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Experimental antibody plus TLR7 agonist maintains viral suppression in monkeys



Dan Barouch presenting at CROI 2018. Photo by Liz Highleyman.

Treatment with a broadly neutralising antibody plus an immune-stimulating drug led to long-term viral remission after interrupting antiretroviral therapy (ART) in a monkey study, according to data presented at the 25th Conference on Retroviruses and Opportunistic Infections (CROI 2018) this week in Boston.

The study involved rhesus macaques infected with a human-simian hybrid virus known as SHIV.

During acute infection, they started a three-drug combination of antiretrovirals. Two years after achieving viral suppression, they received infusions of the broadly neutralising antibody PGT121 (five doses, every two weeks) and the TLR7 agonist GS-9620 (ten doses, every two weeks), or placebo treatment. ART was discontinued four months after the last doses of PGT121 and GS-9620.

PGT121 is a broadly neutralising antibody that targets the V3 glycan site on the outer envelope of HIV and SIV, a related virus that infects monkeys. GS-9620 is a TLR7 agonist that stimulates tolllike receptors on immune cells, part of the innate immune system that promotes recognition and response to viruses. Activating TLR7 enhances the activity of T-cells, natural killer cells and other immune cells. This is a 'kick and kill' strategy that aims to reactivate the reservoir of latent virus and help the immune system attack it.

The treatment substantially delayed and controlled viral rebound following discontinuation of antiretrovirals. Monkeys that received the experimental treatment maintained an undetectable viral load without antiretrovirals for a median of 112 days. Five of eleven treated animals still remained virally suppressed at six months.

Even after rebounding, monkeys that received the experimental treatment had lower viral load setpoints and lower viral DNA levels in their lymph nodes than monkeys that received placebos. This suggests a decrease in the viral reservoir and some level of immune control over the virus.

This is the first evidence of a cure strategy being able to induce immune control in monkeys. Achieving a similar result in humans would be a major advance.

Dr Dan Barouch of Beth Israel Deaconess Medical Center in Boston was cautious in interpreting his study's results. He noted that even if this approach prevents viral rebound for several months, that doesn't preclude the possibility that virus is still present and could reactivate months or even years later. Even the most sensitive tests available today cannot detect all latent virus, he said.

Gilead Sciences is working on early, phase I trials of this combination in humans.

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Women more vulnerable to HIV infection during pregnancy and post-partum



Renee Heffron presenting at CROI 2018. Photo by Liz Highleyman.

An analysis presented at CROI 2018 shows that women are nearly three times more likely to become infected with HIV while they are pregnant, and four times as likely in the six months after giving birth, compared with the risk of HIV infection at other times.

Previous studies on this issue have been inconclusive: a meta-analysis found a 30% raised risk of HIV infection during pregnancy, but two studies in that analysis found almost double the risk while the others found no raised risk.

The new analysis looks at data from 2751 HIV-negative women who had an HIV-positive male partner and were taking part in one of two HIV prevention trials, Partners in Prevention and Partners PrEP. The studies were done in a total of seven African countries.

Sex was more or less frequent at different reproductive stages – on average, more sex and more condomless sex during early pregnancy than when women were not pregnant, but less frequent later on in the pregnancy and in the six months after giving birth.

During follow-up, 82 women acquired HIV from their primary partner, an annual HIV incidence of 1.62%. The crude incidence rates differed according to reproductive stage.

Dr Renee Heffron of the University of Washington then calculated the risk of HIV infection per 1000 sex acts. This was estimated for a 25 year old, not using pre-exposure prophylaxis (PrEP), whose partner had a viral load of 10,000 copies/ml.

- Neither pregnant nor post-partum: 1.05 infections per 1000 sex acts
- Early pregnancy (0 to 13 weeks): 2.19 infections per 1000 sex acts
- Late pregnancy (14 weeks to birth): 2.97 infections per 1000 sex acts
- Post-partum (birth to 6 months): 4.18 infections per 1000 sex acts.

Hormonal changes while women are pregnant or lactating may make HIV infection more likely, but more research is needed to understand the mechanisms. PrEP may be recommended for periods when women are at a particularly high risk of infection.

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One-month TB prevention regimen just as effective as nine-month regimen



Richard Chaisson presenting at CROI 2018. Photo by Liz Highleyman.

A one-month course of the antibiotic rifapentine in combination with isoniazid was just as effective as a nine-month course of isoniazid alone in preventing the development of tuberculosis (TB) in people with HIV in a large international study.

Although isoniazid preventive therapy (IPT) is recommended by the World Health Organization for the prevention of TB in people living with HIV in many countries, international coverage is extremely poor. The most commonly cited barrier to increasing IPT coverage is the duration of treatment, which can be six months, nine months or even 36 months.

The A5279/BRIEF TB study was designed to test the efficacy of isoniazid and rifapentine, given daily for one month, compared to isoniazid, given daily for nine months. People living with HIV in areas with high rates of TB or with a positive TB skin test were eligible for inclusion in this multicentre, randomised, open-label study.

A total of 3000 individuals in ten countries took part. Half were female, two-thirds were black, half were taking antiretroviral therapy, the median CD4 cell count was 470 cells/mm³ and a fifth of people had a reactive TB skin test.

The aim of the study was to test the non-inferiority of the isoniazid/rifapentine regimen. The primary study outcomes were active TB, death related to TB or death from any cause.

A primary study endpoint was met by 32 people in the isoniazid/rifapentine arm and by 33 people taking standard isoniazid prophylaxis. Overall incidence rates were 0.65 vs 0.67 per 100 personyears, therefore showing the non-inferiority of the ultra-short course of preventative therapy.

Professor Richard Chaisson of Johns Hopkins University, Baltimore, told the conference: "This 1HP [one-month] regimen could dramatically alter the landscape for the prevention of TB in people with HIV. The likelihood of completing it is extremely high and the likelihood of it preventing TB is extremely high."

"We think it is a large enough, clear enough result, that it can form the basis of new guidelines."

However, the major barriers are the cost of the regimen (\$72) and drug supply (there is only one manufacturer).

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Rapid HIV infection rate in young and Hispanic gay men in US

An American study of HIV gene sequences in networks with a particularly high HIV infection rate has found the highest rates in clusters containing more young gay men, which is not unexpected, but also in more Hispanic than black men. This may signal a shift in the demographics of those most at risk of HIV in the United States.

The Centers for Disease Control and Prevention (CDC) now routinely analyses the gene sequences of HIV viruses in newly diagnosed people. Such phylogenetic analysis can identify clusters of infection – groups of two or more people whose viruses are so similar that they must share a common origin. This can identify clusters that are unusually 'active', in other words where new infections turn up frequently.

This allows local health departments to intervene – for example, to offer testing, linkage to care and pre-exposure prophylaxis (PrEP).

Examining 60 clusters involving at least five new HIV diagnoses within 12 months, the CDC found that the ongoing transmission rate was eleven times the average for people with HIV in the United States (44 transmissions per 100 person-years vs 4 transmissions per 100 person-years).

Members of these clusters were more likely than other people in the CDC's gene sequence database to be men who have sex with men (MSM) (83 vs 59%) and under the age of 30 (70 vs 42%).

More surprisingly, they were more likely to be Hispanic (38 vs 27%) and less likely to be black (31 vs 41%).

This could possibly indicate the beginnings of a change in the racial makeup of those in the US at the highest risk of HIV infection. "These findings suggest rapid transmission in networks involving young MSM, especially young Hispanic MSM," the CDC's Anne Marie France told the conference.

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Drug levels in hair predict HIV treatment response



Monica Gandhi presenting at CROI 2018. Photo by Liz Highleyman.

Antiretroviral drug levels in a sample of hair were the strongest predictor of response to HIV treatment, according to a study presented at CROI 2018.

It's well known that adherence to medication is key to successful treatment, but measuring adherence is challenging. Patients' self-reports are often inaccurate, while testing blood or urine samples only gives information about levels shortly before testing. Some people may take their medication inconsistently, but take a dose just before a medical appointment (this is known as the 'white coat' effect).

In contrast, antiretroviral drug levels in hair samples are a reflection of average adherence over time. It's simple to take and store a hair sample from the scalp.

The ACTG A5257 trial compared antiretroviral therapy regimens containing atazanavir/ritonavir, darunavir/ritonavir or raltegravir, all with tenofovir DF/emtricitabine, in people receiving HIV treatment for the first time. Hair samples were collected from 599 study participants at 2192 visits.

Similar results were seen for all three drug regimens. The rate of virological failure at two years was 3% for participants with the highest third of drug levels, 6% for those with the middle third, and 26% for those with the lowest third of drug levels.

Having processed, coloured, straightened or permed hair didn't interfere with the results, although results were a little different for bleached hair. The correlation between self-reported adherence and measurable drug levels in hair samples was weak.

Another study found that a different approach to measuring drug levels, which can assess changes in adherence over time by comparing levels in hair segments near the scalp and those further away, holds promise for analysing HIV seroconversion among people taking preexposure prophylaxis (PrEP).

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Improved TB screening methods cut deaths in people with HIV



Ankur Gupta-Wright presenting at CROI 2018. Photo by Liz Highleyman.

Screening for tuberculosis (TB) and intensified follow-up of TB cases in people starting antiretroviral therapy (ART) and urine-based screening of inpatients with HIV both have the potential to significantly reduce deaths and improve rates of TB treatment in people with HIV, according to results of two large studies.

The XPRES study in Botswana was a retrospective review of the phased roll-out of the Xpert MTB/RIF assay as a replacement for smear microscopy in the diagnosis of TB, but the researchers concluded that a package of measures to strengthen case finding made the greatest difference.

The study compared three interventions, delivered over time as the Xpert MTB/RIF assay became available: standard-of-care case finding; standard of care plus enhanced case finding (additional staff support and intensified tracing for patients who miss appointments); and standard of care, enhanced case finding and use of Xpert MTB/RIF in place of smear microscopy.

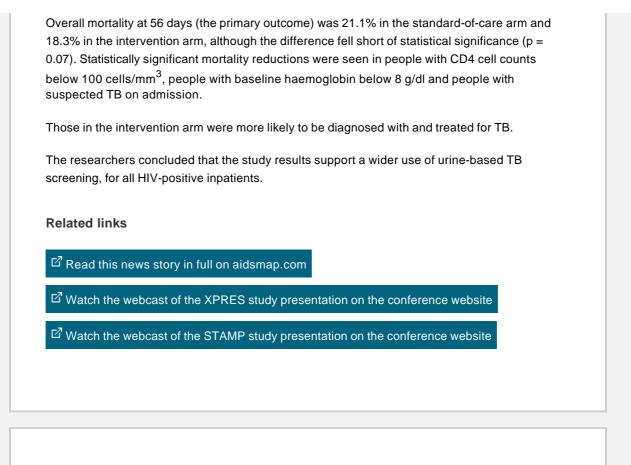
Six-month mortality (the primary outcome) was reduced in both enhanced phases, but there was only a statistically significant reduction for the third phase. The researchers then did an additional analysis, of 12-month mortality. This showed significant reductions in the risk of death during both the second phase (adjusted hazard ratio 0.72) and third phase (0.76), with no significant difference between the two.

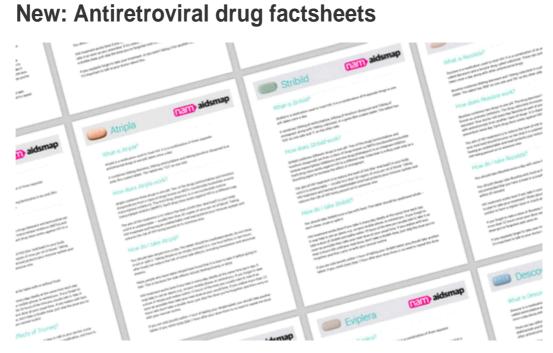
The researchers concluded that it was human resources rather than the diagnostic assay that made the greatest difference, suggesting that although diagnostic speed and sensitivity may make a difference in the short term, actions by healthcare workers to identify TB and to improve retention in care are more important.

The second study, called STAMP, was conducted in South Africa and Malawi. It confirmed that urine-based lipoarabinomannan (LAM) screening improved TB diagnosis and treatment, and reduced mortality in people on ART who had been admitted to hospital.

Active TB in a person with advanced HIV disease can be challenging to diagnose definitively, often requiring TB culture. Urine testing for TB-LAM has the potential to speed up TB diagnosis and its use has been shown to reduce the risk of death in hospitalised patients with HIV with CD4 cell counts below 100 cells/mm³. What was not known was whether LAM testing offers additional value in settings where the Xpert MTB/RIF test is available.

The study randomised people with HIV admitted to hospital to either the standard of care (sputum testing by Xpert MTB/RIF) or the intervention (sputum testing by Xpert MTB/RIF and urine testing by TB-LAM and Xpert MTB/RIF).





We have produced a new series of simple factsheets that provide key information on antiretroviral drugs and drug combinations.

The factsheets are available in English, and a selection of them are available in French, Spanish, Portuguese and Russian.

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