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Aids 2022 preview – Gilead shoots for an HIV cure

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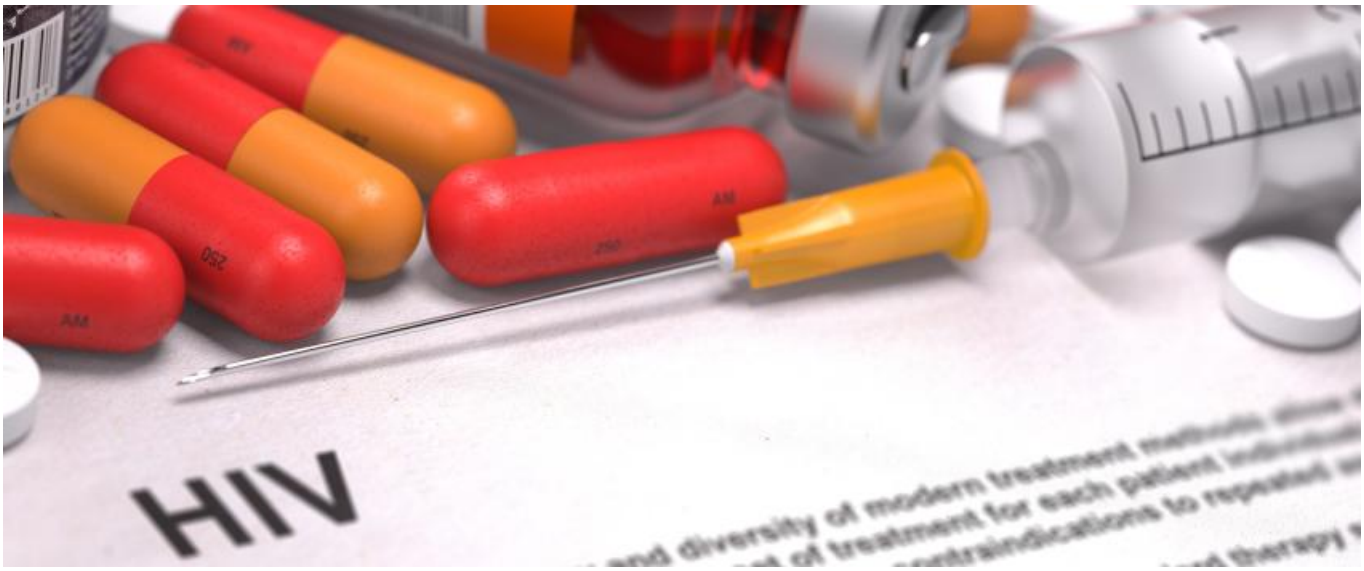

But progress – or lack thereof – with lenacapavir is a more immediate concern.

Gilead has already shot itself in the foot once – from a business perspective at least – by curing hepatitis C. Now the company hopes to do it again with HIV. At the Aids 2022 meeting this weekend the group will present early data with two of its curative efforts, the toll-like receptor 7 agonist vesatolimod and a Flt3 agonist, during a late-breaking session.

However, of more immediate concern is the group's conventional long-acting HIV project lenacapavir. The path forward for this asset's use in a broad patient pool still looks uncertain.

Gilead was hit by last year's clinical hold for Merck & Co's islatravir following a safety scare; the groups had been studying lenacapavir and islatravir in combination. That hold has still not been resolved, Gilead's vice-president of HIV research, Jared Baeten, tells *Evaluate Vantage*.

He says the company "remains committed to exploring the collaboration with Merck", adding: "The first thing that we were testing was the weekly oral therapy, and that would be what we would resume if the clinical hold were to be lifted."

However, Gilead has long sought not to put all its eggs in one basket in terms of finding a suitable add-on to lenacapavir – and to this end the company has already advanced various combinations with projects in its own pipeline. Mr Baeten highlights GS-5894, a non-nucleoside reverse transcriptase inhibitor already in phase 1, and GS-1720, a preclinical integrase strand transfer inhibitor (INSTI), as potential oral candidates.

Gilead is also evaluating a combo of lenacapavir and bictegravir, the INSTI used in its blockbuster triplet Biktarvy. Still, these efforts are all very early, raising the question of whether Gilead will also look elsewhere if islatravir hits a dead end.

Gilead's clinical-stage HIV pipeline		
Project	**Mechanism**	**Status**
Lenacapavir monotherapy	Capsid inhibitor	CRL in Mar 2022 for in heavily treatment-experienced HIV pts, refiled Jun 2022; Purpose 1-4 Prep studies ongoing; +ve opinion in EU as Sunlenca
Lenacapavir + islatravir*	Capsid inhibitor + NRTI	Ph2 of weekly oral combo still on hold
Vesatolimod (GS-9620)	TLR7 agonist	Potential cure; ph2 combo with Aelix's HIT vaccine, data due late 2022; ph2 combo with bNABs completes Feb 2024
Lefitolimod (GS-1703)	TLR9 agonist	Potential cure; ph1/2 completes Dec 2024**
GS-2872 + GS-5423	bNAB combo	Potential cure; ph1 combo with lenacapavir completed Jun 2022
Lenacapavir + GS-5894	Capsid inhibitor + NNRTI	Ph1
Lenacapavir + bictegravir	Capsid inhibitor + INSTI	Ph1
ChAdV self-amplifying RNA vaccine^	Self-amplifying RNA vaccine	Potential cure; IND cleared in December 2021
**Islatravir being developed by Merck & Co; **investigator sponsored; ^being developed in partnership with Gritstone Bio. bNABs=broadly neutralising antibodies; INSTI=integrase strand transfer inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor. Source: Evaluate Pharma, clinicaltrials.gov & company presentation.*		

At least in the niche of heavily treatment-experienced HIV patients, Gilead has had some good news.

Lenacapavir also went on hold last December, amid contamination concerns, followed by an FDA complete response letter in March. But that hold was lifted in May, and Gilead resubmitted its application in treatment-experienced patients at the end of June, Mr Baeten says. He is quick to point out that this “was a container issue, not a molecule issue”, and that lenacapavir is now being stored in a new container.

The Purpose-1 and 2 studies in pre-exposure prophylaxis have also restarted; these were initially set to yield data in 2024, although Mr Baeten is now reluctant to put a timeline on their readouts. In addition, Gilead plans two new Prep trials, Purpose-3 and 4, in US women and IV drug users respectively, which should start enrolling this year.

Functional cure

Prevention is one thing, but if Gilead could develop a functional HIV cure this would take things to a whole new level. One problem that has held such efforts back is the HIV reservoir. “Basically, the virus is hiding in this reservoir, and antiviral therapy doesn't do anything to the reservoir,” says Gilead’s senior vice-president of virology research, Tomas Cihlar.

The company therefore hopes to “wake up” the latent virus in this reservoir, so it can then be eliminated.

Gilead’s most advanced potential cure is the TLR7 agonist vesatolimod. The group reported data last year from a small phase 1 study in HIV controllers, people who have HIV but have low viral loads despite not receiving treatment. The late-breaking presentation at Aids 2022 comes from an extension of that study, looking at markers that could help predict response to vesatolimod.

Mr Cihlar describes these monotherapy data as “somewhat encouraging. Ultimately, the virus woke up but was not eliminated – but it was a step in the right direction.”

Combos

Gilead’s hopes for vesatolimod therefore rest on combinations, currently with Aelix Therapeutics’ T-cell vaccine, where mid-stage data are due fairly soon, and with broadly neutralising antibodies.

The other Gilead project to feature at Aids 2022 will be a currently unnamed agonist of Flt3, a tyrosine kinase required for dendritic cell activation. Gilead also has a Flt3 receptor agonist fusion protein, GS-3583, in phase 1 for cancer.

"It's the same principle," Mr Cihlar says. Dendritic cells are needed to present antigen to the immune system, and agonising Flt3 "boosts the capability of the host immune system to either fight cancer or fight the virus". A separate role for Flt3 is where this kinase is mutated and drives AML; Astellas's Xospata is a Flt3 inhibitor approved for AML.

The Gilead data come from a non-human primate study in which the Flt3 agonist was combined with Hookipa's arenavirus vaccine candidate HB-500, so this approach has a long way to go.

Mr Cihlar says that other, similar studies are ongoing with the Hookipa vaccine in combination "with different types of immune modulatory mechanisms and, from there, we will decide which one is the best to take into early-stage clinical trials".

This could include vesatolimod, as well as the TLR9 agonist lefitolimod, or a PD-1 inhibitor, he adds. Gilead's latest HIV presentation mentions Arcus's anti-PD-1 zimberelimab as a potential component of an HIV cure; however, this has only so far been trialled in cancer.

The table in this story has been updated to clarify the status of the Gilead-Gritstone HIV vaccine.