HVTN 703/HPTN 081 and HVTN 704/HPTN 085

Antibody Mediated Prevention (AMP) Trials

Efficacy Results

01 October 2020
Today we will be sharing with you the efficacy results from the AMP studies. As a reminder for everyone, if the news of the results is shared publicly before it is published in a scientific journal, the publication can be jeopardized. Please understand the importance of keeping this information confidential until sites are notified that they can release the information widely.
Our presenters will be our study co-chairs, Nyaradzo Mgodi of Harare, Zimbabwe (left), and Sri Edupuganti of Atlanta, Georgia, US (right), shown in front of their AMP poster at the HIVR4P conference, 2018, Madrid, Spain.
Presentation Outline

• AMP Studies Overview
• Studies’ Findings
  • Safety and Tolerability
  • Efficacy
  • Novel findings
• Summary
(photo: Study chairs Mike Cohen (left) and Larry Corey (right) pose in the booth at the 2018 International AIDS Conference in Amsterdam, in front of the AMP study panel)
What is AMP?

• These are proof of concept studies.
• AMP stands for Antibody Mediated Prevention.
• This is the idea of using a broadly neutralizing antibody against HIV that was made in a lab and giving it to people using an intravenous infusion.
• The common name for this procedure is an “IV” or “getting a drip.”

The AMP studies are proof-of-concept studies, done to see if it was possible for a broadly neutralizing antibody to the AIDS virus to prevent someone from getting HIV. AMP stands for Antibody Mediated Prevention. This is the idea of giving people antibodies that are directed at the virus to see if they will protect people from getting HIV. These antibodies are also known as monoclonal antibodies, which mean that they were manufactured in a lab, rather than being made naturally by the human body. The AMP studies tested an antibody called VRC01 administered by intravenous infusion (IV, also known as a drip) to prevent acquisition of HIV.
Antibodies are one of the natural ways that our bodies fight infection. Giving people antibodies to prevent an infection is an accepted medical practice that is more than 100 years old. For example, doctors give people antibodies to prevent infections like hepatitis A and B, chicken pox, and a respiratory infection in infants called RSV.

VRC01 blocks many different strains of HIV from getting into human cells in the laboratory and can protect laboratory animals from some HIV infections. HVTN 703/HPTN 081 and HVTN 704/HPTN 085 are the first studies to test whether this antibody can work in people. They were designed to test whether the VRC01 antibody could prevent people from getting some strains of HIV that were predicted to be preventable based on results in the lab.

ONLINE VERSION: https://vimeo.com/285909197
Study Schema

<table>
<thead>
<tr>
<th>Treatment</th>
<th>1 (W0)</th>
<th>2 (W8)</th>
<th>3 (W16)</th>
<th>4 (W24)</th>
<th>5 (W32)</th>
<th>6 (W40)</th>
<th>7 (W48)</th>
<th>8 (W56)</th>
<th>9 (W64)</th>
<th>10 (W72)</th>
<th>W80*</th>
<th>W104**</th>
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</thead>
<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>VRC01 30 mg/kg</td>
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<td>+</td>
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<td>Control</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

+ = IV infusion administered every 8 weeks

*Week 80: Last study visit to evaluate efficacy (results reported here)

**Week 104: Final study visit to evaluate safety and tolerability; TBD, final study visits expected in Q1, 2021

The randomized, placebo-controlled studies were designed to test two doses of VRC01, 10mg/kg and 30mg/kg, against a placebo which was salt water (saline). That means that participants were placed into one of the 3 groups in a similar way to flipping a coin. They were not able to choose which group they were placed in, and they will not know which dose they were given until the end of the study.

I want to call your attention to the last 2 visits on the right. Week 80, or 2 months after the last infusion, was when the studies planned to evaluate whether VRC01 was effective for preventing HIV acquisition. We have reached this point in time, and the first set of analyses have been completed. That is why we are able to share the prevention efficacy results now. Efficacy for the AMP studies means, “What is the risk of HIV diagnosis if you got VRC01 compared to the risk of HIV diagnosis if you did not get VRC01” or “By how much does VRC01 reduce your risk of HIV diagnosis compared to placebo.”

Week 104 (2 years) is when the studies will evaluate safety and tolerability. We have not gotten to this point for all participants yet. Those visits are expected to be completed in early 2021. We expect to be able to share the results from those analyses later in 2021.
The AMP studies are two parallel studies, with the same design, in two different populations that were at risk for HIV acquisition. One of the AMP studies, HVTN 703/HPTN 081, enrolled heterosexual cisgender women in Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zimbabwe, who were 18-50 years old and at risk of HIV. HVTN 703/HPTN 081 enrolled 1,924 cisgender women. Participants enrolled from May 2016 to September 2018. Of these participants, 642 received 10 mg/kg of VRC01, 645 received 30 mg/kg of VRC01, and 637 received the placebo.

The last infusions in the AMP studies were given in April 2020. However, follow-up of participants for safety, with ongoing HIV testing, is planned to continue into early 2021. To support this ongoing safety follow-up, the unblinding of participants to tell them what they received – VRC01 or placebo – will occur in early 2021 when this follow-up is complete.
The second AMP study, HVTN 704/HPTN085, enrolled men and transgender persons, 18-50 years old, living in Brazil, Peru, Switzerland, and the United States, who have sex with men and transgender persons. All participants were in good general health. HVTN 704/HPTN 085 enrolled 2,699 men and transgender persons. Participants enrolled from April 2016 to October 2018. Of these participants, 899 received 10 mg/kg of VRC01, 897 received 30 mg/kg of VRC01, and 903 received the placebo.
Main Research Questions

We embarked on proving a new concept in HIV science: does an HIV antibody called VRC01 prevent HIV acquisition?

• Is the VRC01 antibody safe to give to people?
• Are people able to tolerate the antibody without becoming too uncomfortable?
• Does VRC01 lower people’s chances of getting HIV?

In general, the studies were designed to answer these research questions among many others:

• Is the VRC01 antibody safe to give to people?
• Are people able to tolerate the antibody without becoming too uncomfortable?
• Does the antibody lower people’s chances of getting HIV?
Main Research Questions (continued)

- Does the efficacy of VRC01 vary according to the different strains of HIV encountered in various geographic regions and by sex assigned at birth?
- If the antibody does lower people's chances of getting HIV, how much of it is needed to provide protection from HIV?
- If someone gets HIV, how does VRC01 make a difference in their infection?

Another key question was to understand if there was a marker that would predict the amount VRC01 needed for protection, what strains of HIV it might protect against, and perhaps explain how protection was happening.
AMP STUDIES FINDINGS

HVTN 703/081 and HVTN 704/085

(photo: one of our models at the Soshanguve site, who agreed to be photographed for use in outreach materials)
Is VRC01 Safe and Well-tolerated?

- VRC01 has been safe & well-tolerated.
- Safety follow-up is still ongoing. Full analysis will happen in 2021 after the final study visits are completed.
- Most side effects have been mild to moderate, within the first hours to days after an infusion. Uncommonly, they were severe enough to interfere with daily activities.
  - Some tenderness at the infusion site, headaches, tiredness, body aches, nausea, fever, and chills.
  - Low rates of infusion reactions (e.g., itching, rash, or shortness of breath during or immediately after an infusion).
  - These side effects are often seen in monoclonal antibody and vaccine studies, and with approved monoclonal antibodies and vaccines.

Safety follow-up is still ongoing. However, so far we have learned that people were able to take VRC01 without becoming too uncomfortable. When side effects occurred, most were mild to moderate reactions in the first hours to days after an IV infusion. These side effects included pain or tenderness at the infusion site, headaches, tiredness or feeling unwell, body aches, nausea, fever, and chills. Some participants reported that some symptoms were severe enough to interfere with normal daily activities or cause them to miss work for a day. About 5% of participants had itching, a rash, or shortness of breath during or immediately after the infusion. These reactions did not last long and the people who had them recovered without any problems. These side effects are often seen in monoclonal antibody and vaccine studies, and also happen with approved monoclonal antibodies and vaccines. The rest of the safety data analysis will take place after the studies conclude, and it will be reported in 2021.
Overall Prevention Efficacy of VRC01

Prevention efficacy is defined as having a reduced probability of HIV acquisitions in the combined treatment groups (lower dose and higher dose together) compared to the placebo group.

The graph shows the efficacy of VRC01, with both the lower and higher doses pooled across the two trials, in the solid line in the center of the graph. The dotted lines show the 95% confidence interval. We can see that there was some efficacy (about 50%) in the earlier part of the trial that gradually dropped over time at Week 80.

The dip in efficacy at around 8 weeks is not statistically significant, as there were very few participants who had acquired HIV at this early point in their study participation. Any analysis of HIV acquisition rates at this early point in the trial is not statistically meaningful or "valid."
Overall Prevention Efficacy at Week 80

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Primary Endpoints</th>
<th>Endpoints 10 mg/kg</th>
<th>Endpoints 30 mg/kg</th>
<th>Endpoints Placebo</th>
<th>Estimated Cumulative Efficacy</th>
<th>95% Confidence Interval</th>
<th>2-sided P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVTN 704/HPTN 085</td>
<td>98</td>
<td>32</td>
<td>28</td>
<td>38</td>
<td>26.6%</td>
<td>(-11.7% to 51.8%)</td>
<td>0.15</td>
</tr>
<tr>
<td>HVTN 703/HPTN 081</td>
<td>77</td>
<td>29</td>
<td>19</td>
<td>29</td>
<td>8.8%</td>
<td>(-45.1% to 42.6%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Pooled AMP Trials</td>
<td>175</td>
<td>61</td>
<td>47</td>
<td>67</td>
<td>18.1%</td>
<td>(-12.2% to 40.2%)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

This table shows you the numbers behind the graphs on the previous slide. [continue to press enter until p values are shown].

Total number of HIV infections or primary end points in each trial and the prevention efficacy in each trial and also pooled data from both trials are shown here.

The 95% confidence interval means that we are 95% confident that the true mean efficacy lies in between these numbers. When the CI crosses zero, it means there is no statistical significance. Statistical significance is how positive are we that this efficacy is caused by our intervention and not due to chance. Another way of showing statistical significance is to use p values. A p value of 0.05 or less is usually considered to be significant. Since these values are all much larger than 0.05, we can say that the results are not statistically significant.
A Key Research Finding - 1

- VRC01 administered at 8-week intervals over 20 months reduced acquisition of HIV strains that were sensitive to VRC01 (IC80 < 1 µg/mL)
  - The high dose of VRC01 (30 mg/kg) achieved 85% protection against Clade B and Clade C viruses that were sensitive to VRC01.
  - This suggests that the main factor in determining efficacy is the virus itself, and whether it is sensitive to VRC01.

The graph on the right shows how the prevention efficacy differed based on the sensitivity of the virus to VRC01, known as the IC80. The IC80 tells you how much VRC01 would be needed to reduce infection of 80% of cells with HIV in the lab. This is done by a neutralization test. The blue line shows that VRC01 had strong prevention efficacy against sensitive viruses, and this efficacy was sustained. The other colors show the more resistant viruses where VRC01 provided transient protection reaching zero efficacy by 80 weeks.

We designed the AMP studies assuming that 70% of the HIV would be susceptible to VRC01 at an IC80 < 10 µg/ml. But we found that only 25% of the viruses were susceptible at an IC80 < 1 µg/ml.
A Key Research Finding - 2

• Showing HIV acquisition based on how sensitive the virus is to VRC01:
  • 3 categories: IC80 < 1 µg/ml, 1-3 µg/ml, and >3 µg/ml
  • the blue line shows that HIV incidence was lower among people who appear to have been exposed to viruses that were sensitive to VRC01 at the <1 µg/ml level.

This graph shows how HIV incidence varies based on the sensitivity of the virus to VRC01. There are 3 categories of IC80. The blue line shows that HIV incidence was lowest when the IC80 was also low i.e.<1 µg/ml. The other colors show the more resistant viruses where the IC80 was higher and there was higher HIV incidence.
Did VRC01 Prevent HIV Acquisition?

• We proved the concept that a bnAb can prevent HIV acquisition.
• We learned some of the characteristics of an antibody required to provide lasting prevention of HIV.
• The studies also proved that a neutralization test can help predict an antibody’s ability to prevent HIV. Without using human studies, the test can be used to:
  • Estimate the amount of a given antibody in the blood needed to protect against HIV.
  • Predict the efficacy of a given antibody against different types of HIV in people.

First and foremost, YES, we proved the concept that a bnAb can prevent HIV infection. This will support future bnAb research.

We also learned the characteristics of an antibody, specifically the potency and breadth, that are important in prevention of HIV. VRC01 was effective in blocking infection from viruses that are very sensitive to the antibody. Viruses that weren’t as sensitive were not neutralized by VRC01. This means we may need more than one antibody, or a combination of antibodies given together, to be useful in preventing the many strains of HIV-1 that circulate in people around the world.

You can think of this as similar to HIV treatment where it requires 2 or more drugs to work effectively. The results of this trial can be thought of similarly to when we only had the single drug AZT for treatment. AZT’s impact was limited and not enough, but it opened the door to the work that happened to bring about combination antiretroviral therapy.

Another important finding from the AMP studies is that a lab test called the TZM-bl neutralization assay has been proven as an effective marker. Without doing human testing, the assay can be useful to estimate the amount of a given antibody in the blood needed to protect against HIV, and predict which HIV strains will be susceptible to the antibody. Therefore, the TZM-bl assay can be used to advance the development of current and future study antibodies, and streamline the studies in animal models.
NOVEL INSIGHTS

HVTN 703/081 and HVTN 704/085

(Photo: San Francisco’s Bridge HIV community engagement staff tabling, sign showing “Rise of the bnAbs” with upraised fist, mirrored by staff)
Novel Insights

• We found a relationship between VRC01 in the blood (serum titer) and neutralization (IC80)
  • We can predict how much antibody is needed to be effective against strains of HIV in various geographic regions of the world.
    • Clade B strains in the Americas and Switzerland
    • Clade C strains in Africa
  • This allows selection of better antibodies for future studies, and will enable us to make more efficient progress advancing them.

We learned several new things, and as always, every good research study presents us with new research questions that we can explore in future studies. Here are a few highlights:

We found a relationship between the level of VRC01 needed in the blood (called a titer) and the neutralization sensitivity of the virus. This is a major advance. Using this relationship, we can predict how much antibody is needed to prevent HIV in various geographic regions of the world where the various strains of the viruses circulate, such as clades B and C in the Americas and Africa, respectively. This allows us to choose better antibodies for future studies and make more efficient progress advancing them.
Observations that need further research - Possibility of Suppressed Infections

- It appears that VRC01 may have temporarily suppressed viruses until the viruses learned to become resistant over time.
  - During this time, the infection may not have been detected through routine lab tests of blood at the time of initial acquisition.
  - This idea is preliminary and needs additional analyses to confirm it.
- Studies in PLWH show bnAbs suppress virus in the blood, and that resistant viruses “escape” being suppressed.
- Although these participants were undiagnosed for a period of time, they could not transmit HIV during this time (U=U) because they had an undetectable viral load.
- This is a preliminary finding - additional analyses are planned to help us further understand this observation.

This idea suggests that VRC01 can not only block HIV acquisition completely in some cases, but may also be suppressing HIV in tissues even if it isn’t able to block acquisition completely. If there is a resistant virus in the swarm of viruses at the time of acquisition, it appears that VRC01 can contain it for awhile and then eventually the virus escapes. We think that the virus may have been contained in the tissue because we were not able to detect it in blood tests. This has been seen in HIV treatment and cure studies that showed HIV can reside in certain tissues without being detected for a period of time.

One important thing to remember about these suppressed infections is that because people had an undetectable viral load, they were not able to transmit HIV to anyone else. This is similar to the idea of treatment as prevention (U=U) – the VRC01 was helping to control viral load.

And remember, these concepts need further data analysis, and we need to specifically study the viruses found in AMP participants. It is still early, and we have only completed the first set of analyses to announce these results. In the coming months there will be additional analyses done to help us further understand suppressed infections.
HVTN 703/081 and HVTN 704/085

SUMMARY

(Photo – AMP Flash Mob in Lima, Peru)
Summary

• We proved that this approach is acceptable globally, and we will have additional data about safety next year.

• We proved that a bnAb can prevent HIV acquisition. We are not trying to license VRC01, because we know that more powerful bnAbs exist.

• We found that it is not only the concentration of antibody in the blood at the time of HIV acquisition that is important, but it is also the sensitivity of the virus to the antibody itself that determines whether HIV can be prevented by VRC01. HIV continues to be a very clever virus!

• We can use a neutralization lab test to predict how well an antibody can prevent acquisition of viruses that people may be exposed to.

• We completed a remarkably successful clinical study that is revealing new aspects of HIV biology, similar to the pioneering AZT studies that led to the development of combination ART.

The AMP studies showed that a broadly neutralizing antibody can prevent some HIV acquisitions. We now have a better understanding that it isn’t just the bnAb that matters, but also the virus itself, and whether the strain of HIV that someone is exposed to is sensitive to the particular bnAb they received.

When the AMP studies began in 2016, laboratory and animal studies suggested that VRC01 was capable of preventing HIV. VRC01 was the first and only antibody ready to use for testing the AMP study concept. We knew that there were more powerful antibodies that had been discovered, but they were not yet ready to use in an efficacy trial, so we knew and said from the start that there was not a plan to license VRC01. Through the AMP studies, we have proved that such an antibody can prevent HIV, but this particular antibody was not strong enough to be able to prevent enough acquisitions.

The AMP studies also taught us that we can predict how well an antibody can prevent HIV if we know the neutralization sensitivity of the viruses people may be exposed to. Through the AMP studies, we have confirmed that the specific lab test called the TZM-bl assay can identify the antibodies that may prevent HIV acquisition more effectively, even before we start studies in people using those antibodies. This is known as a “surrogate marker.” This will enable scientists to choose better antibodies to move forward into human studies, so that we can evaluate them more efficiently in future human studies.
We completed a remarkably successful clinical study that is revealing new aspects of HIV biology, similar to the pioneering AZT studies that led to the development of combination ART.
AMP Results Communication Plan

• **Please hold this information confidential.**
• Results are preliminary; laboratory data need additional analysis.
• We will provide clinical research sites with materials to share with their participants and CABs.
• These materials need to be approved by regulatory bodies before distribution to participants.
• Sharing the results with participants will take place close in time to when the first results manuscript is published, and a press release will also be issued then.
• Additional webinars to share the results with stakeholders will also be planned.

So what happens next? At this time, we are reminding everyone that these AMP Study results are still highly confidential, and you are asked **NOT** to share the information or discuss the news with others. We are preparing a set of materials for sites to use to share the results with their study participants and Community Advisory Boards. These materials will require IRB or Ethics Committee approval before they can be used. We are also preparing text to be posted on the AMP Study websites, and that will also need IRB/EC approval. It is our intention to have these materials ready to go so that as soon as we know when the first manuscript about the study results will be published, notification of participants can happen at the same time. There will also be a press release at that time to notify the general public of the results. We are planning to hold additional webinars after the publication of the results to share the news with stakeholders.

As a reminder for everyone, if the news of the results is shared publicly before it is published in a scientific journal, the publication can be jeopardized. Sharing the news publicly too early also can compromise the sites’ opportunities to tell their participants about the results directly. Please understand the importance of keeping this information confidential until sites are notified that they can release the information widely.
The way forward for bnAb research

The AMP Studies laid the foundation for future prevention efficacy bnAb studies.

We are conducting research on newer bnAbs, including combinations, that are more potent and have broader coverage than VRC01.

The studies taught us that in order to better prevent HIV, we need an antibody or combination of antibodies that can prevent acquisition by more strains of HIV (i.e., antibodies with more breadth or coverage against HIV), and with even smaller doses of antibody (i.e., with more potency). Fortunately, we have already been identifying broader, more potent antibodies, and potential combinations of these antibodies. One of our goals with proving this concept in the AMP studies was to inform future research so that we could improve the efficiency of efforts to advance bnAbs as another HIV prevention tool, and we have accomplished that. The HVTN and HPTN are moving these broader, more potent antibodies into future studies, individually and in different combinations.

This information is a big step forward in the effort to expand the HIV prevention toolbox to include monoclonal antibodies!

[Note for translation: items in the toolbox image that need labeling: PrEP, U=U, KY gel (lubricant). Other items that do not need labels are condoms, needle exchange, and vaginal ring.]
Acknowledgements

- The study chairs, Larry Corey (HVTN) and Mike Cohen (HPTN)
- The study co-chairs, Sri Edupuganti (HVTN) and Nyaradzo Mgodi (HPTN)
- The NIAID Vaccine Research Center team, led by John Mascola
- HVTN Protocol Team Leader Shelly Karuna and HPTN Clinical Research Manager Phil Andrew
- The members of the AMP Studies Protocol Teams, including community representatives Monica Pule, Mark Hubbard, Jim Wick, Luciana Kamel, and DaShawn Usher
- The Network Community Engagement staff members led by Gail Broder (HVTN) and Jonathan Lucas (HPTN)
- The members of the HVTN 703/HPTN 081 and HVTN 704/HPTN 085 AMP Community Working Groups
- The study sponsor and funder, the Division of AIDS at the National Institute of Allergy and Infectious Disease
- And most importantly, the HVTN 703/HPTN 081 and HVTN 704/HPTN 085 Study Participants
Questions