent to stay on drug/on study, to collect pregnancy PK and pregnancy/infant safety outcomes, but ISL studies on clinical hold
Lenacapavir LAI	--No human pregnancy/lactation data	--No human pregnancy/lactation data	--Women who become pregnant in PrEP trial (NCT 04994509) may consent to stay on drug/on study, to collect pregnancy and breastmilk PK and pregnancy/infant safety outcomes

MK-8507	--No human pregnancy/lactation data	--No human pregnancy/lactation data	--Women who become pregnant in (combination of ISL/MK-8507, study MK-8591-013) may consent to stay on drug/on study, to collect pregnancy PK and pregnancy/infant safety outcomes, but ISL studies on clinical hold
Tuberculosis*			
Rifapentine LA	--IMPAACT 2001 trial of weekly oral rifapentine/isoniazid TB preventive therapy in 50 pregnant women; adequate pregnancy PK exposures --No human pregnancy/lactation data with LA formulations	-- No specific safety concerns in IMPAACT 2001 participants [53] --No human pregnancy/lactation data with LA formulations	

Bedaquiline LA	--No human pregnancy/lactation data	--Virtually no human pregnancy/lactation data [54]	
Rifabutin LA	--No human pregnancy/lactation data	--No human pregnancy/lactation data	
Delamanid LA	--No human pregnancy/lactation data concerns from pre-clinical DART studies	--Virtually no human pregnancy/lactation data (DART studies: embryofetal toxicity in rabbits at maternally toxic doses) [54]	
Malaria			

Atovaquone LA	--Minimal pregnancy PK data with oral atovaquone-proguanil (low plasma concentrations) [55]	--Observational studies of safety of oral atovaquone-proguanil inconclusive [56, 57]	
ELQ-331 [57]	--No human pregnancy/lactation data	--No human pregnancy/lactation data	
Hepatitis C			
Glecaprevir / pibrentasvir	--No human pregnancy/lactation data [59]	--No human pregnancy/lactation data	

[#] Long-acting formulations of some existing drugs are currently in preclinical development for malaria and tuberculosis prevention, and hepatitis C cure in the LONGEVITY project being implemented by the University of Liverpool in collaboration with partners.

* Several tuberculosis treatment trials of standard oral therapy are permitting women who become pregnant on-study to stay in the study: endTB (NCT02754765), endTB-Q (NCT03896685), and BEAT Tuberculosis (NCT04062201).