Until very recently, the World Health Organization (WHO) recommended two drugs – dolutegravir and efavirenz – for the treatment of HIV infection. However, these two treatments had never been compared to each other under the conditions usually encountered in countries heavily affected by HIV. Conducted jointly by the University of Geneva (UNIGE) and the University Hospitals of Geneva (HUG) in Switzerland, the Institut de recherche pour le développement (IRD) in France and the Central Hospital of Yaoundé in Cameroon among 613 patients from various Cameroonian hospitals, the NAMSAL study now removes this ambiguity. If the two molecules lower patients’ viral load equally, the risk of drug-induced resistance is much lower with dolutegravir, an essential benefit both in terms of public health and individual health. These results, to be read in the New England Journal of Medicine, provided WHO with the first solid data on this subject. They also highlight the need to conduct high quality studies among the populations concerned, rather than only on patients living in high-income countries, despite the operational complexities of such studies.

Many antiretroviral drugs are available on the market to reduce HIV viral load (the number of viruses per ml of blood) to an undetectable level. Among the treatments often used, efavirenz, which exists since 1998, and the most recent dolutegravir, introduced in 2013. “While the two drugs are well known, they had never been compared to each other in low-income countries”, says Professor Alexandra Calmy, Vice-Dean of the UNIGE Faculty of Medicine in charge of international and humanitarian medicine and head of the HUG HIV/AIDS Unit, who participated in this work. “We have therefore decided to do so, with the support of ANRS and UNITAID, in order to base international recommendations on solid evidence.”

A double-blind study

The NAMSAL study (New Antiretroviral and Monitoring Strategies in HIV-infected Adults in Low-income countries) took place in Cameroon between July 2016 and October 2018. 613 individuals with HIV who had never received treatment were randomly assigned to one of the two recommended therapies: a daily dose of dolutegravir or a 400 mg dose of efavirenz (a lighter dose than the usual 600mg dose to reduce adverse reactions), in combination with two other molecules (triple therapy). While the results in terms of viral load after 48 months of treatment are similar between the two groups – about three-quarters of patients have seen their viral load drop to an undetectable level– the difference resides in viral resistance for patients for whom the treatment has not worked as desired. “Dolutegravir does not
cause resistance mutations in the virus and therefore makes it possible to opt for other treatments”, says Eric Delaporte, a professor at the University Hospital of Montpellier and the IRD, who led this work. “Efavirenz, on the other hand, has triggered important resistance mechanisms, which can be problematic: people are then more difficult to treat and may also transmit a much stronger virus to others.”

**Taking into account populations’ specificities**

In addition, the results of the NAMSAL study show that the effect of both drugs on viral load is less than expected. “Clinical trials conducted for marketing authorization take place on Western patients, the vast majority of whom are men, who also benefit from early detection and general good health”, explains Dr. Charles Kouanfack, of Yaoundé Central Hospital and the first author of this work. “Our patients are very different: two-thirds of them are women who are screened late, and therefore present a very high initial viral load, and who often receive little medical follow-up. The treatments then take longer to work.”

**Scientific data essential to WHO**

These results illustrate the importance of such studies in the development of international recommendations. “We must have data that are representative of the populations receiving treatment in all their diversity and not select the people included in the studies according to criteria that are too narrow”, says Alexandra Calmy, who is also a WHO expert in the field of HIV/AIDS, as well as Professor Delaporte. “I would also like to stress the importance of not excluding women from clinical trials, especially when they constitute the majority of patients.” Without these data, WHO could not recommend one drug over another. Today, the UN agency clearly recommends dolutegravir for the reasons detailed in the study. The update of its recommendations, made in August 2019 following the publication of this work, will now allow countries and funding agencies to negotiate attractive prices with generic manufacturers of dolutegravir and combinations based on this molecule.

This work also illustrates Geneva’s expertise in this field, as well as the emphasis placed by the UNIGE and the HUG on global health. Indeed, both Geneva institutions have mechanisms to encourage research and education in low-income countries and frequently participate in the work of international and humanitarian organizations present in Geneva.

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