ADVANCE study provides evidence for shift to dolutegravir-containing ART in SA

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Professor Francois Venter at Ezintsha, Wits Reproductive Health and HIV Institute (Wits RHI) is Prinicipal Investigator of the ADVANCE study and a plenary speaker at IAS 2019 in July. Credit: Wits University

The South African study shows that dolutegravir-containing regimens perform as well as the current efavirenz-containing one used for first-line antiretroviral treatment (ART) in South Africa and most of Africa.

These data are important in showing how dolutegravir and a new form of

tenofovir (called tenofovir alafenamide—or TAF) perform in African populations, and in providing the scientific backing for the move to dolutegravir-containing regimens from efavirenz-containing ones worldwide.

The initial study results are also published today in the prestigious *New England Journal of Medicine* (NEJM).

Professor Francois Venter of Ezintsha, a sub-syndicate of the Wits Reproductive Health and HIV Institute (Wits RHI) at Wits University, today presented 48-week results from the ADVANCE study at the International AIDS Society scientific conference in Mexico City.

All Regimens—Dolutegravir, Taf And Efavirenz—Rapidly And Effectively Suppressed Hiv

The ADVANCE study showed that at the 48-week mark, dolutegravir-containing regimens perform as well as the current efavirenz-containing regimens used for first-line antiretroviral treatment (ART) in South Africa and many other African countries.

ADVANCE is a 96-week study comparing two alternative antiretroviral drugs to the current first-line regimen of tenofovir disoproxil fumarate, emtricitabine and efavirenz, replacing tenofovir with TAF, replacing tenofovir with TAF, and replacing efavirenz with dolutegravir.

All three regimens were safe, with few side effects reported, other than weight gain. Discontinuations from treatment were mainly related to social and personal factors (people who were employed or older tended to be able to stay on treatment more), and not the drug regimens.

"These two new drugs are really important for our region—they will

improve patients' lives, decrease the use of more toxic second-line drugs, and save money. In summary, all regimens, the new ones studied [dolutegravir and TAF] and the one South Africa uses currently [efavirenz], rapidly and effectively suppressed HIV. The regimens were also all very safe, with minimal side effects that we generally worry about—to bone, kidneys, liver and neuropsychiatric side effects. The one surprising side effect was weight gain, especially among women. To better understand the weight gain, and its longer-term consequences, more follow-up is needed, and this is being explored in the study in more detail," says Venter.

Keeping An Eye On Weight Gain

The issue of weight gain in patients on integrase inhibitors (dolutegravir is an integrase inhibitor) received significant attention in March 2019 during the Conference on Retroviruses and Opportunistic Infections (CROI) held in Seattle, USA. There were several reports from studies, mainly in the US and Europe, that showed greater weight gain for those on integrase inhibitor-containing ART regimens.

ADVANCE is one of two studies on the African continent that provides an opportunity to investigate this issue. The other is a study called NAMSAL, conducted in Cameroon. More information on the weight gain seen in ADVANCE and NAMSAL was presented at IAS on Monday, 22 July 2019.

ADVANCE, similarly to those early reports at CROI 2019, found a steady rise in weight with the new drug regimens containing dolutegravir, especially among women and people who had more advanced HIV (low CD4 counts, higher viral loads), of around 5-6 kg on average at 48 weeks. The effect was worse when dolutegravir was combined with TAF. As the study is continuing to 96 weeks, this is an issue the study team continues to monitor, and further analysis on the

weight gain will be forthcoming. As yet, there is no impact clearly evident on weight-linked health problems, including diabetes, lipids and blood pressure, but it may still be too early to see these.

Dolutegravir-Containing Regimens For South African Public In September 2019

The data generated from ADVANCE have been shared with the South African Department of Health, the South African Health Products Regulatory Authority, the Food and Drug Administration and European regulators, as well as the World Health Organization to inform both local and international ART guidelines. The study team has been actively involved in assisting with the development of the new 2019 ART guidelines for South Africa.

South Africa will be introducing dolutegravir-containing regimens in September 2019 in the public sector (it is now available in private), a change that will affect millions of people living with HIV.

Dolutegravir-containing regimens are cheaper than efavirenz-containing ones, with fewer side effects and a greater resistance barrier. This study confirms the results in other studies in Europe and North America, and will revolutionise ART in South Africa and beyond, although the weight gain side effect has only been recently recognised.

Towards 90-90-90 Targets

The savings in drug cost—as well as its robust resistance barrier stopping people from moving to more toxic and more expensive drugs—would allow South Africa to continue to scale up access to ART in order to meet the UNAIDS/WHO/SA Department of Health 90-90-90 targets. This refers to the goal of 90% of people living with HIV knowing their

status, 90% of those being on ART, and 90% of those being virally supressed.

It was proposed that the new drugs investigated in ADVANCE might have benefits relating to cost to the public sector, resistance and side effects that would significantly impact the well-being of people living with HIV. To investigate if a new ART drug regimen could mitigate the side effects and low barrier to resistance of the current first-line of treatment, the ADVANCE study was designed with input from local and international collaborators, and funded by USAID, Unitaid, the South African Medical Research Council. ViiV Healthcare and Gilead Sciences donated the drugs.

About The Advance Study

The study enrolled 1053 ART naïve people living with HIV, of which around 60% were female, at two sites in Yeoville and Hillbrow, Johannesburg, South Africa. At 48 weeks, the virological suppression rates in all three study arms were very similar. This finding is important, as there has long been concern about rising transmitted drug resistance in South Africa. Additional analysis on pre-treatment drug resistance is ongoing.

The ADVANCE study was conceived by a team of research collaborators from Ezintsha (a subdivision of Wits RHI), the Clinton Health Access Initiative, the Bill and Melinda Gates Foundation, ViiV Healthcare, HIV i-Base, Mylan, the University of Liverpool, and Chelsea and Westminster Hospital, with subsequent input from ViiV Healthcare and Gilead Sciences, as well as the Department of Health, Treatment Action Campaign, WHO and others.

South African researchers from Wits University lead the study in an international alliance with public health and clinical researchers, the

South African government, activist groups, and pharmaceutical manufacturers in a programme linked to community education programmes about the new drugs across the region.

The study was funded in 2015 through a grant from USAID (AID-OAA-A-15-00069), and in 2016 through a grant from Unitaid (2016-07-Wits RHI), with additional financial support from the South African Medical Research Council, and investigational study drugs donated by ViiV Healthcare and Gilead Sciences.

The study commenced in January 2017, and by May 2018 the recruitment of 1053 participants, mainly from inner-city Johannesburg, was finalised. Participants were randomised into three arms of 351 participants each: arm 1 receiving TAF (25mg), FTC (200mg) and DTG (50mg); arm 2 receiving TDF (300mg), FTC (200mg) and DTG (50mg); and arm 3 receiving TDF (300mg), FTC (200mg) and EFV (600MG).

In April 2019 all participants had completed their 48-week study visit, and it is this primary outcome that was reported at the 10th International AIDS Society Conference on HIV Science (IAS 2019), held in Mexico City from 21-24 July.

The study continues to provide valuable insights into antiretroviral treatment in a local cohort (with around 40% of the study population being from other African countries, reflecting the demography of inner-city Johannesburg). The study will complete 96 weeks in mid-2020, and additional analyses will be forthcoming.

This study shows the value of investing in local research, and aside from the funders listed, has had strong support from the South African government, through the Departments of Health, as well Science and Technology.

More information: Willem D.F. Venter et al, Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV, *New England Journal of Medicine* (2019). DOI: 10.1056/NEJMoa1902824