3. Schindler SD, Ortner R, Peternell A, Eder H, Opgenoorth E, Fischer G. Maintenance therapy with synthetic opioids and driving aptitude. Eur Addict Res 2004;10:80-7.
4. Wollman SC, Hauson AO, Hall MG, et al. Neuropsychological functioning in opioid use disorder: a research synthesis and meta-analysis. Am J Drug Alcohol Abuse 2019;45:11-25.
5. Maglione MA, Raaen L, Chen C, et al. Effects of medication-assisted treatment (MAT) for opioid use disorder on functional outcomes: a systematic review. Santa Monica, CA: RAND, 2018 (https://www.rand.org/pubs/research_reports/RR2108.html).

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Health Care Autonomy of Women Living with HIV

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In sub-Saharan Africa, more than 60% of all adults living with HIV in 2018 were women, according to the Joint United Nations Programme on HIV and AIDS (https://aidsinfo.unaids.org). Largely as a result of early access to HIV testing and antiretroviral treatment (ART) at antenatal clinics, women were the first to benefit from "Treat All" approaches to ART; with the introduction of Option B+ policies starting in 2011, all pregnant and breastfeeding women were offered immediate ART initiation and lifelong treatment, regardless of their CD4+ T-cell count or clinical staging. Women accounted for 67% of the 13.5 million adults receiving ART at the end of fiscal year 2018 in programs supported by the President's Emergency Plan for AIDS Relief (PEPFAR) globally (www.pepfar.gov).

Providing the best available ART regimens to women requires complex decision making related to their childbearing potential, including weighing women's health needs and experiences with medications, along with possible safety concerns for infants exposed to HIV medications during any current or future pregnancy. When a potential association with neural-tube defects (NTDs) in infants born to women receiving dolutegravir (DTG)-based ART was identified in May 2018, the risks of possible adverse outcomes for infants exposed to DTG became a major focus of HIV policy discussions.[1] Yet such discussions should include consideration of all the risks, including those for women who might receive inferior ART regimens, if we are to ensure the best achievable access to treatment options and improved health outcomes for women living with HIV.

Before May 2018, global HIV programs were poised to transition the preferred first-line ART regimen rapidly from tenofovir, lamivudine, and efavirenz to tenofovir, lamivudine, and DTG, which poses a lower risk of treatment failure and causes rapid viral suppression.[2,3] The momentum behind this shift waned, however, after the release of interim World Health Organization (WHO) guidance in July 2018 that included a note of caution advising that adolescent girls and women of childbearing potential be given a DTG-based regimen only if it was used in tandem with a consistent and reliable form of contraception; other regulatory bodies followed with similar statements of caution. Despite the release of more permissive WHO guidance in December 2018, the response to the NTD safety signal has varied among countries, with a limited number allowing women to make an informed decision, some providing access to the regimen only for patients using contraception, and others not offering access to DTG-based regimens for any women of childbearing potential.

Policy discussions have focused primarily on the possible increased risk of having a child with an NTD — largely overlooking the importance of shared decision making between a woman and her health care provider and the possible risks of adverse outcomes for pregnant women who might receive inferior ART regimens and their infants. When global policymakers and national HIV programs make recommendations that restrict women's access to medications on the basis of uncertain — or even known — safety concerns related to childbearing potential, women's ability to make their own decisions about treatment options that best fit their life circumstances and beliefs is severely limited. By contrast, nondirective counseling is a key strategy for ensuring that women are empowered to participate in their own health care decisions. Health care providers taking this approach lay out information and clearly describe all the risks as they are currently known, along with options for avoiding or mitigating these risks.

Respecting the autonomy of women to participate actively in their own health care decision

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making promotes adherence to treatment regimens. Such participation is especially important for decisions regarding lifelong HIV treatment, since adherence is critical to averting development of drug-resistant HIV strains and maintaining viral suppression. In addition, it's important that discussions of a woman's intentions regarding pregnancy occur before conception, because most pregnancies are not recognized until after the critical window for development of major organs and structures, such as the neural tube. Early conversations about pregnancy intentions can avert unnecessary changes in ART regimens during pregnancy that might increase the risks of adverse health outcomes for the mother and infant (e.g., reduced HIV viral suppression, with resulting increased risks of complications and death, and a potentially higher risk of mother-to-child HIV transmission), without conferring benefit to either one.

Treatment decision making related to future and current pregnancies is complicated by the lack of data on medication safety during pregnancy. Despite the common use of prescription medications in pregnancy, a review of 172 medications approved by the Food and Drug Administration between 2000 and 2010 showed that only 4 (2%) of these medications had data on teratogenic risk in humans.[4] Clinical trials examining drug efficacy and safety routinely exclude pregnant and breast-feeding women, thereby contributing to the dearth of evidence on which to base treatment decisions. Moreover, even if participation of pregnant women were increased, premarketing clinical trials often include relatively small numbers of people and so are unlikely to have sufficient statistical power to detect rare outcomes, such as birth defects, especially if a drug's teratogenic potential is low.[5]

Collection of postmarketing data through pregnancy registries and birth-defects surveillance is therefore essential. Pregnancy registries are typically designed to monitor the safety of a particular drug or class of drugs for a specific indication; one example is the Antiretroviral Pregnancy Registry, which monitors exposures to HIV medications, relying on HIV clinical providers to voluntarily submit reports. Unfortunately, there is a paucity of systems for monitoring birth defects in much of the world. This gap, compounded by factors such as limited population exposure to a new teratogen, the heterogeneity of causes of birth defects, and difficulties in maintaining enrollment in prospective systems, continues to limit our capacity to rapidly detect teratogenic risk. Attention to critical knowledge gaps about risks associated with use of medications in pregnancy and enhancement of existing systems for identifying these risks are key public health priorities, especially given the certainty that additional safety signals will emerge as new medications enter the market.

Our knowledge about the relation between periconceptional use of DTG-based ART and NTD risk will advance and be refined as new data continue to become available (see the article by Zash et al. [pages 827–840] and the letter to the Editor by Raesima et al. [pages 885–887]). Similar early safety signals seen with another HIV medication, efavirenz, and with the anticonvulsant lamotrigine were not borne out by additional data, and these medications are now considered safer alternatives than others used for HIV and epilepsy, respectively, in women who are or might become pregnant. These experiences highlight an inherent tension in policy decisions: the desire to react quickly in order to avoid one poor outcome may result in another, unintended negative outcome. If the current suspected association between DTG and NTDs turns out not to exist, or continues to weaken, the delays that have occurred in global expansion of DTG-based treatment since the safety signal was reported in mid-2018 will represent missed opportunities for improving global and individual health.

At home and abroad, achieving and maintaining control of the HIV epidemic will require sustained viral suppression, and moving to improved regimens is important for reaching this goal. We believe that global HIV programs have an imperative to provide the option to choose DTG-based regimens — which have been shown to achieve superior outcomes — to all people living with HIV, regardless of their sex or childbearing intentions. Enhanced attention to the needs of HIV-positive women of childbearing potential must be part of the epidemic-control strategy; this includes ensuring that women's autonomy is respected, that their pregnancy intentions are known and supported, and that systems are in place to monitor the safety of drugs for women and infants during clinical trials and after approval for widespread use.

In this period of uncertainty regarding the potential NTD risk conferred by DTG-based regimens, women's autonomy to make their own health-related decisions must

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remain a central tenet of public health programs. Public health leaders can ensure that global guidance considers all risks related to DTG, including those associated with receiving inferior regimens, and that women receive all the information they need to make their own, informed choices about treatment.

The views expressed in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, the Department of Health and Human Services, or the U.S. government.

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1. Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. N Engl J Med 2018;379:979-81.
2. Kandel CE, Walmsley SL. Dolutegravir — a review of the pharmacology, efficacy, and safety in the treatment of HIV. Drug Des Devel Ther 2015;9:3547-55.
3. d'Arminio Monforte A, Cozzi-Lepri A, Di Biagio A, et al. Durability of first-line regimens including integrase strand transfer inhibitors (INSTIs): data from a real-life setting. J Antimicrob Chemother 2019;74:1363-7.
4. Adam MP, Polifka JE, Friedman JM. Evolving knowledge of the teratogenicity of medications in human pregnancy. Am J Med Genet C Semin Med Genet 2011;157C:175-82.
5. Friedman JM. In bed with the devil: recognizing human teratogenic exposures. Birth Defects Res 2017;109:1407-13.

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Insight Medicine Lacks — The Continuing Relevance of Henrietta Lacks

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At my mother's first oncology appointment, I sat beside her, swaddled in my Harvard sweatshirt. I hoped that the name of the august institution where I was an undergraduate would, in the doctor's eyes, transport my mother from the wasteland of "difficult," "noncompliant," and "welfare queen" to which black female patients are often relegated and deliver her to the promised land of "human being." Perhaps the doctor would think a woman with the perseverance to support her child to and through Harvard was worth saving from cancer. In retrospect, I wonder whether she instead saw my skin tone and assumed I had bought the sweatshirt as a tourist, not a student.

In the past, there had been doctors who confused my mother's medical charts with those of other black female patients. There was a doctor who dismissed her medication side effects as the result of psychosocial stress. There was also the kind physician who empathetically asked about my mother's hypertension and diabetes — except that she didn't have either disease. Too often, as a black woman, going to the doctor's office is about trying to minimize the medical errors you can see coming and praying for a miracle to thwart the ones you don't.

Early on in that initial oncology appointment, the doctor asked my mother to enroll in a clinical trial of a combination of chemotherapy drugs. Each drug worked well individually, she told us, and her team wanted to see whether they would work even better together. She emphasized that the drugs were safe. The silence that ensued while the doctor glossed over countless pages of side effects was terrifying and painful.

Unbeknownst to her, the doctor had already lost our trust. She had not explained my mother's diagnosis or prognosis as she had promised to do when we made the appointment. Instead, she asked my mother to donate her time and possibly risk her health and life for science. Nothing had been done to address my mother's fears about her disease, its treatment, or her own mortality. And nothing had been said to allay the fear that had kept me up tossing and turning the night before: that I would have to go back to my senior year of college and leave behind a mother with metastatic cancer. The history of medical experimentation on black Americans aside, that decidedly non–patient-centered approach to care made me weary.

My mother had only one question: "So, I do have cancer, then?"

"Oh, yes," said the doctor.

I asked the rest of the questions. Were there any nonexperimental treatments? Could we have at least a day to think over our options? Yes, the doctor answered, and yes.

Even in the moment, I wondered what happens to patients who didn't know to ask these questions. A few months later,

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