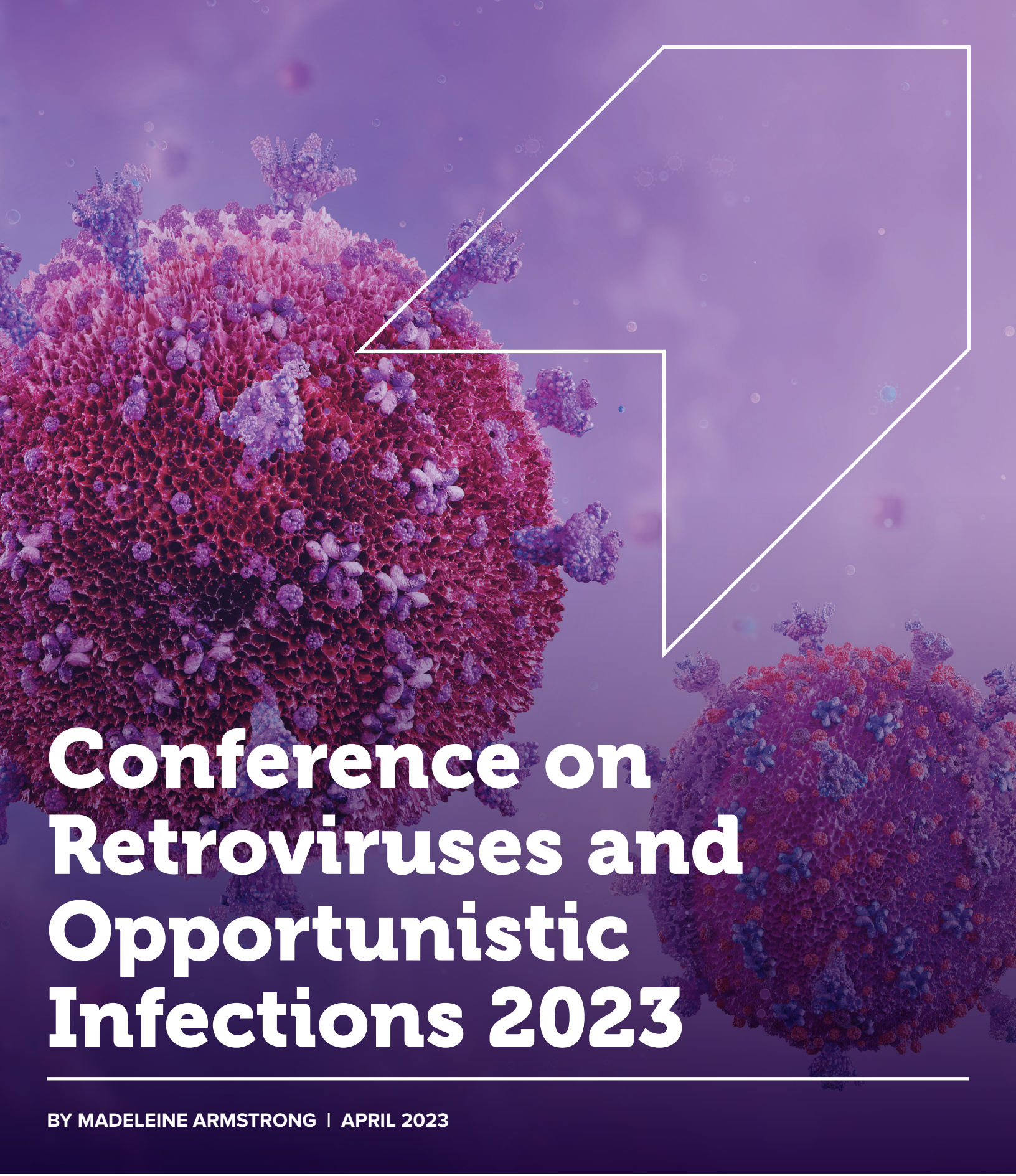

Conference on Retroviruses and Opportunistic Infections 2023

BY MADELEINE ARMSTRONG | APRIL 2023

ARTICLE PACK

Evaluate Vantage

Contents

CROI 2023 – progress on efforts to cure HIV

BY MADELEINE ARMSTRONG
FEBRUARY 27, 2023

Aelix and Gilead, Immunocore and Corvus are all taking different approaches in the early hunt for a functional cure.

Gilead is trying to cure HIV, but it is not the only one. The recent Conference on Retroviruses and Opportunistic Infections (CROI) featured several projects that, it is hoped, could pave the way to a functional cure.

Companies are taking various approaches to hit the HIV reservoir, which is thought to be the key to success, but the work here is early – in some cases, very early indeed.

THERAPEUTIC VACCINE

One of the most advanced potential functional cures is a combination of Gilead's TLR7 agonist vesatolimod with a therapeutic vaccine candidate being developed by Aelix. The HIVACAT T-cell immunogen (HTI) vaccine is designed to elicit an immune response to HIV. While therapeutic vaccines have fallen short in the past, Aelix reckons that it could have found the answer by hitting regions of the virus that are also targeted by patients who naturally control HIV.

Data from the phase 2 Aelix-003 study suggested that patients receiving the vaccine/vesatolimod combo were less likely to experience a rebound in viral load versus those on placebo. This was tested by interrupting antiretroviral therapy for up to 24 weeks; plasma viral load was monitored weekly, and therapy was resumed if viral load went above a predetermined threshold.

Of the 30 vaccine/vesatolimod-treated patients, 33% remained off antiretroviral therapy over 24 weeks, versus 24% of those on placebo.

Privately held Aelix's chief scientific officer, Christian Brander, conceded that the absolute difference was not as great as in the previous Aelix-002 trial, which tested a more complex HTI vaccine regimen without vesatolimod. However, he put this down to a "number of placebo controls that presented with beneficial host genetics and low reservoir".

In the 003 trial there was a more pronounced difference in patients with a high viral reservoir at baseline.

Mr Brander said it was too early to comment on whether Aelix would take a vaccine/vesatolimod combo into phase 3. The company is awaiting data from the BCN03 trial, evaluating a T and B-cell vaccine combo, before deciding on future steps.

T-CELL RECEPTOR

Immunocore is also aiming to harness T cells with its bispecific candidate IMC-M113V, which comprises a T-cell receptor domain and an anti-CD3 effector function. The latter recruits T cells while the former targets a peptide derived from the Gag protein that is presented on the surface of HIV-infected cells; the ultimate goal is redirecting non-exhausted T cells to target and kill the infected cells in the viral reservoir.

Data on this project are still early, with CROI featuring initial phase 1 results from a phase 1/2 study called Strive. In the single-ascending dose portion, 12 patients received IMC-M113V at 1.6µg, 5µg and 15µg.

Immunocore reckons the signs are good: the group pointed to a fourfold or greater increase in IL-6 in five of 10 patients on the highest dose, saying this was a predefined marker of pharmacodynamic activity. The company has started enrolling HIV patients into the multiple-ascending dose portion of the study, with a target of up to 28 patients.

Like Aelix, the group plans to evaluate viral rebound after interruption of antiretroviral therapy. Immunocore hopes a 12-week dosing period could lead to a persistent effect, a company spokesperson told Evaluate Vantage.

ITK INHIBITOR

Even earlier is the microcap Corvus Pharmaceuticals, which touted preclinical results on its oral interleukin-2-inducible T-cell kinase (ITK) inhibitor CPI-818. Corvus highlighted data from cell models suggesting that the asset could stop the re-emergence of latent HIV.

The company plans to take CPI-818, which is already in phase 1 in T-cell lymphoma, into the clinic in HIV next year – although the group's chief executive officer, Richard Miller, told Evaluate Vantage that it ultimately hoped to find a partner for the infectious disease.

He believes a short course of CPI-818, "on the order of a few months", would be required to effect a functional cure. He noted: "ITK is required for the HIV virus to replicate, assemble and infect cells – so there are multiple modes of action".

There do not appear to be any other ITK inhibitors in active development, according to *Evaluate Pharma*.

Selected functional cure approaches presented at CROI 2023

Project(s)	Company	Description	Study details
HTI vaccine + vesatolimod	Aelix & Gilead	Therapeutic vaccine + TLR7 agonist	Ph2 Aelix-003: 33% (10/30) treated pts remained off ART for 24wks, vs 24% (4/17) with placebo
IMC-M113V	Immunocore	Bispecific soluble T-cell receptor	Ph1/2 Strive: SAD portion found rise in IL-6; MAD portion planned
CPI-818	Corvus	ITK inhibitor	Preclinical; reduction in reversal of viral latency in cell models

TLR7=toll-like receptor 7; ITK=interleukin-2-inducible T-cell kinase;

Source: CROI 2023 & company releases.

CROI 2023 – GSK and Gilead's long-acting HIV battle intensifies

BY MADELEINE ARMSTRONG
FEBRUARY 27, 2023

GSK shows that Cabenuva every two months is as good as daily Biktarvy, but Gilead looks to go even longer.

GSK has long been the trailblazer in long-acting HIV therapies, and at last week's Conference on Retroviruses and Opportunistic Infections (CROI) the group touted data with its doublet Cabenuva, which can be given as infrequently as every two months.

The head-to-head Solar trial showed Cabenuva had non-inferior efficacy to Gilead's rival daily HIV therapy Biktarvy – and that 90% of patients who switched preferred the long-acting regimen. But Gilead has its own long-acting HIV ambitions, and presented early data on lenacapavir in combination with broadly neutralising antibodies, designed to be given just once every six months.

LENA COMBOS

Lenacapavir, injected twice yearly, is already approved as Sunlenca for multidrug-resistant HIV, a small niche. Expanding into the broader HIV population will depend on combining it with other therapies.

The most advanced combo is lenacapavir plus Merck & Co's islatravir; a phase 2 study of a once-weekly oral regimen recently restarted after a clinical hold on islatravir.

Gilead has long sought to keep its options open, however, and other efforts might be starting to bear fruit. CROI saw results from a phase 1 study of

lenacapavir plus the broadly neutralising antibodies (bNAbs) teropavimab and zinlirvimab.

The uncontrolled study tested the combo in virologically suppressed HIV patients, whose baseline antiretroviral therapy was replaced by a single subcutaneous dose of lenacapavir (plus an oral loading dose) and single intravenous doses of teropavimab and zinlirvimab. The primary endpoint was safety, but the study also looked at whether patients maintained virologic suppression at six months.

Of the 20 evaluable patients, 18 were still virologically suppressed at six months.

On safety, there were no grade 4 or 5 adverse events, or any events that led to discontinuations. There were two grade 3 adverse events of injection site reactions.

This was enough for Gilead to push into phase 2, but there are reasons to be cautious. One is practicality, with the bNAb infusions taking one hour apiece, with monitoring periods of 15 minutes between infusions and 30 minutes post-infusion.

A spokesperson for Gilead told Evaluate Vantage that the company was evaluating whether shorter administration and observation periods might be possible. He stressed that the group's ultimate aim was to have several long-acting options available, to suit different patients' preferences.

REBOUND

Potentially more worrying is that one of 20 patients receiving lenacapavir plus the bNAbs experienced viral rebound at week 16. Another patient withdrew from the study, but showed viral suppression at week 12, the last available measurement.

The Gilead spokesperson did not have an explanation for the rebound, saying the patient in question had lenacapavir and bNAb concentrations "consistent with others in the same dosing group". Investigations continue, but this will be something to keep an eye on in future trials in larger numbers of patients. The affected patient was re-suppressed using oral antiretrovirals.

Virologic rebound can be caused by resistance to therapy, something that has long been a concern with doublets.

And the spectre of resistance was raised again with results from Solar, the head-to-head study of Cabenuva and Biktarvy. The phase 3 trial enrolled 670 patients already virally suppressed on Biktarvy, and randomised them either to continue therapy or to switch to Cabenuva. The primary endpoint was non-inferior virologic efficacy at one year, measured via the proportion of patients with HIV-1 RNA of 50c/ml or over, and rates were similar between the two arms.

However, three Cabenuva-treated patients had confirmed virologic failure with resistance-associated mutations, versus none in the Biktarvy arm.

A spokesperson for Viiv, GSK's HIV joint venture with Pfizer and Shionogi, contended that Cabenuva's benefits, including its less frequent administration, "outweigh the low risk of failure with resistance development", which she noted was less than 1%.

She added that the lack of confirmed virologic failure in the Biktarvy arm "should be balanced with the fact that participants were stably suppressed on Biktarvy for over two years when they entered the study, representing those that were already successful on Biktarvy".

GSK has a long way to go to dislodge Biktarvy: the Gilead once-daily is forecast to sell over $12bn by 2028, according to sellside consensus compiled by Evaluate Pharma, while Jefferies analysts predict worldwide peak Cabenuva sales of $3bn.

Evaluate

a norstella company

Evaluate provides trusted commercial intelligence for the pharmaceutical industry. We help our clients to refine and transform their understanding of the past, present and future of the global pharmaceutical market to drive better decisions. When you partner with Evaluate, our constantly expanding solutions and our transparent methodologies and datasets are instantly at your disposal, along with personalised, expert support.

Evaluate gives you the time and confidence to turn understanding into insight, and insight into action.

Evaluate Pharma offers a global view of the pharmaceutical market's past, present and future performance with best-in-class consensus forecasts to 2028, unique broker forecasts, and the application of proprietary methodologies to support highly robust, detailed and accurate analysis.

Evaluate Omnium provides a complete, dynamic view of development risk and commercial return across all phases of the clinical lifecycle – including early-phase and privately-developed drugs not covered by analysts' forecasts. With product-specific data including Predicted Peak Sales, Probability of Technical and Regulatory Success (PTRS), R&D Costs, Net Present Value, Time-to-Peak and more, Evaluate Omnium makes it easier than ever to quantify and compare risk and return across the full pipeline landscape.

Evaluate Epi is curated by epidemiology experts and delivers comprehensive, global epidemiological data in granular detail, on a highly interrogatable platform. Customers have access to impartial data for 15 therapeutic areas, and over 230 indications and 9,500 sub-populations across 27 core markets (up to 49 for some countries).

Evaluate Medtech provides a transparent and trusted source of market intelligence and consensus forecasting for the global medical device and diagnostic landscape, using the same proprietary methodologies as Evaluate Pharma. Customers can quickly understand how the market views products and portfolios – and where their opportunities, risks and priorities lie.

Evaluate Consulting & Analytics are specialists in solving unique and complex biopharma pipeline, portfolio and commercialisation challenges with best-in-class datasets, powerful analytical capabilities, and deep therapy and commercialisation expertise.

Evaluate Vantage provides award-winning, thought-provoking news and insights on current and future developments in the pharma, biotech and medtech industries, and is the only news service underpinned by Evaluate's commercial intelligence and data.

Subscribe to Evaluate Vantage Daily News

www.evaluate.com | **@Evaluate** **@EvaluateVantage**

Evaluate Headquarters
Evaluate Ltd.
3 More London
London SE1 2RE
United Kingdom
T +44 (0)20 7377 0800

Evaluate Americas
EvaluatePharma USA Inc.
60 State Street, Suite 1910
Boston, MA 02109
USA
T +1 617 573 9450

Evaluate Asia Pacific
Evaluate Japan KK
Holland Hills Mori Tower 2F
5-11-2 Toranomon, Minato-ku
Tokyo 105-0001, Japan
T +81 (0)80 1164 4754