ACTG Network

ACTG HIV Reservoirs Cohort (AHRC) Updates

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INSIDE THIS ISSUE:

NEWS FLASH!
A total of 156 lumbar punctures have been done for AHRC. THANK YOU participants & sites!

Study Titles

A5321: ACTG HIV Reservoir Cohort Study

A5341s: Size and Decay of HIV-1 Reservoirs in Tissues and Spinal Fluid

Treated HIV and the Brain: Results from A5321

The Conference on Retroviruses and Opportunistic Infections (CROI) is considered by many to be the most important HIV research conference. Top researchers present and discuss results of their latest studies. Two A5321 investigators presented findings from the A5321 study at CROI 2018, held in Boston. Both presentations focused on **brain**-related issues. Dr. Serena Sputdch, a neurologist from Yale University, presented information about the presence of HIV in spinal fluid. This is a marker of its continued presence in the brain. Dr. Kevin Robertson, a neuropsychologist from the University of North Carolina, presented information about the impact of long-term HIV infection on brain function. (*See Brain Function: Results from A5321*).

Dr. Sputich's talk described the main results so far from the **cerebrospinal fluid (CSF)** collected from 69 A5321 study participants. **A5321 is using CSF as a way to learn more about how HIV affects the brain.** CSF is fluid surrounding the brain that serves to cushion and protect the brain. CSF contains cells, proteins and sugar. In people living with HIV, CSF can contain floating HIV particles (RNA) and cells in the CSF with HIV that is attached or inside.

In A5321, CSF is collected by a routine procedure called a lumbar puncture. (*See Demystifying Lumbar Punctures)*. The results from A5321 participants were compared to results from 19 persons without HIV.

Like most A5321 participants, these 69 people had been taking antiretroviral therapy for a long time – an average of over eight years. Their most recent CD4 count in blood averaged 696 cells/mm^3. Only two of these 69 participants were female. On the day the CSF was collected, 67 of the 69 participants had viral loads in their blood that were very low (less than 40 copies/mL).

Dr. Serena Spudich at CROI

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AHRC By the Numbers

A5321 (Main Study)
- 357enrollees
- 63 women & 294 men
- 74 Hispanics/Latinos
- 78 Blacks

A5321 (Main Study)
- Group 1: 321(90%)
- Group 2: 22 (6%)
- Group 3: 14 (4%)

A5341s (Substudy)
- Enrollees 57

A5341s Substudy Cohorts
- A Spinal Tap: 35
- B Leukapheresis: 29
- C Gut Biopsy: 16
- D Genital Secretions: 38
- Multiple cohorts: 39

TREATED HIV AND THE BRAIN: RESULTS FROM 5321 (FROM PAGE 1)

Dr. Spudich reported that almost half of the participants had HIV in the cells in their CSF (cell-associated DNA).

The researchers measured HIV in the CSF in three ways:

1) HIV RNA floating in the CSF outside of cells
2) HIV that is part of the DNA (genetic code) inside human cells
3) HIV that is found and made within those cells (RNA).

HIV stimulates (makes) the immune system to respond to its presence. This leads to a state of chronic inflammation, including in the brain. The researchers measured levels of inflammation within the CSF.

MAIN FINDINGS:

Dr. Spudich reported that almost half of the participants had HIV in the cells in their CSF (named cell-associated DNA). The presence of cells with HIV in CSF was *not* associated with the how much HIV DNA researchers found in blood cells at the same visit. The amount of HIV DNA in the CSF cells was not associated with the levels of inflammation in either the CSF or the blood.

However, levels of inflammation in the CSF were related to levels of inflammation in the blood. CSF inflammation levels appeared to be higher in older participants. Far fewer participants had HIV RNA in cells in CSF compared to the number with HIV DNA found in CSF cells. Very few people had HIV RNA detected floating in the CSF outside of cells.

WHAT DOES THIS MEAN?

- Even when people have been taking antiretroviral therapy for years, HIV is often detectable in cells in the CSF .
- It doesn't look like the cells with HIV in the CSF were a result of infected cells coming from the blood to the CSF
- The body's level of inflammation didn't explain why HIV DNA persisted within cells found in the CSF
- HIV DNA found within the CSF didn't explain the levels of inflammation found in the CSF

WHY IS THIS IMPORTANT?

These findings suggest that we still don't understand as much about how HIV persists in the CSF as we need to and that we need to keep studying the CSF. Because the results are almost all from men, it also means that **we need to study more women**. These data show that methods to get rid of HIV from the body will have to be able to work in the brain/CSF.

THE NITTY GRITTY (MORE DETAILS):

CSF is a liquid that sometimes contains cells. In this study, the number of white blood cells in the CSF was very low and was similar between the participants with HIV and without HIV.

Several tests were done to see if HIV could be detected in the CSF of the A5321 participants. Two tests were done to see if any HIV was attached to the CSF cells. One test looked for DNA (deoxyribonucleic acid) inside the cells (cell-associated *HIV DNA). DNA is the material that carries our*

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ENROLLMENT REOPENS FOR GROUP 2

Up to 30 more participants are being sought for A5321's Group 2 from the A5354 study.

Some changes in the AHRC study A5321 protocol were made recently.

The main purpose of the changes is to allow new enrollment in Group 2 of the study. Group 2 are the participants who started antiretroviral therapy (ART) soon after getting HIV infection.

There is an active ACTG study called A5354 that is enrolling participants who have just gotten HIV and who start ART at study entry. Up to 30 more participants are being sought for A5321's Group 2 from the A5354 study. Both studies allow "co-enrollment". Co-enrollment means that it is ok for participants to be in both studies at the same time.

The AHRC study team will compare Group 2 participants to the current study participants who started ART when they had been infected with HIV for a long-time (Group 1).

The information we get will be stronger if we have more Group 2 participants. **Many thanks to ALL our study participants!**

Brain Function: Results from 5321

Dr. Kevin Robertson, A5321 team member and neuropsychologist, presented work looking at the relationship between cerebrospinal fluid (CSF) findings and brain function. This study looked at 65 participants. Participants had lumbar punctures to collect CSF and completed the A5321 set of tests that check brain function. These tests

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Dr. Kevin Robertson

Dr. Robertson presented work looking at the relationship between cerebrospinal fluid and brain function.

Demystifying Lumbar Punctures (LPs)

Overview:

- Lumbar punctures (LPs) are a commonly performed procedure
- Another name for lumbar puncture is a spinal tap
- They are not dangerous and shouldn't be painful
- The fluid collected is called cerebrospinal fluid (CSF)
- CSF can be tested for many things
- The body is constantly producing CSF

More Details:

- There is no special preparation that someone having an LP must do
- LPs are done using sterile (clean) technique
- Skin of the lower back is cleaned, then numbed with a local anesthetic (this stings); a few minutes later, a long, thin needle is placed between backbones in the lower back to collect CSF
- The most common complication is a headache
- Special needles used for research decrease the risk of headache and make headaches very rare

CSF

- Looking at CSF is the most common way to get a sense of what is happening in the brain
- CSF is a fluid that surrounds the brain and the spinal cord
- Adults have about 10-16 tablespoons of CSF
- Adults make about 4 teaspoons of CSF every hour
- CSF may contain proteins, sugar, salts, minerals, antibodies, and cells
- CSF can sometimes contain viruses or other microbes
- Normal CSF is clear and colorless

Procedure

- LPs are done only after a participant has provided consent
- Participants are asked to either lie on their side curled up hugging their legs to their chest or asked to lie face-down in a special procedure chair (like a massage chair) with their back facing the provider
- A sterile antiseptic liquid is used to wash the lower and mid-back
- A tiny, short needle is used to numb the skin with a local anesthetic
- People may feel pressure while the LP needle is placed in position but shouldn't feel pain
- The procedure usually takes about 30 minutes total
- The amount of CSF collected is usually replaced by the body within 1-2 hours

Purpose in A5321 & A5341s:

- To collect CSF one or more times from study participants
- To measure the amount and forms of HIV in CSF
- To look at how the immune system and HIV interact in CSF
- To look at how HIV, the immune system and brain function are related in persons living with HIV on long-term HIV treatment

After the procedure

- Participants are usually asked to remain lying down for about 30 minutes
- Participants are asked to avoid heavy lifting or vigorous activity for the rest of the day
- Participants are asked to drink extra non-alcoholic fluids after having a LP

Spinal taps are not dangerous and shouldn't be painful.

Special needles used for research decrease the risk of headache and make headaches very rare.

The amount of CSF collected is usually replaced by the body within 1-2 hours.

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The mission of the ACTG Network is to reduce the burden of disease due to HIV, tuberculosis, and viral hepatitis.

ACTG AIDS CLINICAL TRIALS GROUP

actgnetwork.org

It shows a link between the presence of HIV in the brain and brain function.

***ACTG HIV Reservoirs Cohort** study (**AHRC**, A5321) is a long-term study, designed to assess patterns of reservoir decay, including what factors determine both the size of HIV reservoir and its decay in people living with HIV on long-term ART*

AHRC PATHWAY TO THE CURE

- *Substantially larger than previous studies*
- *Samples stored over time available from participants who have received ART for much longer than in previous studies*
- *Greater ability to assess whether participants on long-term ART have different reservoir decay patterns (e.g. a subset with continuous decay) and*

TREATED HIV AND THE BRAIN: RESULTS FROM 5321 (FROM PAGE 2)

genetic code. The other test looked for HIV RNA in the cells (cell-associated HIV RNA, ribonucleic acid). RNA is similar to DNA but is made of different building-blocks. As a reminder, HIV is an RNA virus, meaning that its genetic code is made of RNA. Humans' genetic code is made of DNA. When HIV gets into a human cell, the HIV RNA gets made into DNA, which joins the cell DNA and can make HIV RNA.

A small number of participants had HIV detected floating in the fluid part of the CSF. Almost half of the participants had cell-associated HIV DNA detected in their CSF. Only about 10% had cell-associated HIV RNA detected.

Inflammation is a common way that the body reacts to infection. It is measured by testing for specific chemicals in the blood and CSF. Seven tests of inflammation were measured in CSF and blood in this study.

BRAIN FUNCTION: RESULTS FROM 5321 (FROM PAGE 3)

evaluate 7 different brain functions.

The team studied the relationship between the presence of HIV DNA in cells in the CSF (cell-associated DNA) and brain function. It also checked to see if levels of CSF inflammation were related to brain function.

Like most A5321 participants, these 65 people had been taking antiretroviral therapy for a long time – an average of about 8 ½ years. Their average age was 50 years. Only two of these 65 participants were female. All 65 had graduated from high school. Their most recent CD4 count in blood averaged almost 700 cells/mm3. Almost half had detectable HIV DNA found within cells in the CSF (cell-associated HIV DNA).

Brain function test results are described in 2 ways. One type is called a z-score and one is called a Global Deficit Score.

MAIN FINDINGS:

Participants with HIV DNA detected in CSF had worse average brain function than those without detectable CSF HIV DNA. This was true for both measures of overall brain function. This was true even when researchers adjusted for the participants' ages and CD4 counts in blood at 2 different time points (before antiretroviral therapy and at their most recent CD4 count). There was no relationship between CSF inflammation levels and brain function.

WHAT DOES THIS MEAN?

- Brain function is worse in persons living with HIV who have HIV DNA in cells in the CSF (even after they have taken antiretroviral therapy for many years).
- Current inflammation may not be responsible for the brain injury seen with HIV.

WHY IS THIS IMPORTANT?

It shows a link between the presence of HIV in the brain and brain function. It shows how long-term follow-up can teach us about the impact of HIV.