uncommon.[11] Accordingly, the syndrome will hopefully not be a substantial problem in the future for patients living with HIV. Although virologically effective, thymidine analogues were associated with unbearable fat toxicity, recalling what the Warden of the Houses of Healing told Lady Éowyn "...it is a thing passing strange to me that the healing hand should also wield the sword".[12] The availability of new, fat-friendly antiretrovirals should help end the effects of the damnific sword.

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A link between antiretrovirals and perinatal outcomes?

Because starting combination antiretroviral therapy (ART) as early as possible is now the norm, all women with HIV should be on treatment before becoming pregnant (although some women might not be diagnosed until they are pregnant). The benefits of ART are overwhelming, but the risks include adverse pregnancy outcomes, which encompass a wide range of birth defects and maternal, obstetric, and perinatal complications.

A systematic review and meta-analysis[1] by Olalekan A Uthman and colleagues in *The Lancet HIV* shows a significant increase in preterm births associated with ART started before conception compared with ART started after conception. Many, though not all, studies have shown a strong association between ART and preterm births.[2] This review is the first in which adverse pregnancy outcomes by timing of ART are specifically assessed. The risk ratios are quite coherent among studies from low-income and high-income countries, although background risks differ. The increased risk concerns not only moderate preterm birth (ie, delivery between 34 and 37 weeks' gestation) but also deliveries at less than 34 weeks' gestation, which can lead to death or permanent disabilities.

The relation between timing of ART initiation and other outcomes is less clear. Low birthweight was significantly more frequent when ART was started before pregnancy than after pregnancy, but the frequency of small for gestational age did not differ significantly between groups. Low birthweight can be a proxy for preterm birth. By contrast, small for gestational age is, by definition, adjusted for


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See **Articles** page e21

gestational age. It is also an important indication for preterm induction or caesarean section. In the French Perinatal Cohort,[3] ART was mostly associated with induced preterm birth for complications. Uthman and colleagues report that the incidence of pre-eclampsia was independently associated with starting ART before conception (rather than after conception). Small for gestational age and pre-eclampsia are both related to placental dysfunction, which is a consequence of faulty trophoblast invasion in early pregnancy. However, other studies showed no association between ART and pre-eclampsia.[4]

There was a non-significant risk of stillbirth, which is less frequent than preterm birth and small for gestational age, when ART was started before conception compared with after conception. The risk of congenital anomalies is a major outcome. Congenital anomalies were an outcome in only one study[5] included in Uthman and colleagues' analysis because preconception initiation of ART was not distinguished from initiation after conception in other studies. The teratogenic potential of efavirenz in first-trimester ART exposures is controversial.[6] In the French Perinatal Cohort,[7] CNS malformations were increased after first-trimester exposure to efavirenz, but that study was not included in the systematic review because the publication did not specify that all these exposures had begun before conception (unpublished).

The association between ART and preterm birth is intriguing and elusive. Multicentre observational cohorts are a good way to study outcomes in large populations, but are not designed to inform whether starting ART before pregnancy has an effect on outcomes. An important treatment bias to remember is that, until recently, ART used to be reserved for people with advanced immune deficiency. The timing of initiation of ART could be important for interactions between HIV and the immune system. HIV infection is a state of chronic inflammation. The effect of ART on this inflammatory state is complex: it depends on immune deficiency and the viral reservoir at the time of treatment initiation. Inflammation is also a major factor in preterm birth, intrauterine growth restriction, and pre-eclampsia. Concentrations of inflammatory markers related to microbial translocation were higher in pregnant women with HIV than in HIV-negative pregnant women,[8] and were associated with preterm delivery.

One might thus assume that treating HIV infection improves pregnancy outcomes, but the opposite has been described.[9] The effects could differ regarding spontaneous and induced prematurity, with HIV infection increasing the frequency of spontaneous preterm birth and boosted protease-inhibitor-based ART possibly increasing the frequency of induced preterm birth.[10] Other researchers suggest that ART favours spontaneous preterm birth and adverse outcomes via the T helper cell 1 and T helper cell 2 shift or via decreased progesterone concentrations.[11] Whether the adverse effects of ART on pregnancy will be increased or decreased by starting treatment earlier in the course of HIV infection—ie, before immune dysregulation occurs—is unknown,

Another cause for caution is the potential for toxicities in the developing fetus and the resulting short-term and long-term risks, including mitochondrial diseases, cardiac dysfunction, genotoxicity, and cancer, which were not topics of Uthman and colleagues' review but are of crucial importance when assessing risks related to use of ART in pregnancy. The next step in research should be to analyse outcomes according to the individual antiretrovirals used and the causes of adverse perinatal outcomes.

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Actionable adherence monitoring to optimise intervention

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See **Articles** page e31

In *The Lancet* HIV, Steve Kanters and colleagues[1] identify several practical and effective adherence interventions for antiretroviral therapy regimens. Specifically, they report that supportive and behavioural strategies (eg, peer support, text messaging, counselling, and training) improve adherence (and in some cases viral suppression) compared with standard of care. These findings are great news for the 17 million people currently taking antiretroviral therapy and the 20 million additional people who could benefit from it through universal access programmes.[2]

As Kanters and colleagues note, many programmes are already implementing these interventions. However, the observed benefit is probably limited because we often do not know who needs them or when they need them. Kanters and colleagues[1] show that intervention effects tend to wane with time, yet antiretroviral therapy is for life. People might need serial interventions over time, but again we do not know when to provide them. Moreover, while many of these interventions are relatively inexpensive, they do impose on the limited resources of most clinics, especially in low-income settings. Providing interventions when needed specifically should improve their effect at lower cost. Additionally, Kanters and colleagues find greater effectiveness when adherence interventions are used in combination, but we do not necessarily know which interventions to implement when. Answers to these questions come through actionable adherence monitoring.

Standard adherence monitoring is typically based on self-reporting, which only identifies adherence challenges among individuals in care who feel comfortable reporting their struggles.[3] Pill counts are also often used and might identify people with adherence challenges, but they are easy to manipulate (eg, dumping pills before clinic).[4] These monitoring strategies do not identify individuals who never pick up their first prescription, do not attend clinic, or stop antiretroviral therapy. Better objective adherence monitoring strategies are needed.

The most practical, initial approach to addressing these challenges is an actionable pharmacy refill record system.[5,6] Nearly every pharmacy keeps account of their stocks, but often stand-alone records are not connected to treatment support services. Good communication between pharmacists and clinicians is needed to act when individuals do not pick up their prescriptions. Simple team meetings might be highly effective and are easy to implement. Automated electronic database queries can improve the efficiency and yield in identifying individuals with adherence challenges, but require investment in computers and human resources. Either way, adherence support can then be provided for those who need it when they need it, and clinicians can identify the interventions best suited for each individual.

Pharmacy refill records, however, are a blunt measure. A more precise understanding of adherence can be achieved through electronic monitoring, in which a pill container records each opening as a proxy for medication ingestion (ingestion monitoring devices are becoming available, but are in early stages of clinical research[7]). Depending on