HIVR4P 2018

HIV RESEARCH FOR PREVENTION

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Contents

Broadly neutralising antibodies

Lynn Morris at HIVR4P 2018. Photo by Gus Cairns.

The HIV Research for Prevention conference (HIVR4P 2018) was dominated by studies of one type of molecule – broadly neutralising antibodies (bNAbs). These complex molecules, which develop in some people with HIV after years of infection, are natural entry inhibitors, stopping the virus from attaching to and infecting cells. They target highly conserved parts of the virus – parts of its proteins that are important to its functioning and which it finds difficult to alter.

HIVR4P heard about a large number of studies of bNAbs. They can be infused 'passively', i.e.

made outside the body and given in drips as long-lasting drugs. The reason researchers are interested in bNAbs for HIV is not only because they could treat virus resistant to other kinds of drugs – which they could. Neither is it simply because a single infusion of antibodies can last weeks in the body – though it can, and bNAbs are therefore of interest as a kind of new-generation pre-exposure prophylaxis (PrEP).

It is also because of the way they alert other parts of the immune system, with an effect that can be maintained for long after they have disappeared from the body. Most exciting is the possibility that – since they arise naturally in response to infection – a finely tuned vaccine could induce people to make their own bNAbs. In theory a bNAb-stimulating vaccine could prevent HIV infection altogether.

The prevention potential of bNAbs is being tested in the large AMP (Antibody-Mediated Protection) studies, with results anticipated by late 2020. Participants are receiving a bNAb called VRC01 or a placebo. It is unlikely that that AMP will be the last study of its type: further studies are likely to test combinations of bNAbs.

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The Miami monkey

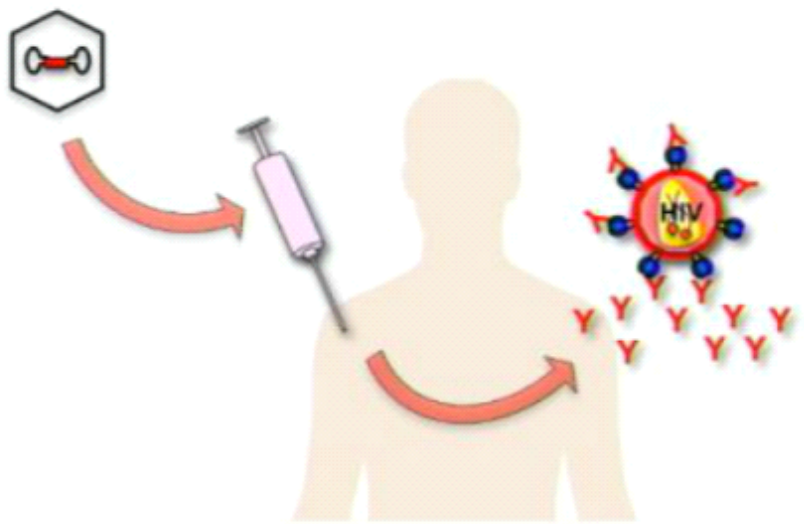

Image from José Martinez-Navio's presentation slides at HIVR4P 2018

The conference heard about a University of Miami study that used sophisticated gene therapy to induce monkeys to make their own broadly neutralising antibodies (bNAbs) and produced an apparently functional cure in one animal.

The two antibodies used were the same two bNAbs, 10-1074 and 3BNC117, that were recently used in a promising experiment in humans. They were given as a gene therapy – two modified genes introduced into the monkey's own immune system by means of a vector, the shell of an

inert virus called AAV (adeno-associated virus), which induced the monkey's immune system to express the bNAbs.

The monkeys were infected with SHIV-AD8, received no treatment for 86 weeks and were then given the AAV-vector vaccine. One of four animals developed a viral load that was consistently undetectable and still is just over three years after vaccination. The monkey still appears to have HIV in some of its cells but the persistent levels of antibody and the presence of a functional anti-SHIV CD8 response indicate prolonged recession of HIV infection or even a permanent functional cure.

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HIV prevention choices

Jim Pickett leading a protest at HIVR4P 2018. Image credit: @HIVpxresearch

'Choices' was the buzzword of the conference. Activists took to the stage during both the opening and closing sessions to express their concern about decisions by the US National Institutes of Health to reduce funding for the development of microbicides and other topical products. Investment will be concentrated on systemic and long-acting products, such as injectables and implants, as well as vaccines (which have always received the lion's share of funding).

Activist Lillian Benjamin Mwakyosi told delegates: "The research agenda is moving away from what people want: choices." Jim Pickett expressed his concern about "an HIV prevention research agenda that does not include choices that are user controlled, that does not include short acting choices and that neglects options that are non-systemic."

Craig Hendrix of Johns Hopkins University made an eloquent plea for research to continue into topical pre-exposure prophylaxis (PrEP), calling on the National Institutes of Health, the HIV Prevention Trials Network and other actors to ensure that topical products can be chosen for PrEP. He said the lesson from contraception was clear – an increased range of contraceptive options is associated with higher levels of usage and better health outcomes. For each

additional contraceptive method provided, there is a 12% increase in the proportion of women using contraception.

He asked: “I wonder how much this increase will be for every additional product we license for PrEP?”.

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Read *Going local – prevention conference hears about rings, douches, and soluble suppositories* on aidsmap.com

Future PrEP products

Raphael Landovitz at HIVR4P 2018. Photo by Roger Pebody.

Raphael Landovitz of the University of California gave the conference a high-level overview of the pipeline of potential future pre-exposure prophylaxis (PrEP) products. Oral PrEP based on tenofovir disoproxil fumarate/emtricitabine *(Truvada)* has set a high bar for prevention effectiveness, but a range of alternative products are in development, he said.

An ongoing trial is evaluating the use of oral tenofovir alafenamide/emtricitabine *(Descovy)* as an alternative to *Truvada.* While the newer formulation of tenofovir is an attractive option for HIV treatment, it remains to be seen whether it will work well for PrEP. Intracellular drug levels are high, but they are relatively low in plasma and genital tissues, he said.

Long-acting injectable formulations of PrEP drugs are likely to become available imminently, with cabotegravir furthest along the development process. However the ‘long tail’ of injectable PrEP (see next item) may be a problem.

Long-acting implants may not have the same drawbacks as injectables: they do not have a ‘long tail’ and can be removed in the event of intolerance. Studies are at an earlier stage but the technology of implants is progressing rapidly, including multipurpose implants that could deliver a contraceptive together with an antiretroviral. Combining protection against unwanted pregnancy and HIV in a single device may make it more attractive to women.

The dapivirine vaginal ring has demonstrated partial efficacy and is under review by regulatory agencies. The conference heard that adherence has been higher in the ongoing open label study than in the placebo-controlled trials; this is likely to have a positive impact on effectiveness. Different types of vaginal rings may also be used as multipurpose devices.

At earlier stages of development are vaginal films, vaginal or rectal inserts, rectal gels and rectal douches.

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Injectable cabotegravir's long tail

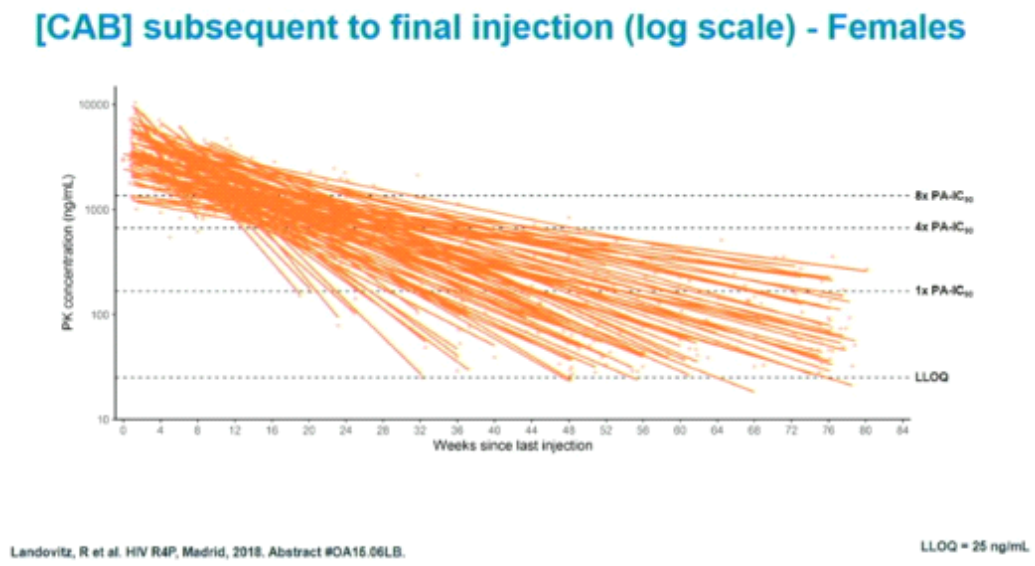

Image from Raphael Landovitz's slides at HIVR4P 2018.

Around four in ten women and one in ten men taking injectable cabotegravir as pre-exposure prophylaxis (PrEP) still have evidence of the drug in their body around 18 months after their last injection, the conference heard.

The findings raise concerns about the potential development of drug resistance. If people stop receiving PrEP injections, they will be vulnerable to HIV unless they start or continue another method of HIV prevention, such as oral PrEP. The 'long tail' means that there could be a lengthy period during which, if they caught HIV, individuals could develop drug resistance. Drug resistance only arises in situations like this when there is some drug in the body but not enough to fully suppress an infection.

Data were collected from participants in the phase II HPTN 077 study for up to 76 weeks after participants' last injection.The median time for drug levels to fall below the lower limit of quantification (LLOQ) in women was 66 weeks, ranging from 18 to 182 weeks. In men, the median was 43 weeks, ranging from 20 to 134 weeks.

People who have used injectable cabotegravir could be recommended to take oral PrEP for a period after their last injection, to cover the long tail, but will this be a feasible approach in routine clinical care?

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Women's product preferences

Ariane van der Straten at HIVR4P 2018. Photo by Roger Pebody.

A number of studies presented at HIVR4P investigated people's preferences for possible prevention products. A study conducted with young women in South Africa and Zimbabwe found that there is no single formulation which will suit everyone – after trying four different vaginal products, there was no one product that was much more popular than the others.

The participants tried four different placebo products for a month at a time. Ratings for all products improved over time and after using them.

After trying all four, they were asked to rank them in order of preference:

- The vaginal ring was the preferred choice of 29%, but also the least favourite of 42%.
- The vaginal film was preferred by 29%, but also the least favourite of 23%.
- The vaginal insert was preferred by 26%, but the least favourite of 12%.
- The vaginal gel was the preferred choice of 16%, but also the least favourite of 23%.

"Young women want choice," commented researcher Ariane van der Straten. "They want a product that is low burden, provides peace of mind, is fool proof and multi-purpose, but what form this product takes does vary."

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Rising uptake of PrEP

Laura Fitch at HIVR4P 2018. Photo by Roger Pebody.

At least 380,000 people have started to take pre-exposure prophylaxis (PrEP) in 68 countries, but most of them are in the United States and African countries, according to a global analysis tracking demonstration projects, implementation initiatives and national programmes.

The latest figures show that 225,000 people who are taking PrEP are in the United States, most of whom are men who have sex with men (MSM). A further 103,000 are in sub-Saharan Africa, with usage overwhelmingly concentrated in Kenya, South Africa, Uganda, Zimbabwe and Lesotho. Numerous other African countries have hardly any PrEP users. The majority of African PrEP users are adolescent girls and young women.

Only around 22,000 people are taking PrEP in Europe, mostly in England, France and Germany. The exercise identified 8000 PrEP users in Asia, over half of whom are in Thailand.

But many more gay men and MSM may be using PrEP than these figures suggest, some believe. The figures do not include people obtaining PrEP informally (for example, purchasing medication online), but the practice appears to be widespread. Large numbers of gay Chinese tourists are visiting Thailand to buy PrEP there. Surveys conducted by the dating app Hornet have found that 7% of Brazilian respondents were taking PrEP and that 18% of European respondents who were taking PrEP were living in Russia (not a country frequently mentioned in relation to PrEP).

“PrEP is available online *everywhere*,” Michelle Rodolph of the World Health Organization said, “and its use is not monitored”.

Meanwhile, evidence is emerging of the real-world impact of providing PrEP to clinic populations. The Fenway clinic in Boston is a community health centre with a special focus on sexual and gender minorities; it was one of the first to institute a large PrEP programme. Their figures show that HIV incidence in people never prescribed PrEP is 1.34%.

In those with a current PrEP prescription, incidence is 0.13%, a reduction of 90%. The handful of infections which occurred in PrEP users appear to be either people with acute HIV infection at the time they started PrEP or people with adherence difficulties.

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Stop talking about ‘risk’

Sarit Golub at HIVR4P 2018. © HIVR4P/ Leon Gutierrez

It’s unhelpful to frame the use of pre-exposure prophylaxis (PrEP) in terms of ‘risky behaviour’, Sarit Golub, professor of psychology at the City University of New York told the conference. She argued that while risk assessment tools may have validity across a population, they tend to be quite poor at accurately predicting an individual’s risk of acquiring HIV. As many people are not comfortable discussing their sexual behaviour with clinicians, the information they gather is not always complete.

Moreover, the language is stigmatising and alienating. “People do not ‘engage in risk behaviour’, we ‘have sex’,” she said. Public discussions about ‘risk compensation’ and ‘behavioural disinhibition’ are particularly damaging, she believes. Healthcare providers who have concerns about PrEP being associated with more condomless sex and increases in sexually transmitted infections are less willing to prescribe PrEP than other clinicians.

Instead of conducting risk assessments, Golub said that healthcare providers should ask patients about their sexual health concerns and their sexual health goals. Providers should focus on the reasons why people might want to take PrEP other than because they are ‘high risk’, including reducing anxiety, increasing intimacy and taking control of their health.

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Barriers to PrEP

Image from Albert Liu's slides at HIVR4P 2018 promoting a PrEP demonstration project for transgender people.

The conference heard about barriers that are slowing access to pre-exposure prophylaxis (PrEP) and preventing it having as great an impact as hoped.

In the United States, the persistent inequalities of the healthcare system continue to mean that PrEP is not reaching those who need it most. Whereas 26% of white men who have sex with men (MSM) have an indication for PrEP and 14% are taking it, 44% of black MSM have an indication, but only 1% are taking it.

There are also substantial gaps in the PrEP care continuum for transgender women. A San Francisco study found that 79% were aware of PrEP, 35% had discussed it with a healthcare provider, 12% were using it and 10% were adherent to PrEP. Social disparities and medical mistrust are likely to contribute to this situation.

In Brazil, political and structural conservatism have led to slow uptake of PrEP. A failure to integrate the PrEP programme with the existing HIV treatment programme was slowing down implementation. It's unclear what will happen to the programme following the election of right-winger Jair Bolsonaro as president.

In eastern Europe there have only been a couple of small implementation studies. One of the challenges is establishing a network of supportive and knowledgeable healthcare professionals to provide PrEP.

Poor retention and adherence could also severely limit PrEP's impact. A number of American studies have reported problems with retention, while a study with female sex workers in Benin, west Africa found that only one in seven women stayed in the study and remained on PrEP.

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Rectal douches

Ethel Weld at HIVR4P 2018. Photo by Roger Pebody.

There is interest in developing prevention products that are 'behaviourally congruent' so that people do not need to make substantial changes to their lifestyles. Craig Hendrix said that adding fluoride to drinking water and fortifying milk with vitamins A and D were examples of 'behaviourally congruent' health interventions.

Adding an active pre-exposure prophylaxis (PrEP) drug to a rectal douche would fit in with people's existing sexual practices. A survey of users of a gay hook-up app found that 80% reported douching before having receptive anal sex. The respondents were very interested in the idea of a douche to prevent HIV and sexually transmitted infections – 98% of men who currently douche and 94% of men who do not said that would be very interested in such a product.

In a phase I study of a tenofovir rectal douche, the product achieved adequate coverage, i.e. it travelled as far up the colon as semen was likely to go. High tissue concentrations of tenofovir were achieved.

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