Newer anti-HIV drugs safest, most effective during pregnancy

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A variety of antiretroviral drugs used to treat HIV. Credit: NIAID

The antiretroviral drugs dolutegravir and emtricitabine/tenofovir alafenamide fumarate (DTG+FTC/TAF) may comprise the safest and most effective HIV treatment regimen currently available during

pregnancy, researchers announced today. Their findings come from a multinational study of more than 640 pregnant women with HIV across four continents. The study results affirm updated recommendations for HIV treatment in pregnant women set forth by the World Health Organization (WHO). Previous research clearly has demonstrated that antiretroviral therapy (ART) to suppress HIV prevents perinatal HIV transmission and benefits the health of both mother and child. The current study compared three antiretroviral drug regimens and found that regimens containing dolutegravir (DTG) were more effective in suppressing HIV than a commonly used regimen containing efavirenz (EFV).

The Phase 3 clinical trial is called IMPAACT 2010 or VESTED (Virologic Efficacy and Safety of Antiretroviral Therapy Combinations with TAF/TDF, EFV and DTG). It was sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health. VESTED was conducted by the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network, which receives support from NIAID, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Institute of Mental Health, all parts of NIH.

Lameck Chinula, M.B.B.S., M.Med., presented the findings today at the 2020 Conference on Retroviruses and Opportunistic Infections (CROI). Dr. Chinula is an assistant professor in the UNC Department of Obstetrics and Gynecology's Division of Global Women's Health at the UNC School of Medicine and Clinical Research Site Leader at UNC Project Malawi, a collaboration between UNC-Chapel Hill and the Malawi Ministry of Health.

"When a woman living with HIV is expecting, she can be confident that the same antiretroviral therapy she takes every day to protect her own

health also helps protects her future child from acquiring HIV," said Anthony S. Fauci, M.D., NIAID Director. "Findings from the VESTED study suggest that a drug regimen containing dolutegravir provides the safest, most effective HIV treatment available during this critical time for women and their infants."

An estimated 1.5 million women worldwide living with HIV give birth each year. Since 2013, the WHO has recommended a regimen of three antiretroviral drugs—EFV, lamivudine (3TC) or FTC, and tenofovir disoproxil fumarate (TDF)—to treat HIV in pregnant women in resource-limited settings. In July 2019, the WHO updated their recommendations to include DTG-containing regimens.

Beginning in January 2018, VESTED investigators randomly assigned 643 women to begin HIV treatment 14-28 weeks into their pregnancies with EFV/FTC/TDF or two newer regimens: DTG+FTC/TAF and DTG+FTC/TDF. EFV/FTC/TDF is formulated as a single tablet, while the newer regimens each consist of a DTG tablet taken with a combined FTC/TAF or FTC/TDF tablet. The researchers found that nearly 98% of women who received either of the DTG-containing regimens were virally suppressed at the time of delivery, meaning their viral load (amount of HIV in the blood) was undetectable using standard tests. In contrast, 91% of women who received EFV/FTC/TDF were virally suppressed at delivery. Two infants, one in each of the groups that received DTG-containing regimens, were diagnosed with HIV within 14 days of birth. Researchers are currently investigating data on medication adherence and drug levels at the time of delivery.

The researchers found that 24% of women taking DTG+FTC/TAF had an adverse pregnancy outcome compared with 33% of women taking DTG+FTC/TDF or EFV/FTC/TDF. While these rates are high, they are consistent with adverse pregnancy event rates in low- and middle-income countries, where most participants live. These outcomes included

pregnancy complications of preterm delivery, low infant birth weight based on gestational age (a measure of the age of a pregnancy which is taken from the beginning of the woman's last menstrual period), and stillbirth.

Together, these findings show that while all three regimens are safe and effective in pregnancy, HIV is better controlled by DTG-containing regimens, and DTG+FTC/TAF may lead to lower adverse pregnancy outcomes. The findings affirm WHO recommendations for use of DTG in pregnant women.

"A woman's choice of HIV treatment regimen should be based on the best evidence available," said Nahida Chakhtoura, M.D., of the Maternal and Pediatric Infectious Disease Branch at NICHD. "These results from the VESTED study represent the most up-to-date evidence on HIV treatment regimens during pregnancy and childbirth."

VESTED—co-chaired by Dr. Chinula and Shahin Lockman, M.D., M.Sc., of Brigham and Women's Hospital in Boston—enrolled participants at clinical research sites in Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, the United States and Zimbabwe. At enrollment, all participants were living with HIV, 14 to 28 weeks into their pregnancies and not currently on ART. Participants began receiving ART at enrollment during their second trimester of pregnancy. After childbirth, the women's infants received local standard-of-care interventions for HIV prevention after birth. Mothers were counseled on infant feeding options consistent with local standards of care, which included breastfeeding or formula feeding. The investigators are continuing to monitor the health of both mothers and infants up to 50 weeks after delivery.

"These findings include the first of many insights we hope to glean from the VESTED study," said Dr. Chinula. "My fellow researchers and I

extend our heartfelt thanks to the study volunteers. Each played a vital role in supporting the wellbeing of women and babies around the world."

The VESTED results build on evidence that DTG is a safe and effective antiretroviral drug for people of childbearing potential. No cases of neural tube defects (serious congenital disorders of the brain and spine) were found in the VESTED study, though with treatment beginning after the first trimester in a moderate sample size, the study cannot accurately assess the risk of neural tube defects.

In 2018, investigators conducting the observational, NIH-funded Tsepamo Study in Botswana reported a 0.9% risk of neural tube defects in infants born to women who were taking DTG at the time of conception. A more recent analysis presented at the 10th International AIDS Society Conference on HIV Science in 2019 dropped that risk to 0.3%, relative to a 0.1% risk of neural tube defects found in newborns in the general Botswana population. At the same scientific conference, two complementary studies of infants born to women who were taking DTG at the time of conception also indicated a lower risk of neural tube defects than the Tsepamo Study had originally reported. Based on this evidence, WHO issued updated HIV treatment guidelines that reconfirmed recommendations to use DTG-containing regimens as the preferred ART option for all populations, including pregnant women and people of childbearing potential.

NIAID and NICHD provided funding to the IMPAACT 2010 (VESTED) clinical research sites. Gilead Sciences, Mylan and ViiV Healthcare Ltd. provided antiretroviral drugs for the study. ViiV also provided funding to IMPAACT for non-participant costs. For more information about the IMPAACT 2010 (VESTED) study, visit ClinicalTrials.gov using identifier NCT03048422.

More information: WHO updated guidelines:

www.who.int/hiv/pub/arv/arv-update-2019-policy/en/

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