Doctopic: Analysis and Interpretation
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High volume subcutaneous delivery of long-acting HIV bNAbs

In *The Lancet HIV*, Sharana Mahomed and colleagues[1] report results of a phase 1 safety and pharmacokinetics study of a combination of two long-acting anti-HIV broadly neutralising monoclonal antibodies (bNAbs), CAP256V2LS and VRC07l523LS, in women in South Africa. CAP256V2 targets the V1/V2 loops of HIV gp120 and VRC07-523 targets the CD4-binding. The combination shows complementary breadth and potency against large panels of multiclade viruses.[2]

Despite recent progress in HIV prevention, approximately 1·5 million new infections were reported last year and the vast majority occurred in sub-Saharan Africa. Adolescent girls and young women are three times more likely to acquire HIV than adolescent boys and young men in sub-Saharan Africa and are often at risk of physical or sexual violence from their partner.[3] Low uptake and adherence to daily pre-exposure prophylaxis (PrEP) with oral antiretrovirals remain challenges among this and other key populations in Africa, and long-acting injectable or vaginal ring delivery of antiretrovirals are not yet available in the region. In the absence of an effective vaccine, alternative prevention strategies are needed. A promising strategy is the passive transfer of anti-HIV bNAbs.

Many different bNAbs targeting a variety of epitopes on the viral envelope glycoprotein have been isolated, several of which have been tested in clinical trials.[4] As macromolecules, bNAbs must be administered parenterally but have a much longer half-life (typically weeks to months) than small molecules (typically hours to days). Their expected safety profile, potency and breadth of activity, and long half-lives are desirable features for HIV prevention. The recently reported Antibody-Mediated Prevention (AMP) trials revealed both the promise and challenges of implementing bNAbs as PrEP. The AMP trials tested the ability of bimonthly intravenous infusions of VRC01 (a CD4-binding site bNAbs) to prevent acquisition of HIV in different populations. Although VRC01 did not lead to an overall reduction in HIV acquisition, it showed 75% efficacy in reduction of infection due to VRC01-sensitive HIV isolates. These studies also showed the feasibility and acceptability of repeated intravenous bNAb administrations.[5] However, the studies highlighted the importance of ensuring that bNAbs used for prevention have high-titre neutralising activity against HIV variants circulating in a region. Studies using combinations of bNAbs for PrEP are now being designed. Use of bNAbs containing the LS modification in the Fc domain to prolong half-life could allow dosing every 3–6 months, thereby increasing the feasibility of sustained delivery of bNAbs outside of the clinical trials setting.

The study by Mahomed and colleagues adds to the current body of data with bNAbs in different study populations. This is the first study of a dual long-acting bNAb combination administered subcutaneously and intravenously to a cohort of young African women. CAP256V2LS and VRC07-523LS in combination were found to be generally safe, and subcutaneous injections were well accepted by trial participants. Of note, one of the challenges of subcutaneous delivery of antibodies is the volume needed to achieve concentrations expected to mediate protection against widely diverse circulating viruses. This study tested higher subcutaneous doses than previously evaluated by adding recombinant human hyaluronidase, which temporarily breaks down subcutaneous tissues, allowing larger volumes to be delivered.[6] The pharmacokinetics profile of each bNAb was not significantly altered by inclusion of hyaluronidase or by parallel administration of both antibodies, although measured concentrations of CAP256V2LS were slightly higher when combined with VRC07-523LS. Although the target serum through levels for protection have not been established for this bNAb combination, antibody concentrations were measurable in serum for 6 months after injection at the highest doses tested, and both antibodies showed expected neutralising activity in serum. Overall, these are promising findings from a study conducted in an endemic region with a highly active bNAb combination.

Efforts are ongoing to select promising bNAb combinations to enter future HIV prevention efficacy studies. The choice of bNAbs for advanced development will probably rely on their in-vitro activity against recent circulating viral isolates, and possibly on their efficacy in preventing reservoir viruses from causing rebound viraemia in small, proof-of-concept antiretroviral treatment interruption studies. In parallel and as experienced with COVID-19, the assessment of different methods of antibody delivery (eg, intravenous infusions

or high-volume subcutaneous injections), infrastructure needs, and overall cost will be fundamental to the success of this prevention strategy.

I report receiving consultation fees from Gilead Biopharmaceuticals.

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