Dolutegravir becomes first choice for HIV

WHO's new guidelines recommend dolutegravir for HIV treatment after concerns over neural tube defects were assuaged. Susan Rahimi reports.

WHO has updated their HIV treatment guidelines to recommend dolutegravir as the preferred first-line and second-line treatment for all patients with HIV, including pregnant women and those with child-bearing potential. Announced during the International AIDS Society 2019 conference in Mexico City, the guidelines were based on new clinical data and mathematical models on the benefits and harms of dolutegravir as well as the preferences of communities living with HIV, especially women, who represent half of those affected by the disease globally.

Dolutegravir is a second-generation HIV integrase strand transfer inhibitor and the most recent antiretroviral drug approved for treatment of HIV-1 infection. In comparison to other antiretrovirals, dolutegravir has fewer side effects and fewer drug interactions, and so is easier to take. Its greater effectiveness than previous regimens was demonstrated in the SINGLE study, a randomised controlled trial of 833 patients published in 2013. The trial showed that a dolutegravir-containing regimen improved viral suppression at 48 weeks compared with an efavirenz-containing treatment. Dolutegravir is better tolerated than efaverenz as efiverenz had been associated with neuropsychiatric side-effects such as mood changes, depression, sleep disturbances, and mild-to-moderate neurocognitive impairment. Dolutegravir also has fewer drug interactions and does not interact with the tuberculosis drug rifampicin, unlike efavirenz.

Dolutegravir also has a higher genetic barrier to the development of drug resistance compared with first generation non-nucleoside reverse transcriptase inhibitors such as efavirenz and nevirapine, which are currently the most widely prescribed drugs for HIV-1. A single mutation can result in complete loss of activity of efavirenz and nevirapine. In the SINGLE trial, four efavirenz-associated mutations were identified in patients with virological failure, compared with none in patients taking dolutegravir-based treatments. Because HIV is less likely to become resistant to dolutegravir, fewer expensive second-line boosted protease inhibitor treatment will be needed, which is predicted to reduce overall programme costs.

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The change to a drug that is less prone to resistance comes at a key time. HIV drug resistance is increasing globally, as outlined in a 2019 WHO report, which found that pretreatment resistance to non-nucleoside reverse transcriptase inhibitors exceeded 10% for people who had never had antiretroviral therapy in 12 of the 18 countries that were surveyed. Thus, the need for new first-line treatments alongside improved viral load and resistance monitoring and patient-centred care delivery models in order to achieve the WHO/UNAIDS 90-90-90 targets for 2020.

Dolutegravir received its first approval as treatment for HIV in 2013, and in June, 2016, Botswana became the first country to recommend the use of dolutegravir during pregnancy. However, the practice was halted in May, 2018, after the Tsepemo study (a large surveillance study done in Botswana of birth outcomes in women being treated for HIV) highlighted a possible link between taking dolutegravir at the time of conception and neural tube defects in babies. Neural tube defects affect the brain and spinal cord by the end of the sixth week of pregnancy and can cause conditions such as spina bifida. The study found four cases of neural tube defects out of 426 women who became pregnant while taking dolutegravir, which was significantly more than in the comparator groups.

For **WHO's report on HIV drug resistance** see https://www.who.int/hiv/pub/drugresistance/hivdr-report-2019/en/

International AIDS Society/Steve Forrest/Workers' Photos

Subsequently, several countries, including South Africa and Botswana, advised against the use of dolutegravir in pregnant women and those of childbearing potential and recommended treatment with efavirenz instead. Since 2018, new data have emerged. A Brazilian study included 392 women taking dolutegravir when falling pregnant, with no cases of birth defects. The Tsepamo study also continued to recruit participants. It included more than 119 000 deliveries between 2014 and 2019, of which close to 1700 women were taking dolutegravir at the time of conception. Since the initial 2018 report, the estimated prevalence of neural tube defects has diminished to approximately three cases per 1000 births, compared with one per 1000 deliveries among women taking other antiretroviral drugs. Rebecca Zash of Harvard University and lead author of the dolutegravir safety studies, told *The Lancet Infectious Diseases* that "although the increased risk of neural tube defects remained, the absolute difference was very small, 0·20% higher than women on all non-dolutegravir-based antiretroviral therapy at conception. With this new estimate and all the other considerations around community input, risk/benefit analysis, and lack of data for other alternative antiretroviral therapy, WHO decided that the benefits of dolutegravir likely outweigh the risks of neural tube defects in a public health approach".

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The guidelines are an important advance in HIV treatment, but some questions remain. Andrew Phillips from University of College London explained that "these recommendations only cover people who are initiating treatment. They do not cover people who are currently on a first-line efavirenz-based regimen". He went on to say "there is a particular concern over those [who] do not have access to a (recent) viral load test, as is the case for many people in sub-Saharan Africa currently. Currently there is no WHO recommendation to switch from efavirenz to dolutegravir in this situation". The WHO guidelines considered the value and preferences of people living with HIV; a large criticism of the 2018 guidelines from many activists was that they took away women's choice of medication. "It's important that health care providers really understand the magnitude of all the risks and benefits and also the values and preferences of the patient when making treatment recommendations" said Zash. "This kind of risk/benefit counselling is challenging, and takes time, but ultimately is the best approach to treatment decisions, not just in this circumstance, but more broadly."

Susan Rahimi

Infectious disease surveillance update

For more on **wild poliovirus** see http://polioeradication.org/polio-today/polio-now/this-week/

For more on **West Nile virus** in the USA see http://outbreaknewstoday.com/maricopa-county-az-107-human-west-nile-virus-cases-7-deaths-60670/

For more on **malaria in Burundi** see https://www.theguardian.com/global-development/2019/aug/08/burundi-malaria-outbreak-at-epidemic-levels-as-half-of-population-uninfected

For more on **tuberculosis in Germany** see https://www.dw.com/en/tuberculosis-outbreak-at-german-school-infects-over-100/a-49854829

For more on **yellow fever in Nigeria** see https://www.ncdc.gov.ng/news/189/the-ncdc-is-aware-of-a-suspected-outbreak-of-yellow-fever-in-ebonyi-state

Wild poliovirus in Pakistan

A case of wild poliovirus (WPV) was reported in Pakistan, bringing the number of cases there this year to 48, as of Aug 7. The case was reported in Balochistan province with a date of paralysis onset of July 2. Eight WPV1 positive environmental samples were also reported, from Sindh province (n=3) and Punjab province (n=4). Globally, 60 cases of WPV have been reported so far this year from two countries: Pakistan and Afghanistan.

West Nile virus in Arizona, USA

As of Aug 9, county health officials in Maricopa county in Arizona, USA, have reported 107 cases of West Nile virus infection including seven deaths (a case fatality rate of 6·5%). Most of the cases reported have been severe, suggesting that milder or asymptomatic cases have been missed. In 2018, 24 cases were reported in the USA.

Malaria in Burundi

WHO has reported that cases of malaria in Burundi reached epidemic levels in May, 2019. Almost 6 million cases were reported during Jan–July, including 1800 deaths as of Aug 4. This is almost double the number of cases reported in the same period in 2018. As of June 17, 34 districts in Burundi had crossed the emergency threshold. Only six of the 46 districts in Burundi reported normal malaria incidence in this period.

Tuberculosis in Germany

As of Aug 1, 109 teachers, students, and other employees in schools have been affected in a tuberculosis outbreak in Karlsruhe, Germany. Four patients (two teachers and two students) have active tuberculosis, while the remaining patients have latent tuberculosis. The cases were first reported in July, when two children from two different schools were found to have active tuberculosis.

Yellow fever in Nigeria

A suspected outbreak of yellow fever virus infection is being investigated in Izzi (Ebonyi State, Nigeria). Following reports of cases and deaths from a fever of unknown origin, the Ebonyi state public health team began investigations on July 30. As of July 31, three cases have tested positive. Retrospective analysis showed that between May 1 and Aug 7, several cases of illness that match the case definition of yellow fever had occurred, including 20 deaths. The response teams are focusing on active case finding, contact tracing, and risk communication; a reactive vaccination campaign is also planned.

Ruth Zwizwai