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Understanding clinical outcome measures reported in HIV pregnancy studies involving antiretroviral-naive and antiretroviral-experienced women

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Abstract

HIV infection is a clinically significant public health disease and contributes to increased risk of maternal and fetal morbidity and mortality. HIV pregnancy studies use outcome measures as metrics to show how people with HIV feel, function, or survive. These endpoints are crucial for tracking the evolution of HIV illness over time, assessing the effectiveness of antiretroviral therapy (ART), and comparing outcomes across studies. Although the need for ideal outcome measures is widely acknowledged, selecting acceptable outcome measures for these HIV pregnancy studies can be challenging. We discuss the many outcome measures that have been implemented over time to assess HIV in pregnancy studies, their benefits, and drawbacks. Finally, we offer suggestions for improving the reporting of outcome measures in HIV in pregnancy studies. Medical professionals can best care for pregnant women living with HIV receiving ART by having a thorough understanding of these outcome metrics.

Introduction

HIV infection is an important global obstetric health burden that contributes to an increased risk of maternal and fetal morbidity and mortality.[1] An estimated 38 million people are living with HIV globally, of whom 1·3 million become pregnant each year.[2] Most pregnancies in women living with HIV occur in low-income and middle-income countries

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We declare no competing interests.

(LMICs).[3] HIV, especially the pharmacokinetics and pharmacodynamics of antiretroviral therapy (ART), is one of the most studied of any infections during pregnancy,[4] and the majority of perinatal HIV research suggest a priori outcome measures (endpoints) to monitor clinically significant alterations after exposure to ART.

Although HIV research since 1994 has had a substantial focus on pregnant women, there are still remarkable information gaps regarding the safety and efficacy of novel ARTs during pregnancy, since pregnant women are often excluded from phase 1, 2, and sometimes phase 3 clinical trials.[5] Despite the need for more trials being acknowledged, several obstacles and ethical challenges prevent crucial therapeutic trials in pregnant women living with HIV from being done.[6] In addition, clinical trials frequently have stringent criteria for the involvement of participants, short follow-up periods, and assess only standardised endpoints.[7] Because randomised trials are frequently unable to evaluate all scenarios in clinical practice, many conclusions drawn from these studies cannot be directly applied in actual clinical settings, limiting external validity of some study results.

An important component of the quality of most HIV studies is the type of clinical outcome measures examined. Although most endpoints are clinical outcome measures that portray benefits to patients (how patients feel, function, or survive), a few are validated surrogate endpoints (outcomes that have been shown to predict clinical benefits).[8] Several clinical and a few validated surrogate outcome measures have been reported in pregnancy HIV studies. These endpoints are critical in determining HIV disease-related progression that occurs over time, evaluating the effect of clinical and laboratory evaluation, illustrating the effectiveness of interventions including ART, pinpointing areas in need of improvement, and comparing results between pregnancy HIV studies. Despite these advantages, choosing appropriate outcome measures can be difficult even though the necessity for optimal outcome measures is widely recognised.

The discussions in this Personal View focus on the many outcome measures that have been implemented over time to assess HIV in pregnancy studies, their benefits and drawbacks, and suggestions on how to enhance the reporting of outcome measures in HIV pregnancy research. A detailed analysis of these outcome measures will assist physicians in providing optimal care for pregnant women living with HIV who receive ART. We have summarised key evidence available on the outcome measures associated with use of ART in pregnant women living with HIV (table).

HIV viral load and CD4 count

The amount of HIV RNA in plasma (viral load) and the CD4 T-cell count have historically been the two most frequently reported, validated surrogate outcome measures in the management of HIV infection in pregnancy.[9,10] As pharmacodynamic measures, both CD4 count and viral load measure the degree of HIV progression and the efficacy of ART. A decline of viral load to undetectable levels (expressed as $\log_{10}$ copies per mL) is typically consistent with viral suppression and no viral transmission to the fetus. Although a high viral load and a low CD4 cell count should raise suspicion for non-adherence to ART, or therapeutic failure from low ART plasma concentrations as a result of the physiological

changes that occur during pregnancy, it should also raise concerns for increased maternal morbidities and the potential for perinatal transmission. As a result, trends in viral load and CD4 cell counts during pregnancy are useful indicators of treatment compliance, the extent of HIV infection, and ultimately, the mode of delivery (vaginal *vs* caesarean).[11]

A challenge in using viral load as a validated surrogate outcome measure in pregnancy HIV studies is the extensive variability in the lower limits of quantitation (LLQ) and lower limits of detection (LLD) for several viral load assays.[12] The LLQ and LLD vary extensively across studies, with LLD values commonly reported between less than 20 to up to 200 copies/mL.[13] As a result, many perinatal HIV studies have used a wide range of LLD viral load thresholds.[14,15] The risk of virological failure (failure to attain and keep HIV RNA levels below a predetermined target) remains a concern with increasing viral load. In addition, persistent low-level viraemia (persistent HIV RNA levels above the LLD of an assay but below a predetermined target) can increase the risk of virological failure.[16] In pregnant women living with HIV, these risks have been shown to be clinically significantly lower in women with viral loads of less than 50 copies per mL compared with women who have higher viral loads. For example, in a prospective cohort study in the UK and Ireland, vertical transmission risk was lower in women with viral loads of less than 50 copies per mL compared with women whose viral load was between 50 and 399 copies per mL (0·09% *vs* 1·0%, p<0·05) regardless of when ART was initiated.[17] Although there is a direct correlation between increasing maternal viral load and vertical transmission of HIV, there is no evidence that elective caesarean section provides any further protection against vertical HIV transmission in women with low (50–999 copies per mL) or undetectable viral loads who are receiving ART and concurrently monitoring therapy with viral load assays.[17,18]

The question of the best cutoff (optimal) viral load for preventing vertical transmission, rebound, and drug resistance to be used in pregnancy studies is pertinent because of the implications regarding the risk for perinatal HIV transmission. The optimal HIV viral load cutoff differs between LMICs and high-resource settings. Even though WHO recommends a threshold of 1000 copies per mL[19] to define virological failure, which has been implemented by many LMICs, most high-resource countries use thresholds defined by the US Department of Health and Human Services (ie, <200 copies per mL) or less than 400 copies per mL.[20–22] Although an exact cutoff has not been established, the optimal viral load threshold used for preventing vertical transmission during vaginal deliveries was 1000 copies per mL in 5 of 23 countries, 400 copies per mL in 3 countries, and 50 copies per mL in 11 countries,[23] emphasising extensive variations in clinical care based on predetermined viral load thresholds.

In situations of virological failure during pregnancy, a comprehensive examination should be done, considering aspects linked to HIV, medication adherence, and type of ART regimens used. For all pregnant women living with HIV who are ART-naive and have HIV RNA levels greater than the resistance testing threshold, medication resistance testing is indicated before starting ART treatment during pregnancy. While awaiting results of resistance testing, starting ART should not be postponed, but changes to ART regimens can be made, if necessary, once the results are known. Pregnant women living with HIV who have detectable HIV RNA levels before entering prenatal care while taking ART, or who have poor

virological suppression to a new regimen begun in pregnancy, should undergo resistance testing before changing their ART regimens.

The CD4 T lymphocyte count is usually a measure of immune status. Although a decline in CD4 count often indicates worsening HIV disease, it can also occur as a result of physiological changes related to pregnancy.[24] Despite no cutoff CD4 count being recommended (above which increased risk of vertical transmission occurs), some HIV pregnancy studies have used the US Centers for Disease Control and Prevention cutoff value for CD4 of 500 cells per mL as the upper limit signifying immunosuppression.[25–27] Even though viral load and CD4 count are usually used together in HIV pregnancy studies to establish the risk of vertical transmission and disease progression,[28,29] CD4 counts were shown to be independent risk factors for HIV vertical transmission in some HIV pregnancy studies.[25–27]

Timing of CD4 and viral load measurements during pregnancy is crucial. Baseline viral load assays should be done approximately 2–4 weeks after the start of ART. Checking viral load at least once per trimester (or as clinically indicated) is reasonable; at approximately 35–36 weeks of gestation; and at the time of delivery. In addition, in women with virological failure, viral load should be evaluated before switching ART and after approximately 4–8 weeks of ART change to ensure an appropriate response to therapy. Afterwards, monitoring viral load every 4–8 weeks is recommended until the load is lower than the LLD of the assay used.[30] The availability of viral load testing, ART medication adherence, and drug–drug interactions can all have an effect on the frequency of viral load testing in pregnancy.

Nevertheless, viral load and CD4 counts are still effective measures of compliance, vertical transmission, and ART adherence, and they are unlikely to be replaced by other pharmacodynamic surrogate outcome measures in HIV in pregnancy research, considering that they are typically the only metrics used to assess patients' health when evaluating the efficacy and cost of interventions.[31] We recommend that viral load and CD4 counts continue to be used as proxies for medication adherence, control of HIV infection, and prevention of perinatal HIV transmission.

Congenital anomalies

Congenital anomalies are conditions that can have harmful effects on the health, development, and survival of babies. Congenital anomalies can be single defects or multiple defects and can be associated with one or more ARTs. Similar to most drugs used during pregnancy, the risk of congenital anomalies associated with ART has been an issue of concern and debate for several years. As such, several pregnancy HIV studies have reported congenital anomalies as outcome measures.[32–34] Fortunately, despite early reports linking some ART, such as efavirenz and dolutegravir with teratogenicity, more recent data have not.[35,36] Congenital anomalies associated with ART are most commonly reported to the European Pregnancy and Paediatric HIV Cohort Collaboration and the Antiretroviral Pregnancy Registry.[37,38]

Challenges exist with reporting congenital anomalies as the primary outcome in pregnancy HIV studies. There must be a large enough sample size to rule out a three-fold increase in congenital anomalies with a prevalence of 0·1% or less to establish a causal link between a drug and a rare outcome such as a congenital malformation.[39] Because most congenital defects are rare outcomes, a fundamental problem with most prenatal HIV research is low statistical power to show a causal association between ART and congenital anomalies. A second problem in using congenital anomalies as outcome measures in HIV studies of pregnant women treated with ART is the inability to prove causality. The existence of a causal relationship between an exposure (eg ART) and an outcome (eg, congenital anomaly) has been traditionally determined with the Bradford Hill causal criteria.[40] Although some of the Bradford Hill criteria have been identified as having a probable causal effect on the development of congenital anomalies in pregnant women living with HIV on ART (eg, temporality—the link between use of ART early in pregnancy and the development of congenital anomalies, supported by the implementation of two initiatives—Prevention of mother-to-child transmission of HIV and the test-and-treat HIV initiatives), relying on one or a few Bradford Hill's criteria to prove a causal relationship between ART exposure and congenital malformations is typically challenging. Other Bradford Hill's criteria, such as dose–response (increasing doses of a drug linked to increasing severity of a congenital anomaly) and consistency of data (demonstration of reproducible and distinctive effect of an exposure on organs or systems under different circumstances)[41] have undergone considerable debate as criteria for causality. Dose–response relationships (ie, the biological gradient) between an exposure and an outcome offer strong support for the existence of a causal relationship,[42] but the absence of such a relationship (eg, between ART exposure and congenital anomalies) should not be interpreted as evidence against it,[42] because an induction threshold might exist between ART exposure and the development of congenital anomalies. Similarly, as some causal agents are only causal in the presence of other co-factors, inconsistency does not rule out a causal link.[42]

Future studies should attempt to tackle these challenges. Selection bias that can occur in the association between individual ARTs and congenital anomalies could be mitigated by properly selecting and classifying women into those who commence ART preconception versus during pregnancy. Increased use of directed-acyclic graphs, sufficient component cause models, and counterfactual models in prospective studies involving pregnant women living with HIV on ART can improve our understanding of causal links between ART and congenital anomalies. As the ability to identify congenital anomalies requires a large number of ART exposures, adequately powered, well designed prospective studies done in phase 2b or phase 3 of the drug development process, increased pharmacovigilance after drug approval, and enhanced reporting of ART-associated anomalies to Antiretroviral Pregnancy Registries would mitigate the problem of sample size and improve detection of congenital anomalies associated with ARTs.

Preterm birth

Preterm birth (birth occurring between 20 [SD +0 weeks] weeks and 36 [SD +6 weeks] weeks of gestation) is reported as a primary or secondary outcome measure in a number of prenatal HIV research studies,[43–45] which is important because even though pregnant

women living with HIV have a 3–4 times higher risk for preterm birth than pregnant women who do not have HIV, there are conflicting data regarding the association between ART and preterm birth.[46]

In perinatal HIV research, preterm birth should be reported as often as is feasible because it is an important outcome measure. Whereas personal history, low socioeconomic status, and history of sexually transmitted infections increase the risk for preterm birth, some predictors of preterm birth have not consistently shown increased risk for early delivery in pregnant women living with HIV. For example, mid-trimester cervical length assessments have been shown to be a powerful predictor of preterm birth in women without HIV, but this has not been consistently shown to predict preterm birth in pregnant women living with HIV.[46] In a cohort of pregnant women with HIV on ART in Botswana, mid-trimester cervical length shortening was not associated with increased risk for preterm birth.[47] There was no evidence that living with HIV or being on ART predisposes to a short cervix or preterm birth in the Zambian Preterm Birth Prevention Study, a prospective cohort study of pregnant women living with HIV on ART.[48] Similar differences exist between pregnant women with and without HIV when preterm birth was reported as an outcome measure in preterm birth prevention studies. For instance, whereas the randomised trial by Meis and colleagues[49] showed a statistically significant decrease in preterm birth rate in pregnant women without HIV treated with 17 alpha-hydroxyprogesterone caproate, the Improving Pregnancy Outcomes with Progesterone randomised trial of 17 alpha-hydroxyprogesterone caproate in pregnant women with a history of preterm birth and HIV yielded negative results.[50] As a result, although preterm birth is an important outcome measure to report in HIV pregnancy studies, more research is needed to evaluate the relationship between cervical length and the risk of preterm birth in pregnant women living with HIV on ART. Assessing for effect modification by ART type, time of ART initiation (preconception *vs* during pregnancy), CD4 count, and HIV RNA viral load, will also be crucial.

Small for gestational age (SGA) and low birthweight

Several studies of HIV in pregnancy have reported SGA and low birthweight as primary outcome measures. SGA, defined as birthweight below the 10th percentile, and low birthweight, defined as birthweight less than 2500 grams, are convenient, easy-to-use outcome measures in pregnancy HIV studies.[51,52] Data from several pregnancy HIV studies have shown that, even after controlling for known risk factors, SGA still occurred more frequently in pregnant women living with HIV than in women without HIV, suggesting that HIV in pregnancy might be associated with more SGA and low birthweight babies compared with no HIV infection during pregnancy.[53–55]

Despite the fact that some studies intended to report intrauterine fetal growth restriction (IUGR) as an outcome measure, they instead reported SGA.[56] Because SGA and IUGR are frequently used interchangeably in HIV in pregnancy research, understanding the differences between the two is crucial. IUGR is an estimated fetal weight below the 10th percentile for gestational age (when the patient is still pregnant), whereas SGA is actual birthweight below the 10th percentile for gestational age (when the patient has delivered the baby).[57] Although reporting SGA and low birthweight as outcome measures in HIV research is

simpler (because establishing whether a fetus has IUGR is mostly dependent on ultrasound measurement of fetal growth), IUGR seems to be a better outcome measure to report in these studies for a few reasons. In the event that IUGR is identified while the patient is still pregnant, antenatal fetal testing with Doppler, biophysical profile scoring, and non-stress tests can be initiated. These tests can identify fetuses at risk of intrauterine demise and lead to earlier delivery (based on abnormal Doppler measurements, biophysical profile, or non-reassuring fetal assessments), which has the potential to lower the reported incidence of intrauterine fetal deaths in these studies. As LMICs improve their technology and ultrasound capabilities, future research can shift to reporting IUGR over SGA.

Miscarriage

Miscarriage, defined as spontaneous loss of pregnancy before the age of fetal viability, is a rarely reported outcome measure in HIV pregnancy studies. The miscarriage rates reported in HIV pregnancy studies are typically higher than in non-HIV pregnancy studies, suggesting that HIV disease itself with or without ART use might be associated with an increased risk of pregnancy loss.[58] In addition, miscarriage rates are higher in LMICs compared with high-income countries, with miscarriage rates in HIV in pregnancy as high as 20% reported in LMICs.[59] Most miscarriages do occur in the first trimester of pregnancy (<14 weeks of gestation), but a few cases occur after 14 weeks.[60]

The use of miscarriage as an outcome measure in perinatal HIV studies has several drawbacks. Most pregnancy HIV studies done in LMICs establish the expected date of delivery almost entirely based on the last menstrual period, a metric which has been consistently shown to be incorrect in dating pregnancies.[59] Miscalculating delivery dates can be problematic, since incorrectly estimating the gestational age has a direct effect on patient care. When reporting miscarriage as an outcome measure, many studies rely on patient self-reports rather than chemically and histologically verified specimens.[59] Additionally, because the majority of miscarriages happen before the start of ART, particularly in LMICs, specifics of the ART regimen are often not accessible to investigate potential correlations between ART and miscarriage. However, in the test and treat era, in which the majority of pregnant women living with HIV conceive while on ART (or begin ART early during pregnancy), the ART regimen used can be accounted for. The stigma surrounding miscarriages might prevent people from reporting them, which could pose clinically significant problems for reporting real incidence and prevalence. Since miscarriage is frequently reported with other non-viable outcomes (ectopic pregnancy, elective abortion, and stillbirth), establishing the actual prevalence and the effect of HIV or ART on miscarriage is difficult.[59] The varied gestational ages used to define miscarriage across different continents (ranging from 20 to 28 weeks) pose a substantial challenge for reporting miscarriage as an outcome measure in HIV studies.[61,62] The management of pregnant women living with HIV is affected by all of these challenges.

For future studies, standardising approaches to defining miscarriages, and implementing unified approaches for gestational age determination would improve comparability between studies. To overcome the challenge of pregnancies being incorrectly dated, mostly due to the absence of technical expertise (trained sonographers and perinatologists) in many LMICs,

studies in the past few years have shown that data obtained from simple ultrasound sweeps of the pregnant uterus, when incorporated into a machine learning model, can estimate gestational age with similar accuracy to that of a trained ultrasound specialist.[63] Use of these artificial intelligence models for determining gestational age are encouraged in regions where ultrasound expertise is scarce.

Stillbirths

In many pregnancy HIV studies, stillbirth has been established as an outcome measure.[59,64,65] Pre-ART studies show that pregnant women living with HIV who were not taking ART had much greater rates of stillbirth than women without HIV.[66] Further research indicates that when used during pregnancy, maternal ART lowers but does not completely eliminate the higher stillbirth rates seen in pregnant women living with HIV compared with women without HIV.[61,67] The stillbirth rates in HIV studies range from 4% to 6·3% of all births, higher than rates reported in HIV negative women.[59]

Stillbirths share many of the same difficulties with using miscarriage as an outcome measure. As with miscarriage, stillbirth is a rare outcome, and usually reported simultaneously with miscarriage and ectopic pregnancies, making it difficult to ascertain the true prevalence of stillbirth in HIV pregnancy studies. Additionally, reporting stillbirth as an outcome measure in HIV studies is substantially complicated by the variable gestational ages used to define stillbirth in different countries. Omission and misclassification of stillbirth data are common in pregnancy HIV studies,[68] and can present challenges relying on stillbirth as an outcome measure. Therefore, assessing and comparing stillbirth rates and related risk factors due to these different classifications is methodologically challenging.

Gestational diabetes

Evidence from the literature indicates a potential link between HIV infection and gestational diabetes.[69,70] A potential causal association is that HIV during pregnancy alters placental hormones linked to insulin resistance (human placental lactogen, cortisol), which predisposes the woman to gestational diabetes.[69] The prevalence of gestational diabetes is approximately 2–5% higher in pregnant women with HIV than in pregnant women without HIV.[69,71] Gestational diabetes is therefore considered an important outcome measure to report in various studies involving pregnant women with HIV who are on ART.

The problem with using gestational diabetes as an outcome measure for HIV research in pregnant women is that the reporting of gestational diabetes results can vary depending on the screening criteria used. There are three universally used screening protocols for gestational diabetes: the Carpenter-Coustan criteria, the National Diabetes Data Group (NDDG), and the International Association of Diabetes and Pregnancy Study group criteria.[72] In some settings, haemoglobin A1c has been used to screen and diagnose gestational diabetes.[72] The fact that each of these distinct diagnostic criteria for gestational diabetes have a separate cutoff threshold for diagnosis and that different cutoff thresholds are employed even within one particular criterion makes matters more confusing. The key point is that, when it comes to diagnosing gestational diabetes, the NDDG is the most stringent

and conservative, whereas the International Association of Diabetes and Pregnancy Study group criteria is the least. Because of this, HIV pregnancy studies reporting gestational diabetes rates using the NDDG showed lower rates of gestational diabetes than studies using the other gestational diabetes diagnostic criteria.[71,73] As a result, using gestational diabetes as an outcome measure in prenatal HIV studies seems like an unfair comparison to make.

Ideally, future studies should focus on identifying a single criterion for diagnosing gestational diabetes and differentiating the risk by ART type, but this can be very challenging. Even though advocating for a standardised approach to gestational diabetes screening globally is difficult, the absence of accepted, evidence-based benchmarks for the diagnosis of gestational diabetes as a screening method can cause marked differences in the identification of gestational diabetes in pregnant women, including those living with HIV, which could affect estimates about the prevalence of gestational diabetes, related health outcomes, costs, and quality of life.

Hypertensive disorders of pregnancy (HDP)

HDP are commonly reported outcome measures in HIV pregnancy studies.[74,75] HDP are a group of conditions in pregnancy associated with elevated blood pressure, with or without proteinuria, and evidence of end-organ dysfunction.[76] These conditions include chronic hypertension, gestational hypertension, eclampsia, and HELLP—haemolysis, elevated liver enzymes, and low platelets—syndrome. In addition to gestational diabetes, HIV infection and its link to an elevated risk of pregnancy-related hypertensive problems has been reported and described, with reported rates of 15% in women with HIV and 5% in women without HIV.[71,74]

Reporting HDP as an outcome metric in prenatal HIV research has difficulties, particularly in LMICs where laboratory tests to diagnose HDP and measurement of blood pressure have varying reliability and validity—two metrics critical to evaluating outcome measures.[77,78] Among the many challenges are differences in blood pressure assessment (auscultatory, ambulatory, home-monitoring, automated devices, and invasive monitoring), auscultatory methods (use of mercury *vs* aneroid sphygmomanometers), and assessment of proteinuria in pregnancy HIV studies.[78] Diagnosis of proteinuria also differs between studies. Whereas some professional societies advise using an automated reagent strip reading device to identify proteinuria, and 24-h urine collection or a spot urinary protein–creatinine ratio to quantify proteinuria if results of 1+ or higher are obtained, many other societies rely on one approach or another.[79] The use of different assessments has implications for the diagnosis and management of HDP in pregnant women living with HIV. The reporting of HDP as an outcome measure in HIV pregnancy research might be improved by standardising blood pressure measurements, examining the relationship between ART and HDP, and enhancing the accuracy of proteinuria estimate using dipstick testing.

Weight gain

Weight gain is increasingly being reported as an outcome measure in HIV pregnancy research due to the association between integrase strand inhibitors (eg, dolutegravir),

nucleoside reverse-transcriptase inhibitors (eg, tenofovir alafenamide), and increased maternal weight.[80–82] Although excessive gestational weight gain might increase the risk of pregnancy-related complications such as HDP, gestational diabetes, obesity, and fetal macrosomia, determinining how much of it is due to dolutegravir or tenofovir can be difficult. Conversely, ART-associated weight gain might be protective in a small percentage of pregnant women living with HIV. The implications of ART-associated weight gain in pregnant women living with HIV is still unknown and is the subject of active research.

Hepatotoxity and nephrotoxicity

Hepatotoxicity and nephrotoxicity are commonly reported outcome measures in HIV pregnancy studies.[81,83–85] Although the focus of nephrotoxicity research is the percentage of HIV pregnancies affected by a decline in renal function, manifesting as a rise in serum creatinine or decrease in glomerular filtration rate related with ART use, the interest in hepatotoxicity studies is often the percentage of women having major (grade 3 or higher) adverse events while on ART. Fortunately, the majority of ART have been linked to minor asymptomatic liver damage (grades 1–2) and minimal to no reduction in glomerular filtration rate below baseline, none of which have a substantial effect on clinical management.[80,83] Since follow-up is frequently required in patients with deteriorating renal or hepatic function, continuing to report these as outcome measures in HIV pregnancy studies is crucial.

Conclusion

Reported outcome measures are important because studies are usually powered from the outcome measures reported. Evaluating the applicability and usefulness of an outcome measure plays an important role in formulating and analysing study conclusions in perinatal HIV research. However, deciding whether an outcome measure accurately reflects and clarifies a research study’s central question can be challenging. Although describing frequently occurring outcomes is essential, prenatal HIV researchers often choose which outcome measures to evaluate based on the type of ART being investigated and what policy changes are crucial. Although comparing all outcome measures between high-income countries and LMICs would be challenging, a tiered system of standardisation based on resource setting (LMICs *vs* high-income countries) might be helpful. Even though all the endpoints discussed in this Personal View are important and should be reported whenever HIV pregnancy studies are being done, outcome measures that are uniformly reported and simple to measure in both LMICs and high-resource countries (eg, viral load, CD4 count, low birthweight, diagnosis of hypertension, renotoxicity or hepatotoxicity in pregnancy, and weight gain) should be the focus of all prospective HIV pregnancy studies, with additional outcomes reported if possible to do so. In the end, whichever outcome measures are selected to be reported should be unbiased, objective, simple to study and implement, easily assessable, and have therapeutic relevance in enhancing the lives of pregnant women living with HIV and their unborn children.

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Table:

Commonly used outcome measures in HIV pregnancy research

	Benefits	Drawbacks	Recommendations for improvement
Viral load and CD4 assays	Viral load and CD4 counts are good indicators of ART medication adherence, extent of HIV disease progression, and optimal mode of delivery (vaginal *vs* caesarean)	There is extensive variability in the lower limits of quantitation and lower limits of detection of viral load assays; optimal cutoff for preventing vertical transmission varies across LMICs and high-resource countries	Viral load and CD4 counts are very useful measures of ART adherence, indicators of disease progression and vertical transmission; unlikely to be replaced by other pharmacodynamic surrogate outcome measures
Congenital anomalies	Early diagnosis of congenital anomalies during pregnancy gives parents the opportunity to consider diagnostic testing, genetic counselling, and preparations for postpartum care	Diagnosis of congenital anomalies in pregnancy might lead to maternal anxiety disorders; sample sizes are frequently insufficient to establish causal links between ART and congenital anomalies; and causality can be difficult to establish	Improved pharmacovigilance and reporting to ART pregnancy registries; increased use of direct acyclic graphs, sufficient component cause models, and counterfactual models to better identify causal linkages between ART and congenital abnormalities
Preterm birth	Knowledge of ARTs associated with preterm birth can potentially prevent future preterm birth risk if increased prenatal surveillance is instituted	The use of mid-trimester short cervical length has not been consistently shown to predict preterm birth in pregnant women living with HIV; studies with hydroxyprogesterone did not prevent preterm birth in women with HIV	The association between cervical length and the risk of preterm birth in pregnant women living with HIV deserves further study; assessment of effect modification by ART type, time of ART initiation (preconception *vs* during pregnancy), CD4 count, and HIV RNA viral load is critical
SGA and low birthweight	Easily measurable outcome measures of fetal wellbeing.	Despite IUGR being a better outcome measure, SGA is frequently used in HIV pregnancy research	Use of IUGR as an outcome measure instead of SGA; monitoring IUGR fetuses with antenatal fetal tests such as Doppler, biophysical profile, and non-stress tests can identify fetuses at risk of stillbirth
Miscarriage	Understanding the association between ART and miscarriage might help prevent them in subsequent pregnancies	The effect of ART on miscarriage remains uncertain; gestational age for reporting miscarriages varies widely; incorrect pregnancy dating can affect diagnosis of miscarriages and its prevalence or incidence	Standardising approaches to defining miscarriages, and implementing universal approaches for gestational age determination; increase use of artificial intelligence models to establish gestational age in regions where ultrasound expertise is limited
Stillbirth	If ARTs associated with stillbirths are known, avoiding stillbirths in subsequent pregnancies might be possible	The effect of ART on stillbirths remains uncertain, and might vary by ART regimen; gestational age for reporting stillbirths varies widely; and the diagnosis of stillbirth and its frequency or prevalence can be affected by erroneous pregnancy dates	Standardising approaches to defining stillbirth and implementing universal approaches for gestational age determination
Gestational diabetes	Early diagnosis and treatment of gestational diabetes has been shown to improve fetal outcomes, even in pregnant women living with HIV	The use of multiple gestational diabetes screening protocols (Carpenter-Coustan, National Diabetes Data Group, haemoglobin A1C, and the International Association of Diabetes and Pregnancy Study group criteria) makes comparison between studies difficult	Although a single criterion for diagnosing gestational diabetes and differentiating its risk by ART type is desirable, the use of multiple diagnostic criteria makes it difficult to implement a universal screening criterion for gestational diabetes, which remains an active area of research
HDP	Early diagnosis and treatment of HDP improve fetal outcomes, even in pregnant women living with HIV	Differences in blood pressure measurement and assessment of proteinuria in different settings can affect timing of diagnosis and maternal or fetal outcomes	Standardising blood pressure measurements; examining the relationship between ART and HDP; and enhancing the accuracy of proteinuria estimation using dipstick testing
Weight gain	The negative effects of prenatal weight gain associated with ART could be avoided by being aware of the ARTs linked to increased weight	Increased weight during pregnancy can be associated with adverse pregnancy outcomes, including pre-eclampsia, gestational diabetes, and fetal macrosomia	Although weight gain can be linked to unfavourable pregnancy outcomes, the implications of ART-associated weight gain in pregnant women living with HIV is still unknown and is the subject of active research

	Benefits	Drawbacks	Recommendations for improvement
Hepatotoxicity and nephrotoxicity	Knowledge of ARTs linked to decline in renal function would lead to enhanced monitoring during pregnancy when such ARTs are used	The effect of ART on the liver and kidneys might differ substantially depending on the ART used, and anticipating the degree of renal or hepatic impairment with ART can be challenging	When using ARTs linked to liver or renal toxicity during pregnancy, monitoring of renal and hepatic function is advised; if the patient's liver or kidney function continues to deteriorate, consider changing their ART regimen

Benefits, disadvantages, and suggestions for improvement are shown for each outcome metric that is currently used. ART=antiretroviral therapy. SGA=small for gestational age. IUGR=intrauterine fetal growth restriction. HDP=hypertensive disorders of pregnancy.