ARV breakthrough: trial in South Africa confirms effectiveness of new drug

By Michelle Moorhouse & Willem Daniel Francois Venter

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A new antiretroviral drug regimen has been given the go-ahead by the World Health Organisation. This follows the preliminary results from studies that include an ongoing trial in South Africa.

The drug is set to improve HIV treatment. Shutterstock

The Advance study, conducted by a Johannesburg-based research group from the University of the Witwatersrand, will only be completed next year. But early results show that dolutegravir is an effective and well-tolerated antiretroviral drug. ADVANCE, which will continue for 96 weeks, presented its 48-week results at the International Aids conference in Mexico City.

The results are important because the Johannesburg trial includes a population much more representative of the real-world populations being treated for HIV across lower- and middle-income countries. Study participants are black, and almost 60% female with an average age of 32 years.

Previous studies of dolutegravir involved around 3,000 participants, most of whom were middle-aged white men from high-income countries in the US and Europe. They obviously aren't reflective of the global and South African HIV epidemic, which is comprised of mainly black (more than 70%) and women (more than 52%), many of whom are under 40 years of age.

The drug efavirenz has been used in South Africa's public sector antiretrovial therapy (ART) programme for many years and has served the country well. But it has drawbacks. HIV easily becomes resistant to it; it's relatively expensive and it causes side effects in some people. This explains why dolutegravir is being introduced into many HIV programmes across the world, based on recent guidance from the World Health Organisation. Efavirenz will nevertheless continue to be used, too.

There were other gaps as well, including little to no data regarding the use of dolutegravir in those with advanced disease; pregnant or breastfeeding women; people with HIV and tuberculosis coinfection; infants and children; and the elderly.

The study

All the participants (over 1000) in the Advance study were recruited from inner-city Johannesburg. Only 60% were South African, with the remaining 40% from other parts of sub-Saharan Africa, mainly Zimbabwe.

Advance was designed to be as inclusive as possible. This was in an attempt to fill some of the evidence gaps left by the dolutegravir development programme. These included:

- placing no restriction on CD4 counts;
- allowing participants who developed TB or became pregnant during the study to remain in the study;
- from age 12 years and above; and
- keeping the exclusion criteria to enter the study to a minimum.

Another unique feature of Advance is the fact that it was designed by a consortium of leading international HIV clinicians and researchers. There were also inputs from global bodies such as the World Health Organisation, Clinton Health Access Initiative, as well as treatment advocates and activist groups.

It was funded by USAID, Unitaid, the South African Medical Research Council. Study drugs were donated by Gilead Sciences and ViiV Healthcare.

What's been found so far

The Advance study is comparing two dolutegravir-based ART regimens with an efavirenz-based regimen in people starting ART. It is also comparing the currently used ART backbone containing tenofovir disoproxil fumarate (TDF) to the newer tenofovir alafenamide fumarate (TAF).

The early studies in Europe showed that dolutegravir didn't have many side effects. The most marked of the side effects was insomnia. In addition, both dolutegravir and TAF are cheaper to manufacture at scale and can be easily made into a single, much lower dose pill than the current fixed-dose combination used in the public sector.

The study showed that people starting ART with a dolutegravir-based regimen achieved the same high rates of viral suppression as those starting with efavirenz. We also saw very little treatment failure and in most cases, even those individuals who had a high viral load subsequently had an undetectable viral load after adherence counselling.

Very few people stopped the study because of side effects, although more people on efavirenz experienced side effects.

Hardly any Advance participants developed TB – a common co-infection in people living with HIV – as nearly all received tuberculosis preventative medication.

But there are some concerns. One finding was that we saw weight gain in participants receiving dolutegravir-based ART, which was worse in women and in those who received both dolutegravir and TAF. Obesity carries many health risks in terms of developing high blood pressure, risk of diabetes and other problems. Because of this, we are monitoring obesity levels in Advance participants.

We are not sure what the wider implications of this finding may be. But similar findings of weight gain associated with the use of integrase inhibitors, including dolutegravir, were presented at the retroviruses and opportunistic infections conference in March 2019. The finding highlights the importance of including screening for co-morbidities and appropriate lifestyle interventions when treating people with HIV. More research is needed to understand the cause and implications of weight gain seen with integrase inhibitors.

The number of pregnancies in Advance are too small to draw meaningful conclusions from about the risk of neural tube defects. We have not seen any neural tube defects in the study.

Why it matters

Advance is an important study. It confirms that dolutegravir is an effective and well-tolerated ARV for people initiating ART.

This is reassuring as South Africa is planning to roll it out as part of its antiretroviral programme.

Because Advance included a diverse African population and was much more representative of the demographics of the HIV epidemic, its results are important both to people living with HIV in South Africa, as well as globally.

The results have been shared with the World Health Organisation to inform guideline discussions and with regulatory bodies across the globe.

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