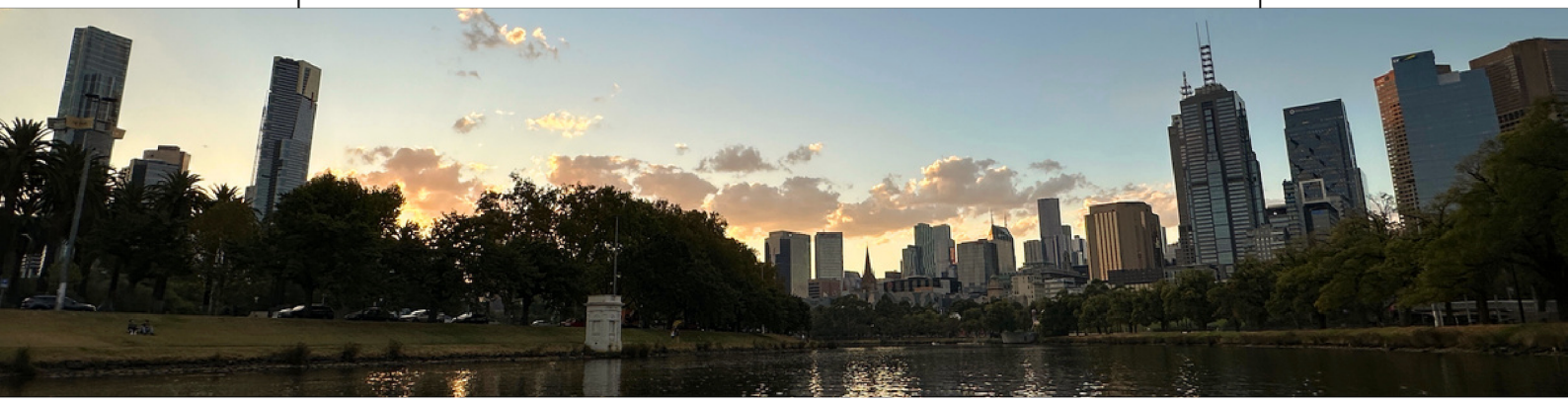
JULY 2024

Newsletter

FOR VICTORIAN HIV CURE VOLUNTEER DATABASE

EDITION #2



So much has been happening in the world of HIV cure this year! In this edition of the HIV cure volunteers newsletter we will bring you updates from the Conference for Retroviruses and Opportunistic Infections (CROI), a critical look into a news story about HIV cure you may have seen in the media recently, and the consensus workshop on analytical treatment interruptions (when HIV treatment is intentionally paused in an HIV cure trial) that took place in Nairobi, Kenya in May.

Updates on HIV cure from CROI

The city of Denver hosted thousands of researchers and advocates at the CROI conference in March. Australian researchers represented at this conference, one of the major international HIV meetings in the calendar. This included **Professor Sharon Lewin** from The Doherty Institute, and the president of the International AIDS Society, gave a mini review about how HIV can impact the brain and its function. She went through the major different classes of drugs being tested for cure, and what's known and unknown about how these drugs work on the brain, and if they have any effect on reservoirs of HIV in brain tissue. The take home point: there is much we don't know about this area as it hasn't been routinely studied. Scientists need to routinely collect and report this information, and Professor Lewin made a call to arms for this to be built into upcoming study protocols.

In the same special session on HIV and the brain, **Professor Melissa Churchill** from RMIT also presented on HIV in the brain:

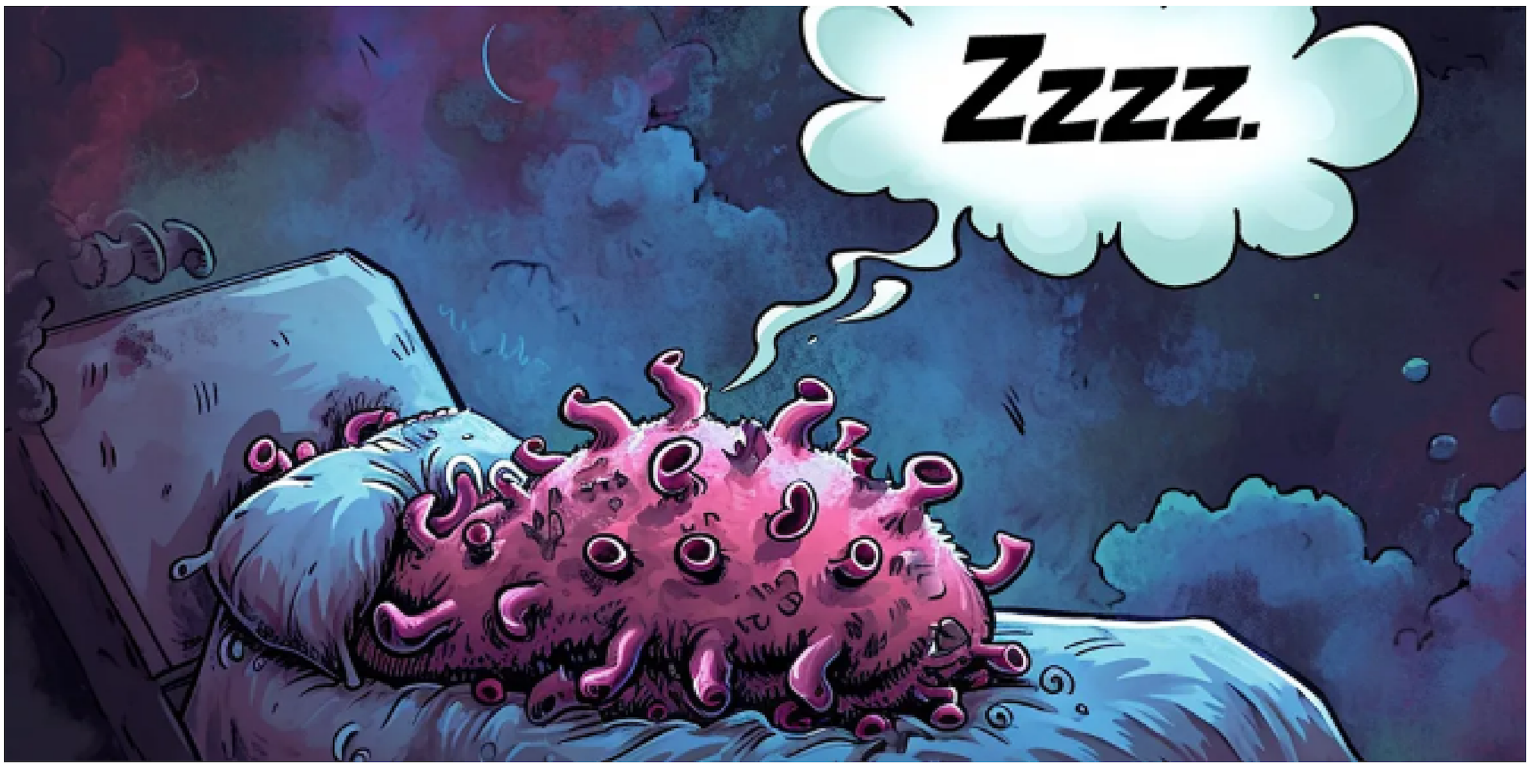
HIV in the brain: Is it truly silent?

HIV in the brain is a barrier to cure, and potentially contributes to the development of neurocognitive disorders. We and others have previously shown that HIV DNA is present in the brain of people with HIV who are virally suppressed with antiretroviral therapy (ART). However, we wanted to investigate whether this DNA can produce the HIV RNA that are needed to make new virus particles.

We found that although HIV can produce minute amounts of RNA in the brain, blocks exist which prevent it from producing all the RNA that is necessary to produce new virus particles. These blocks are more prominent in participants on ART than those who were not on ART.

These findings are important because it demonstrates that although ART inhibits virus production, parts of the replication cycle; namely, the production of viral RNA, can still occur. The presence of these HIV RNA's may contribute to immune activation in the brain, as is the case in the blood, and may constitute an antiretroviral target in the future.

Basic scientists **Bridget Fisher** and **Dr Youry Kim**, both from the Doherty Institute also presented cutting edge work summarised below:



Killing HIV By Bringing It Back to Life : New Developments by Bridget Fisher

HIV can evade our immune defences by entering a sleep-like 'latent' state for decades. One approach to an HIV cure, called 'latency reversal', involves the use of latency reversing agents that force the virus to awake from its slumber, allowing the immune system to find HIV and kill it. Many scientists globally are currently attempting to develop effective latency reversing agents. Bridget Fisher, a PhD candidate from The University of Melbourne and her team have leveraged recent advances in mRNA and lipid nanoparticle technologies to create a new latency reversing agent that can work very effectively to bring HIV back to life in cells donated by people living with HIV. This new agent, called a Tat-LNP, works so effectively that it surpasses what are currently considered to be best-practice latency reversing agents. The team also assessed safety and identified no side-effects as a result of Tat-LNP treatment in their laboratory models. This innovative approach to latency reversal demonstrates unprecedented efficacy in awakening HIV from its slumber. Exciting insights as to whether this will result in the killing of HIV will quickly follow suit.

Dr. Youry Kim from the Doherty Institute presented work showcasing the ability of a class of drugs known as **SMAC mimetics** to eliminate HIV. These are experiments performed on cells from blood donated by people living with HIV. Dr Kim's results showed that treatment of these T cells with SMAC mimetics was able to reverse HIV latency (and also induce death of these cells. This leads to reactivation and identification of the hidden latently infected cells but also provide a pathway to clear them. Such cells contribute to viral rebound when ART is stopped therefore, eliminating latent cells by inducing cell death is one of the keys to a cure.SMAC mimetics present a drug compound of interest in HIV cure research because they have been studied as a cancer therapy for over 10 years and scientists have a great understanding of the drug and its potential side effects.

Dr Kim also showed that treatment with one SMAC mimetic, AZD5582 was also able to **reduce the number of HIV DNA copies** in cells from people living with HIV. This presents as an approach leading to a step closer to testing these compounds in people living with HIV as a cure for HIV.

Other HIV cure highlights...

Another HIV cure highlight for CROI 2024 was a clinical trial of **Budigalimab**, a type of drug known as an **immune checkpoint blocker.** These drugs are very effective in cancer treatments and are being investigated for HIV cure to stimulate our own immune systems to detect and control HIV in the absence of antiviral therapy. In this study, by the company that produces Budigalimab (Abbvie), 9 people with HIV received 4 cycles of a low dose of 10mg Budigalimab during an analytical treatment interruption (where their usual HIV antiviral treatment was stopped). The usual dose of Budigalimab for cancer is 250mg every 2 weeks. 6 of the 9 people demonstrated a delayed time to virus rebounding, and 2 people didn't rebound at all in the study period of 29 weeks. While these are small numbers, this study shows promise of what is known as immunotherapy as an HIV cure strategy. We are running a study on another immune checkpoint blocker called Nivolumab. Read more below about the **NIVO-LD study enrolling now in Melbourne**.

Finally, an interesting study was presented by **Dr Ming Lee** from Imperial College, London, looking at how long it took for people to get back to an undetectable viral load after an analytical treatment interruption (ATI) in HIV cure-related studies. The study included 180 people with HIV from 12 studies since 2015. Reassuringly, all participants **achieved viral suppression** to <50copies/mL after ATI, with 96% doing so by 12 weeks. The use of study drugs, such as broadly neutralising antibodies, did not appear to impact time to viral resuppression. A longer time to viral resuppression were associated with a high viral load at the time of restarting antiretroviral therapy (ART), or using a type of ART called protease inhibitors, which do not lower viral loads as fast as another ART class (integrase inhibitors). Dr Lee concluded that after restarting HIV treatment in ATI studies, people should have viral loads frequently checked until virus is resuppressed.

2nd Consensus Workshop on Analytical Treatment Interruption in HIV Cure Trials

Stopping treatment in an HIV cure study can be controversial, especially in the era of U=U, or undetectable=untransmissible. In 2018 researchers published consensus guidelines providing recommendations on how HIV treatment can be safely paused during an HIV cure study. These guidelines will soon be updated, and this workshop brought together international experts in the field to discuss some of the challenges and nuances of this practice. Importantly, the organisers conducted webinars in the lead up to the workshop to gather grass roots information from Community about their worries and preferences for these types of studies.

Heard the recent news about a “new HIV cure”? Sadly, this won’t have been a real cure story

A recent press release from an international conference contained some premature announcements about HIV cure. The work from a group in Amsterdam showed that HIV infection can be inhibited using CRISPR in laboratory models. CRIPSR knock out is an approach to remove HIV DNA so that when antiretroviral therapy is stopped, it doesn’t lead to viral rebound. CRISPR is heavily investigated in the field and there is a clinical trial testing its safety in people living with HIV at the moment. The results reported are scientifically important, however the models they used are laboratory models which are very different from cells in living bodies. This means that a lot more work is required before this research actually translates into clinical practice. The use of sensational words such as “cured” and “eliminated” is unsuitable to describe findings in such models. The findings do not have immediate implications for the lives of people living with HIV, but there was disproportionate media coverage and public attention. Gene therapy is a very exciting field to keep an eye on but unfortunately there is no HIV cure by gene therapy or anything else, yet.

Click HERE for the full story.

Communicating HIV Science

The Past, Present and Future and why it is important

In this latest issue of NAPWHA's Positive Living magazine, Positive Women Victoria's communications and engagement coordinator Heather Ellis writes about communicating HIV science to the HIV community and how the advances in HIV science for both treatment and cure has grown exponentially in recent years.
Read the story in Positive Living Magazine.

If you're interested in any of the activities listed above, please email clinresearch@alfred.org.au or call 03 90766908 during business hours to let us know!

Or if anyone you know is interested in signing up
to the Volunteers Database or just wants to receive these newsletters, they can sign up here:
https://redcap.link/n506shnh or scan this QR code:

Trials enrolling now in Melbourne!

NIVO-LD

A study investigating a single low dose of nivolumab (a drug used to treat certain cancers) can **boost HIV defences** in the body. This study has **2 phases**:

In the first phase, volunteers receive one infusion of nivolumab through an intravenous drip. Blood and tissue samples are collected to see how good the low dose is at gettinginto the blood and lymph glands.

In the second phase, volunteers are allocated at random to either receive the single dose of nivolumab determined most effective in phase 1, or a placebo (an infusion with no active drug in it). Participants in this phase of the study would not know what they are receiving. This is followed by an antiviral treatment interruption to understand what happens to HIV immune responses and control of virus in the absence of HIV antivirals.

The treatment interruption is closely monitored, with weekly safety visits for blood tests and reviews with a doctor. If you are interested in participating in NIVO-LD you can EMAIL the Cure research team HERE.

If you don't have time to commit to a study like NIVO-LD, there's an option to donate blood or T cells (in a procedure known as leukapheresis) for scientists to study and conduct experiments on in the lab. This only requires two study visits. The leukapheresis procedure takes about 4 hours and you won't miss the T cells you have donated, your body will replenish them in quickly. If you are interested in donating blood or T cells in a leukapheresis click HERE to send an email to the Cure research team.

COMING SOON...

PEACH

PEACH is a clinical trial to investigate if pomalidomide, an **immune-enhancing** drug, can strengthen the body's own immune system to fight HIV. The study has 2 phases. In both phases, volunteers will be randomly allocated to receive either treatment with pomalidomide or a placebo (a capsule with no active drug in it). Participants will not know what they are receiving. In the first phase, volunteers will receive capsules of pomalidomide or placebo and stay on their usual HIV treatment. Blood samples will be collected to see how the immune cells react to the immune-enhancing treatment.

In the second phase, participants will undergo a treatment interruption to understand what happens to HIV immune responses and control of the virus when given pomalidomide in the absence of antiviral medication. Blood samples will be collected to closely monitor the virus levels and participants will have will weekly or fortnightly safety visits with a doctor. Participants will take part in both phases of the study.

The key measures in this trial will be the tolerability of low-dose pomalidomide and assessing whether pomalidomide can improve the anti-HIV immune response and delay time to virus rebound during ART interruption. PEACH is expected to start enrolling participants in Melbourne in the **second half of the year.**

AMBER

AMBER is a clinical trial to investigate if venetoclax, a medication which promotes cell death (apoptosis), can **promote cell death** of long-lived HIV infected cells and lead to a reduction of the latent HIV reservoir. The study has 2 parts and is being conducted in Denmark and Australia. The first part will use different doses of venetoclax to establish the safest dose to use in people with HIV.

The second part of the study will take place in both Aarhus, Denmark and Melbourne, Australia. All participants in part 2 of the study will stay on their ART and receive 3 cycles of the optimal dose of venetoclax determined in the first part of the trial. These cycles are 28 days consisting of 14 days on treatment and 14 days off treatment. Participants will be randomised to either start the 28 day cycles of venetoclax immediately or receive placebo (a capsule with no active drug in it) for the first 28 day cycle. The main outcome of the study is to determine the safety of venetoclax in people with HIV and then blood samples will be collected to understand if veneotclax has an effect on the size of the HIV reservoir and whether the drug is leading to the loss of HIV-infected cells

AMBER is not currently enrolling participants in Australia but is expected to start enrolling later in 2024.

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