SOUTH AFRICAN MEDICAL RESEARCH COUNCIL (SAMRC)
HIV AND OTHER INFECTIOUS DISEASES RESEARCH UNIT (HIDRU)

Responses and feedback with pasted spotlight article

To:
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26 JUNE 2024

Preliminary questions:
-Please state your full name and area of expertise.

Dr Elizabeth Spooner, Clinical Trial Specialist, and Investigator
Mrs Neetha S Morar, Senior Research Manager (focused on Social Science and External Stakeholder Engagement (access, ethics)

1. What does the research currently suggest about lenacapavir and its potential for being used as a long-acting prevention? Do we have an indication of how months of protection are being considered?

Enoxaparin represents a new class of antiretrovirals (ARVs) with a novel mechanism of action as a capsid inhibitor and a unique twice-a-year subcutaneous administration schedule. Lenacapavir when combined with other ARVs has been proven to benefit heavily treatment-experienced (HTE) patients with HIV-1 infection in achieving viral suppression and immune restoration.

Relevance to Patient Care and Clinical Practice in Comparison with Existing Drugs:

Lenacapavir is a new treatment option that patients who are HTE can consider adding as part of an ARV regimen.

Conclusions:

Lenacapavir is an effective and well-tolerated option for HTE patients which is a valuable addition to the arsenal of ARVs.

(Ref: Tailor MW, Chahine EB, Koren D, Sherman EM. Lenacapavir: a novel long-acting capsid inhibitor for HIV. Annals of Pharmacotherapy. 2024 Feb;58(2):185-95.)

Recent use of LEN for HIV prevention with 100% efficacy is a gamechanger but we need to look at timelines for access, costs and plans for verification of the trial results.

2. Are there any key trials coming up around using lenacapavir for HIV prevention?

Yes. Open label trial based on results released (PURPOSE 1). HIDRU, SAMRC contributed approximately 696 to these excellent results of 1005 efficacy.

Research determined the anti–HIV-2 activity of lenacapavir using single-cycle infections of MAGIC-5A cells and multicycle infections of a T-cell line. Lenacapavir exhibited low-nanomolar activity against HIV-2 but was 11- to 14-fold less potent against HIV-2 in comparison to HIV-1. Mutations in HIV-2 that confer resistance to other antiretrovirals did not confer cross-resistance to lenacapavir. Although lenacapavir-containing regimens might be considered for appropriate patients with HIV-2, more frequent viral load and/or CD4 testing may be needed to assess clinical response.

Smith RA, Raugi DN, Nixon RS, Seydi M, Margot NA, Callebaut C, Gottlieb GS. Antiviral Activity of Lenacapavir Against Human Immunodeficiency Virus Type 2 (HIV-2) Isolates and Drug-Resistant HIV-2 Mutants. The Journal of Infectious Diseases. 2024 May 15;229(5):1290-4.

3. A study presented at CROI this year found that there is potential for using CAB-LA as every four-month dose for HIV prevention. Can you please explain as simply as possible what this research found and what the potential implications of this are?

CAB LA is currently completing the open label trial with participants at our three sites. In quarter 3 or 4 the roll over trial funded by ViiV will start. While this is exciting, access to the general public is a challenge as it is costly (details in your spotlight article below)

4. What future studies are being planned for the CAB-LA four-monthly injection?

Adolescent girls and young women in Africa are at high risk of HIV and should be considered a key population for HIV prevention initiatives. Oral Tenofovir/Emtricitabine as pre-exposure prophylaxis (PrEP) has been shown to be effective on an individual and population level among key populations in Europe, Australia, and the US.

However, studies in sub-Saharan Africa in a generalized epidemic have been less promising with adherence to daily tablets identified as a major problem. Long-acting PrEP drugs are being developed as a response to this problem. The first of these long-acting agents, injectable Cabotegravir given every two months has shown superiority to oral PreP and has been approved by the US Food and Drug Administration (FDA).

Another long-acting PrEP drug in development is Lenacapavir which is an investigational, first-in-class long-acting HIV-1 capsid inhibitor that can be given as a six-monthly injection. These long-acting drugs could be a highly effective public health HIV prevention intervention. If made readily available to a vulnerable population of adolescent young women who are at high risk of HIV, they could play an important role in protecting this key population against HIV and potentially reduce the population level risk of HIV.

Owuor S, Kimani M, Kaplan R. The future of PrEP: novel long-acting HIV prevention agents for adolescent women. The Pan African Medical Journal. 2024;47.

5. Do we have any information on how different the production process for the four monthly injections is versus every two months injection of CAB-LA?

No. This is managed by ViiV and not the researchers. However, we may explore directly with ViiV who are open to communication on access plans.

6. Do we currently have any information on whether the four-monthly CAB-LA injection will be covered by the existing license for generics of the two-monthly injection?

No

7. Another study presented at CROI looked at the use of a weekly pill (GS-1720: A Novel Weekly Oral InSTI) as a potential long-acting HIV therapy. Could you explain the results and potential impact/implications of these results?

We are not familiar with the details of this specific trial. Based on data on use of ARVs, users have reported adherence challenges to oral medication and facing stigma. Thus, while oral is an option for both treatment and prevention (oral PrEP), choice and uptake are based on experiences of the users.

8. Are there any other studies whose results were presented at CROI that are worth mentioning when it comes to what might be next for long-acting HIV therapies?

No.

-Is there anything else you would like to add?

Biomedical prevention and treatment options are only effective if we understand and address users' needs. This includes their experiences with sustainability and making choices for different options based on their lifestyle and needs. This area of understanding needs more work and conversations with the users.

ADDITIONAL RESOURCES AND ARTICLES

Please see below several articles and material as background information including the Spotlight Article – 13 June 2024

NEWS PROVIDED BY
ViiV Healthcare
May 13, 2024, 08:01 ET
SHARE THIS ARTICLE
ViiV Healthcare Announces Health Canada Approval for APRETUDE (Cabotegravir tablets and extended release injectable suspension) for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV Français

- Approved for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV infection in at-risk adults and adolescents aged 12 years and older, weighing at least 35 kg, including men who have sex with men, transgender women, and cisgender women.
- APRETUDE (cabotegravir extended-release injectable suspension) is the first and only long-acting injectable PrEP treatment approved in Canada.
- Given as few as six times per year after initiation and demonstrated superior efficacy to a daily oral PrEP option (FTC/TDF tablets) in reducing the risk of HIV acquisition in 2 clinical trials.[1]
- The latest Canadian surveillance data shows that there were 1,833 new HIV diagnoses in 2022, a 24.9 per cent increase from 2021.[2.]

MONTRÉAL, May 13, 2024 /CNW/ **-** ViiV Healthcare, the global specialist HIV company majority owned by GlaxoSmithKline plc (GSK), with Pfizer Inc. and Shionogi as shareholders, announced that Health Canada has granted approval for APRETUDE (cabotegravir tablets and extended release injectable suspension) for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in at risk individuals who are HIV-1 negative.[1] APRETUDE is indicated for at-risk adults and adolescents aged 12 years and older and weighing at least 35 kg for PrEP to reduce the risk of sexually acquired HIV-1 infection.[1]

APRETUDE is the only long-acting injectable HIV PrEP option approved in Canada that reduces the number of doses needed for effective HIV prevention from daily pills to as few as six injections per year. Cabotegravir tablets and extended-release injectable suspension for PrEP has demonstrated superior efficacy to daily oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF tablets) in reducing the risk of HIV acquisition in 2 clinical trials, giving Canadians more options for PrEP.[1]

Jean-Francois Fortin, Country Medical Director, Canada at ViiV Healthcare, said: "With the approval of APRETUDE in Canada, we are proud to be able to offer a new prevention option for Canadians at risk of acquiring HIV. We are confident that by providing another highly effective preventative option for Canadians, we are one step closer to our collective goal of ending the HIV epidemic. We look forward to working with provincial, territorial, and national health authorities to bring APRETUDE to Canadians across the country."

HIV remains a critical public health issue in Canada, with cases of HIV increasing by 24.9 per cent in 2022 from 2021.[2] PrEP has been identified as an effective tool in reducing new cases of HIV, key to ending the HIV epidemic. Despite the wide availability of daily oral PrEP, inconsistent adherence as well as structural and cultural barriers lead to underutilization in key populations.

Health Canada approval was based on the results of two key phase IIb/III studies, HPTN 083 and HPTN 084, which evaluated the safety and efficacy of cabotegravir long-acting for PrEP in men who have sex

with men, transgender women, and cisgender women who were at increased risk of HIV.[3,4] The studies demonstrated that cabotegravir long-acting injectables for PrEP was superior to daily oral emtricitabine/tenofovir disproxil fumarate (FTC/TDF), with clinical trial participants experiencing 69 per cent lower rate of HIV acquisition compared to FTC/TDF tablets in HPTN 083, and a 90 per cent lower rate of HIV acquisition compared to FTC/TDF tablets in HPTN 084.[5,6]

About Cabotegravir extended-release injectable suspension

Cabotegravir extended-release injectable suspension is the first and only long-acting injectable pre-exposure prophylaxis (PrEP) option proven superior to daily oral FTC/TDF in reducing HIV acquisition. It is indicated for at-risk adults and adolescents aged 12 years and older, weighing at least 35 kg for PrEP to reduce the risk of sexually acquired HIV-1 infection. Cabotegravir extended-release injectable suspension is administered as a single 600 mg (3-ml) intramuscular (IM) injection of cabotegravir in the buttocks by a health care professional every two months after two initiation injections administered one month apart. Cabotegravir tablets can be used as an optional oral lead-in to assess tolerability or as short-term oral PrEP in individuals who will miss planned dosing with cabotegravir extended-release injectable suspension. Cabotegravir is an integrase strand transfer inhibitor (INSTI). INSTIs, like cabotegravir extended-release injectable suspension, inhibit HIV replication by preventing the viral DNA from integrating into the genetic material of human immune cells (T-cells). This step is essential in the HIV replication cycle and is also responsible for establishing chronic disease.[1]

About HPTN 083 (NCT02720094)[7]

The HPTN 083 trial is a phase IIb/III double blind non-inferiority trial designed to evaluate the safety and efficacy of long-acting injectable cabotegravir for HIV prevention administered every eight weeks compared to daily oral FTC/TDF tablets (200 mg/300 mg). The trial included the prespecified ability to test for superiority of long acting cabotegravir over FTC/TDF. The trial design included an oral lead-in phase to assess tolerability to cabotegravir before administering the intramuscular injection. HPTN 083 was conducted in 4,566 men who have sex with men and transgender women who have sex with men. The study opened to enrollment in November 2016 at research centers in Argentina, Brazil, Peru, United States, South Africa, and Vietnam.[5]

At a pre-planned interim review of trial data, a multinational Data and Safety Monitoring Board (MDSMB) recommended that the blinded phase of HPTN 083 be stopped due to the demonstration of superior efficacy of cabotegravir when compared to daily, oral FTC/TDF and that subjects randomized to the active FTC/TDF group be offered cabotegravir. The most common adverse reactions (all grades) observed in at least 1 per cent of subjects receiving long acting cabotegravir were injection sites reactions, diarrhea, headache, pyrexia, fatigue, sleep disorders, nausea, dizziness, flatulence, and abdominal pain.[5]

For further information on HPTN 083 please see **https://clinicaltrials.gov/ct2/show/NCT02720094**.

About HPTN 084 (NCT03164564) [6]

The HPTN 084 trial is a phase III double blind superiority trial designed to evaluate the safety and efficacy of the long-acting injectable cabotegravir for HIV prevention administered every eight weeks

compared to daily oral FTC/TDF tablets (200 mg/300 mg) in 3,224 cisgender women who are at increased risk of HIV acquisition. The trial design included an oral lead-in phase to assess tolerability to cabotegravir before administering the intramuscular injection. HPTN 084 opened to enrolment in November 2017 and is being conducted at research centres in Botswana, Kenya, Malawi, South Africa, Eswatini, Uganda, and Zimbabwe.[6]

The MDSMB recommended early termination of the blinded, randomized portion of HPTN 084 after an interim analysis indicated that pre-specified stopping criteria had been met (superiority of cabotegravir compared with FTC/TDF). The most common adverse reactions (all grades) observed in at least 1% of subjects receiving long acting cabotegravir were injection site reactions, diarrhea, headache, fatigue, sleep disorders, nausea, dizziness, abdominal pain, vomiting, myalgia, and rash.[6] For further information please see **https://clinicaltrials.gov/ct2/show/NCT03164564**.

About HIV

HIV (human immunodeficiency virus) is a virus that attacks the body's immune system.[8] HIV is spread by contact with certain bodily fluids of a person with HIV, most commonly during unprotected sex (sex without a condom or HIV medicine to prevent or treat HIV), or through sharing injected drug equipment.[9]

If HIV is not treated, it can lead to AIDS (acquired immunodeficiency virus). AIDS is the most severe stage of HIV (Stage 3).[10] There is currently no cure for HIV, but with proper treatment and care, people with HIV can maintain a high quality of life and avoid passing HIV to others.

At the end of 2022, 39 million people lived with HIV around the world, with 1.3 million new diagnoses that year and 630,000 deaths from AIDS-related illnesses.[11]

Important Safety Information for APRETUDE for PrEP [1]

The APRETUDE Product Monograph includes a Serious Warning and Precautions Box:

RISK OF DRUG RESISTANCE WITH USE OF APRETUDE IN UNDIAGNOSED HIV-1 INFECTION.[1]

Individuals must be tested for HIV-1 infection prior to initiating APRETUDE and should be tested for HIV-1 infection with each subsequent injection of APRETUDE. APRETUDE must not be prescribed until confirmation of negative HIV-1 infection status. Drug-resistant HIV-1 variants have been identified with use of APRETUDE by individuals with undiagnosed HIV-1 infection. Do not initiate APRETUDE if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed.[1] Individuals who become infected with HIV-1 while receiving APRETUDE must transition to a complete HIV-1 treatment regimen.

The Product Monograph also includes warnings and precautions regarding hypersensitivity reactions, hepatotoxicity (liver damage) and depressive disorders.[1]

The Product Monograph, posted at **www.viivhealthcare.ca**, should be consulted for complete administration and safety information, including contraindications, additional warnings and precautions, adverse reactions and drug interactions.[1] Prior to being posted online, the Product Monograph is also available by calling 1-877-393-8448.

About ViiV Healthcare

ViiV Healthcare is a global specialist HIV company established in November 2009 by GSK (LSE: GSK) and Pfizer (NYSE: PFE) dedicated to delivering advances in treatment and care for people living with HIV and for people who are at risk of acquiring HIV. Shionogi became a ViiV shareholder in October 2012. The company's aims are to take a deeper and broader interest in HIV and AIDS than any company has done before and take a new approach to deliver effective and innovative medicines for HIV treatment and prevention, as well as support communities affected by HIV.

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1 APRETUDE Product Monograph (2024), ViiV. Available at: www.viivhealthcare.ca

2 PHAC. HIV in Canada: 2022 surveillance highlights. Available at: HIV in Canada: 2022 Surveillance highlights - Canada.ca. Accessed January 19, 2024.

3 Marzinke M, Grinsztejn B, Fogel J, Piwowar-Manning EM et al, Laboratory Analysis of HIV Infections in HPTN 083: Injectable CAB for PrEP. Conference on Retroviruses and Opportunistic Infections Abstract 153

4 Delany-Moretlwe S, Hughes JP et al. Long acting injectable cabotegravir is safe and effective in preventing HIV infection in cisgender women. HIV Research for Prevention Virtual Conference (HIVR4P 2021) abstract HY01.02, 2021.

5 Clinical Trials.gov - Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women Who Have Sex with Men. Available at https://clinicaltrials.gov/ct2/show/NCT02720094. Last accessed October 2022.

6 Clinical Trials.gov - Evaluating the Safety and Efficacy of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women. Available at https://clinicaltrials.gov/ct2/show/NCT03164564. Last accessed October 2022.

7 DC statement on FDA approval of drug for HIV prevention. News release CDC NCHHSTP Newsroom. July 16, 2012. Accessed September 7, 2021. https://www.cdc.gov/nchhstp/newsroom/2012/fda-approvesdrugstatement.html

8 CDC. About HIV. Available at: https://www.cdc.gov/hiv/basics/whatishiv.html.

9 HIV.gov. What Are HIV and AIDS? Available at: https://www.hiv.gov/hiv-basics/overview/about-hiv-and-aids/what-are-hiv-and-aids/.

10 CDC. About HIV. Available at: https://www.cdc.gov/hiv/basics/whatishiv.html#:~:text=People%20who%20take%20HIV%20treatment,into%20Stage%203%20(AIDS)..

11 UNAIDS. Global HIV & AIDS Statistics – Fact sheet. Available at: https://www.unaids.org/en/resources/fact-sheet

SOURCE ViiV Healthcare