Lenacapavir PrEP: 100% efficacy in cisgender women sets new challenges for global pricing and access

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Twice-yearly lenacapavir demonstrated 100% efficacy and superiority to daily emtricitabine/tenofovir disoproxil fumarate for HIV prevention in the Gilead PURPOSE 1 trial. [1]

On 20 June 2024, the Independent Data Monitoring Committee (IDMC) for the study recommended the blinded phase be stopped after an interim analysis and that open-label lenacapavir be offered to all participants.

The top-line results from this analysis found that the injectable capsid inhibitor – given by subcutaneous injection every six months – demonstrated 100% efficacy for HIV prevention in cisgender women.

The trial met its key efficacy endpoints of superiority of twice-yearly lenacapavir to once-daily oral PrEP using F/TDF (emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg) and background HIV incidence (bHIV).

PURPOSE 1 is a phase 3, double-blind, randomised study, evaluating the safety and efficacy of twice-yearly, subcutaneous lenacapavir for pre-exposure prophylaxis (PrEP) and included two versions of once-daily oral PrEP. It is being conducted in over 5,300 cisgender women and adolescent girls aged 16–25 across 25 sites in South Africa and three sites in Uganda.

Study participants were randomised in a 2:2:1 ratio to lenacapavir, F/TAF and F/TDF, respectively. As effective PrEP options already exist, there is no placebo group and the trial used bHIV as the primary comparator and F/TDF as a secondary comparator.

The press release reports zero incident cases of HIV among 2,134 women in the lenacapavir group (0.00 per 100 person-years) vs 16 incident cases among 1,068 women in the F/TDFgroup (1.69 per 100 person-years).

The results demonstrated superiority of twice-yearly lenacapavir over both bHIV (primary endpoint, incidence 2.41 per 100 person-years) and once-daily F/TDF (secondary endpoint), $p<0.0001$ for both endpoints.

HIV incidence in the F/TAF group was numerically similar (39 incident cases among 2,136 women – 1.8% – incidence 2.02 per 100 person-years) to that in the F/TDF group (16 of the 1,068 women – 1.5%) and was not statistically superior to bHIV.

In the trial, lenacapavir was generally well-tolerated and no significant or new safety concerns were identified.

COMMENT

The PURPOSE programme is well-designed and targets populations most at risk for HIV. [2]

PURPOSE 1 is notable for having permissive contraceptive requirements for the participants. So, unusually for a phase 3 trial, it should generate meaningful information about use of lenacapavir in pregnancy.

Additional PURPOSE trials assessing lenacapavir for PrEP are also ongoing.

Results should be available in late 2024/early 2025 from PURPOSE 2 – the programme's second pivotal trial. This looks at lenacapavir PrEP for gay and bisexual cisgender men, transgender men, transgender women and gender non-binary people who have sex with partners assigned male at birth. It is being conducted in Argentina, Brazil, Mexico, Peru, South Africa, Thailand and the United States.

Gilead states that the regulatory filing for lenacapavir for PrEP will include the results of both PURPOSE 1 and, if positive, PURPOSE 2.

But, the IDMC for PURPOSE 2 appears to plan to only look at efficacy data for the scheduled interim analysis. Instead, the significant results from PURPOSE 1 supports the IDMC checking that the primary endpoint has not already been reached, and this could limit the need for participants to continue to be at risk.

A twice-yearly injectable prevention product has long-been a very desirable option so this news is welcome and has generated much excitement. It will be very interesting to see the full data set, which should be presented at a conference in the not too distant future.

If lenacapavir fulfils this early promise, tens of millions of people will need to be offered this as a new option for PrEP.

The price for such broad access in mass prevention programmes will need to be affordable in all settings.

Unit prices for generic lenacapavir will need to be below $50 per person-year. The amount of drug needed to treat each person is very small, the synthesis of this drug has been well-described and work describing the potential cost is ongoing and soon to be presented.

At the moment, lenacapavir is priced in the US at $40,000 per person-year, with an indication as a treatment for people with multidrug HIV resistance (or intolerance to alternative ART).

Although Gilead issued a second press release stating their commitment to widespread access, there is currently no agreement between the company and the Medicines Patent Pool (MPP) for a voluntary licence which could allow manufacture of low-cost generic versions. [3]

Such agreements need to be made immediately with generic manufacturers, to allow distribution of this drug at prices less than $50 per person-year in ALL low- and middle-income countries. Other community organisations, including the activist AfroCAB network are making similar demands. [4]

In the past, Gilead has excluded key middle income countries from its access agreements. This includes much of South America and South East Asia.

Generic manufacturers will need time to set up mass production and to run bioequivalence trials. The faster these agreements are made, the faster people can benefit from what might prove to be a groundbreaking HIV prevention option.

Finally, the US National Institute of health (NIH) noted the pivotal role of publicly funded research that enables these phase 3 results. [5]

This includes decades of drug discovery and translational research that contributed to the development of lenacapavir with instrumental evidence on the structure of HIV, research into pharmacology, drug resistance, analysing drug levels, and implementing two Gilead-sponsored studies in the US of lenacapavir in cisgender women and people who inject drugs.

References

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