First randomised trial of 'kick and kill' approach to HIV cure leaves puzzles to be solved

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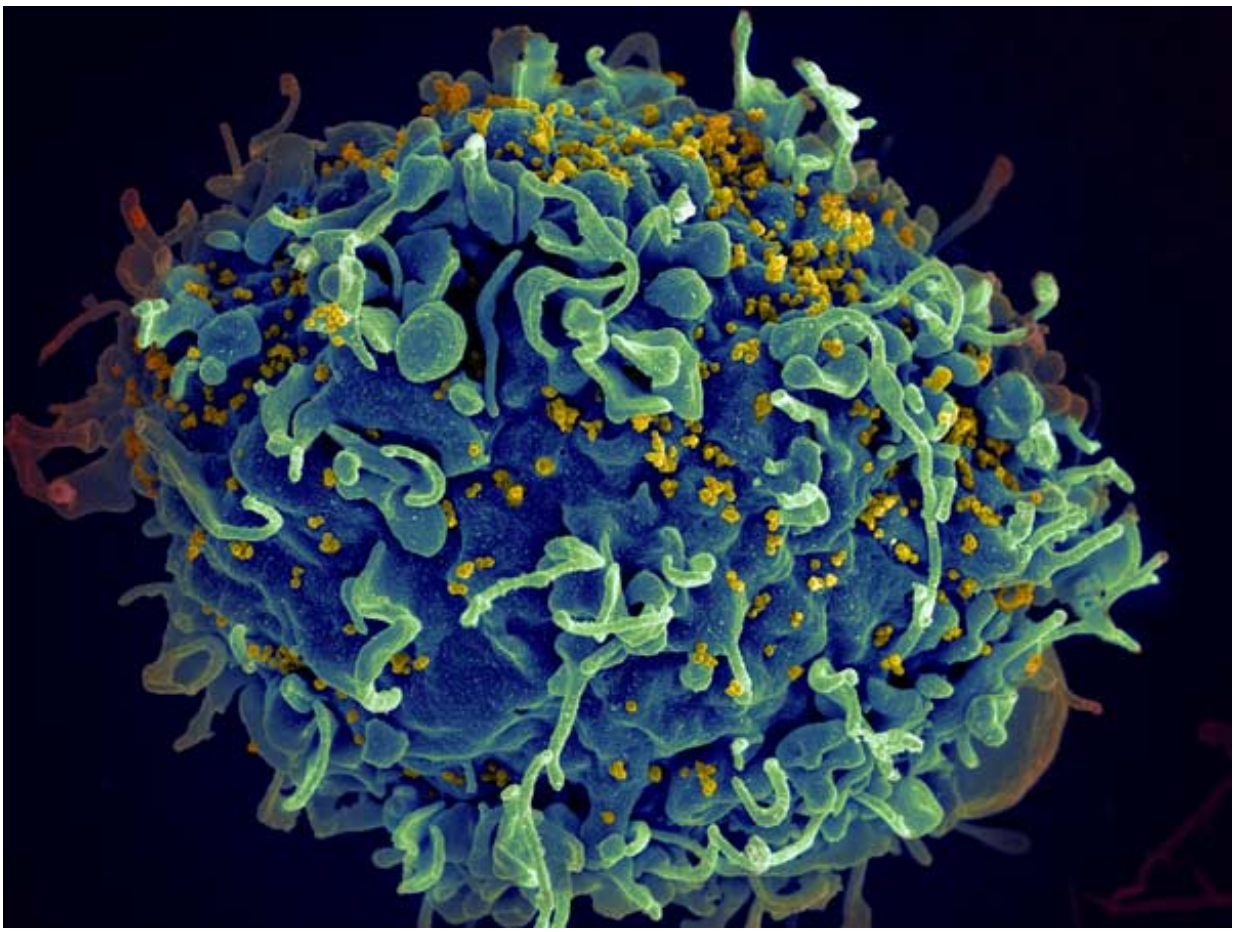

HIV infecting a human cell. Credit: NIH

Researchers have reported the results of the first randomised clinical trial to test a novel strategy involving waking up and then killing the 'sleeping' HIV that is hiding in the body using an experimental approach known as 'kick and kill'.

Led by Imperial College London, the University of Oxford, MRC Clinical Trials Unit at UCL, and the University of Cambridge, the RIVER study aimed to improve on current care by eradicating HIV from the body, which would represent a major step forward in the search for a cure.

Although investigators found no difference in effect between those participants who received the active 'kick and kill' therapy and those who had standard treatment, they say the trial paves the way for testing different combinations of therapies to tackle the HIV that persists in patients who receive antiretroviral treatment (ART). The trial demonstrates how researchers are looking beyond current therapies which, despite revolutionising the lives of people living with HIV, are not a cure and have to be taken for life.

The RIVER study, which ran from 2015 to 2018 in London and Brighton, tested the 'kick and kill' approach in 60 men recently diagnosed with HIV and who had the virus under control by taking ART. Despite having undetectable levels of HIV in their blood, patients on ART are not cured. If they stop taking ART, the virus returns from hiding places in the body known as 'reservoirs'. This has led researchers to propose that a possible cure for HIV would be to target these reservoirs, force HIV out of hiding and then kill it.

To test this idea, RIVER used two medicines on top of the standard ART treatment. First, two vaccines to coach the body's immune system to recognise and destroy HIV, and second, a drug called vorinostat (also used for managing cancer) that would 'wake up' the reservoir cells that

HIV is hiding in and force the virus to reveal itself and face the immune system. This approach to an HIV cure is called 'kick and kill' - the kick is delivered from vorinostat, and the kill comes from the body's own immune system killer cells that have been trained by the vaccines.

To claim success in the RIVER proof of concept trial, the researchers said that those receiving the kick and kill drugs should experience a significant fall in levels of HIV in the reservoir cells, known as CD4 T cells.

However, when the results were first unveiled to researchers in April 2018, they found that the half of trial participants given the kick and kill drugs in addition to ART had similar levels of infected reservoir cells compared to those who only received standard ART therapy.

The RIVER study leaders report these initial findings today in a 'Late Breaker' session at the International AIDS Society's annual meeting in Amsterdam, Netherlands (AIDS 2018). The results of the study will be submitted for publication in a peer-reviewed journal.

RIVER Chief Investigator, Professor Sarah Fidler of Imperial College London said:

"In the RIVER study, we found that all the separate parts of the kick and kill approach worked as expected and were safe. The vaccine worked on the immune system, the kick drug behaved as we expected it to, and the ART worked in suppressing viral load in the body, but the study has shown that this particular set of treatments together didn't add up to a potential cure for HIV, based on what we've seen so far."

"For those who have access to it, ART brings amazing success in managing HIV but people have to take it for most of their lives. We have to think about other, sustainable alternatives, and a cure or at least some

form of remission is a key goal.

"Finding an HIV cure means orchestrating a lot of things. We have to generate new ideas and turn them into trials that will give meaningful results, we have to agree what research tests will tell us whether things are working or not, we need to very carefully monitor study participants and most importantly we need to make sure any trial intervention is safe. RIVER achieved all these things but sadly not the evidence of a possible HIV cure yet."

Based on the findings, the study doctors have told participants that they cannot recommend that all study participants receive the kick and kill drugs as well as their ART and that the trial did not find evidence to recommend that any participants could safely stop taking their ART.

Looking forward to possible next steps, the RIVER co-principal investigator and scientific lead, Professor John Frater of the University of Oxford said:

"We need to think about why we didn't see an effect. The important thing to realise is that despite these disappointing results, it does not mean that the basis of the approach is wrong. This is the very first randomised study of the 'kick and kill' concept in humans and the field now needs to work together to explore how better and more effective agents can have an impact on the HIV reservoir while remaining safe.

"It is possible that the combinations of drugs we used weren't quite right, but for this first study we didn't want to compromise on safety by using stronger agents that might work better but could cause toxicity to the participants. It is possible that vorinostat was not quite potent enough to wake up as much HIV as was needed for the newly trained immune system to recognise. Equally, it is possible that a different sort of immune response to the one we induced is needed to target the HIV

reservoir. All of these possibilities need to be teased out and considered to guide our next move in searching for an HIV cure."

The vaccines used in RIVER, known as ChAdV63.HIVconsv and MVA.HIVconsv, were highly effective at inducing HIV specific immune responses in the active group. Follow-up research may include giving further boosts of this vaccination together with a different kick drug or possibly using the 'next generation' of these vaccines that are now being trialled in other studies.

RIVER was run by 'CHERUB', a UK collaboration of five universities pooling their expertise to develop an HIV cure. CHERUB is supported by the National Institute for Health Research and brings together HIV researchers at Imperial College London, the University of Oxford, the University of Cambridge, Medical Research Council Clinical Trials Unit at UCL, and King's College London. RIVER was funded by the Medical Research Council, UK and the industry partners, MSD and GSK.

RIVER was the first HIV cure study to use a randomised controlled approach, and the authors urge that this should be repeated in future HIV cure trials. Professor Abdel Babiker of the MRC Clinical Trials Unit at UCL, said:

"Although the results are disappointing, they are unambiguous because of the randomisation and completeness of follow up assessments. Because ART is so effective at reducing viral load, without the randomised control group of participants taking ART alone to compare against, we couldn't have been so confident in knowing whether the kick and kill drugs had made any impact. It's important that future HIV cure trials follow this approach and compare their outcomes to an ART-only group."

During its three years, RIVER benefitted from outstanding commitment

from its 60 participants. There was 100% attendance at the primary endpoint study visits, and no participants were lost from the study. In the experience of the doctors and researchers, this was extraordinary and reflects new and deeper levels of commitment from participants.

"They take time off work, they come for lots of visits and tests, and they are an amazingly committed group of people," said Professor Fidler. "They are not just volunteers, they are active advocates for support and they push us to go further all the time. They are helping to define where this research can go next and they are the real pioneers of new treatments."

A participant in the trial said:

"You can be hopeful, but you must be realistic when you take part in a trial. The results from previous trials, the way RIVER was designed and the people running and supporting it, all gave me confidence that it was the right thing to do to take part. So, the initial results are disappointing because of course everyone would have liked to have seen some difference between the control and the active groups. We will have to wait and see what the next move is, but we can't hold back now in the search for a functional cure."

"It's remarkable that nobody dropped out of the trial. It had outstanding commitment from participants because people want to see an HIV cure happen and can see that being involved is the way we are going to push the boundaries back."

Damian Kelly, RIVER community advisory board leader and Director of Patient Advocacy Alliance, said:

"The cost of HIV treatment globally and the new infection rates globally mean that we have to drive towards a cure for HIV or some in-between

point such as remission.

"Everyone involved in RIVER—the participants, the clinic staff who have such a critical role in keeping participants engaged and supported, the doctors, the lab technicians and the scientists—everyone should be proud that they were involved in the first randomised controlled HIV cure trial."

"I'm confident that not an ounce of effort that has gone into the RIVER trial will be wasted as these results will help to direct and inform the design of future trials and move us closer towards the goal of a cure."

Provided by Imperial College London