Modelling Impact of Injectable Cabotegravir for PrEP on Drug Resistance
April 2022

Context

On 7 March 2022, Professor Andrew Phillips from University College London shared the results of an individual-based simulation modelling exercise looking at the impact of the introduction of injectable cabotegravir for Pre-Exposure Prophylaxis (CAB for PrEP) on integrase strand transfer inhibitor (INSTI) resistance. INSTI resistance is a particular concern as this class of drugs includes dolutegravir, which is a current first-line treatment for HIV in Sub-Saharan Africa. Situations which may to lead to INSTI resistance include:

- Initiation of CAB for PrEP by an individual recently infected with HIV whose viral load is not yet high enough to be detected with third generation antibody tests, which are the standard of care for HIV testing in Sub-Saharan Africa.
- Infection breakthrough while taking CAB for PrEP.
- Infection during the pharmacokinetic "tail," where CAB for PrEP remains in the body for several months following discontinuation at levels too low to protect from HIV infection but high enough to lead to INSTI resistance.

Main Findings

INSTI Resistance
In the model, widespread usage of CAB for PrEP could **likely lead to an increase in INSTI resistance**, with an estimated 10% rate of INSTI resistance in individuals initiating antiretroviral therapy (ART) by 2030. This compares to an estimated 0.5% rate of INSTI resistance in individuals initiating ART by 2030 if CAB for PrEP is not introduced.

AIDS-Related Mortality
Despite the projected increase in INSTI resistance, the modelling predicted **a significant decrease in AIDS-related mortality** if CAB for PrEP was widely used, with an estimated 2,600 fewer AIDS-related deaths per year over 50 years.

Testing
Exclusive usage of RNA testing rather than the model's assumed mix of RNA and antibody testing at CAB for PrEP initiation and throughout use could **halve the projected rate of INSTI resistance** from 10% to 5% -- however, the modelling showed this would **not necessarily lead to a reduction in AIDS-related mortality**.

Costs
If CAB for PrEP usage is concentrated within individuals at high risk of HIV infection, it would be **highly cost-effective at an annual cost of $23 USD for medication plus $40 USD for clinical visits**. However, at twice the equivalent annual cost of generic oral tenofovir and emtricitabine (TDF/FTC) ($120 USD for medication and $80 USD for clinical visits), it is only 65% likely CAB for PrEP would be cost effective, unless provided only in populations with over 1% HIV incidence rate.

Limitations

The model used fixed three-month time steps for clinic visits, which is inconsistent with the two-month interval for CAB for PrEP administration as well as the short time scale of changes in test sensitivity in people who have only recently acquired HIV and who may be initiated on CAB for PrEP before testing shows a positive result.

Clarifications Following Audience Questions

- The model presented looked at use of CAB for PrEP only, not for HIV treatment.
- Only heterosexual transmission was modelled.
- The model does not take into account the possibility that other types of injectable PrEP or long-acting methods will become available over the next 50 years (the modelling period) that could displace CAB in the PrEP method mix.

Key Takeaways

When considering the widespread rollout of injectable CAB fo PrEP, the benefits of decreased AIDS-related mortality outweigh the risks of increased INSTI resistance. Increased RNA testing would result in lower projected INSTI resistance, but lack of access to RNA testing should not be an impediment to CAB rollout

Next Steps

AVAC will schedule a follow-up session for Professor Phillips to present on additional modelling scenarios incorporating feedback from participants.