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Statement of Purpose:
AIDS Treatment News reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations which work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

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Antibodies and HIV: New Evidence

Interview with Ruth Ruprecht, M.D., Ph.D.

By David Scondras, Search For A Cure, and John S. James, AIDS Treatment News

Background

HIV infection causes the body to produce large amounts of antibodies -- specialized proteins produced by the immune system to fight infecting bacteria or other organisms. But most of the antibodies produced in response to HIV infection are not effective in stopping the virus -- and some of them may even increase HIV infection. So in recent years, many scientists have given up on antibody approaches to HIV vaccines or treatments. (Instead they are working with the other major branch of the immune system, cellular immunity, which now looks very promising for control of HIV. However, cellular immunity by itself cannot clear most HIV infections.)

At a recent conference on immune research in HIV, held April 27-29 at the Institute of Human Virology at the University of Maryland in Baltimore, Ruth M. Ruprecht, M.D., Ph.D., an immunologist at the Dana-Farber Cancer Institute and Professor of Medicine at Harvard Medical School, presented an update on her team's ongoing work with HIV antibodies. She agrees with her colleagues that most antibodies against HIV are not effective. But some are (as other investigators and Dr. Ruprecht had shown) -- and she has selected three of them for further research. These three, injected together, have successfully prevented infection in monkeys, even when they are given large doses of HIV-like viruses.

If this approach continues to be successful, it could have huge implications:

(1) Vaccines could be engineered to cause the body to produce antibodies already known to work. Such antibody-inducing vaccines might be effective by themselves -- or might be combined with approaches that generate cellular immunity to produce vaccines more effective than either kind alone. Vaccine development could be greatly accelerated, because it would be possible to test quickly, in volunteers, whether or not a candidate vaccine induced production of the desired antibodies. Problems could be found and fixed quickly, before the vaccine went into a large,

multi-year trial.

(2) Antibodies might also be able to prevent mother-to-infant transmission -- without the side effects or potential toxicities of antiretrovirals, without the risk of producing drug-resistant virus, and possibly without requiring the mothers to avoid breast feeding.

(3) It is possible that selected antibodies might help in the treatment of persons already infected. So far there are no data, as this has not been tried even in animals.

But many years ago there were experiments with "passive immunotherapy" for HIV -- collecting serum donated from persons who were doing well for a long time despite HIV infection, and transfusing this serum into persons who were sick. Despite some promising results, this work did not continue. From the modern perspective, these early attempts do make some sense -- Dr. Ruprecht explained that a few patients do produce antibodies that are effective in stopping HIV. But today we also know that some people are slow progressors for different reasons, some of which have nothing to do with antibodies, so there is no reason to think that transfusing their plasma would be beneficial to others. Using rationally selected, engineered antibodies would appear more promising.

Incidentally, passive immunotherapy has long been used to treat certain other infectious diseases. And recently it was found effective in animal tests in both preventing and treating ebola virus infection.[1]

Dr. Ruprecht uses monoclonal antibodies (pure antibodies produced by genetically modified cells) rather than serum or immunoglobulins prepared from serum, that deliver a variable mixture of many different antibodies. So far, monoclonal antibodies have been much too expensive to use as treatments. But now it is becoming possible to produce antibodies in plants, such as tobacco. So price need not be an obstacle -- if it is found that antibodies could work as treatment for someone already infected with HIV, which today is not known.

Note: David Scondras interviewed Dr. Ruprecht on April 28, and prepared a transcript. Since he then had to leave for AIDS work in Malawi, John S. James, who was present at the interview, edited the transcript and wrote the background section above. Dr. Ruprecht made corrections before the interview was published.

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Interview with Dr. Ruprecht

Scondras: What is the goal of your work?

Ruprecht: We want to develop an immunological approach to prevent mother-to-child transmission of HIV. Simultaneously, we are also looking for a way to rationally design an HIV vaccine.

The idea came from how we manage hepatitis B. To prevent mother-to-child transmission, pregnant women are screened for the virus. If they are positive, their infants get two inoculations: the first consists of hepatitis B immunoglobulins [which contain antibodies against the hepatitis B virus, providing passive immunity], and the second is the hepatitis B vaccine.

Used together, the vaccine plus immunoglobulins confer 98% effective protection to the baby. If you use the immunoglobulins alone, they are only 70% effective.

Turning to HIV, people who have HIV infection make very little neutralizing [effective] antibody compared to people with other viral infections. Instead, with HIV, the body makes lots of antibodies to parts of the virus that are not important. This kind of antibody does not stop the virus from infecting cells and damaging the immune system. Indeed, it is now known that HIV makes the body produce antibodies that may even *help* the virus infect cells.

That was part of the reason I decided to stay away from polyclonal sera [such as antibody preparations made from the blood of persons whose HIV was progressing slowly]. You cannot do a rational analysis of the specific antibodies.

Scondras: Hasn't this approach of looking at antibodies been tried before?

Ruprecht: Every once in a while, a patient develops relatively high titers of neutralizing antibodies [meaning that they produce antibodies that effectively block HIV]. It is also known that monoclonal antibodies can be made from these people. But in scientific research, the pendulum had swung away from antibodies.

Scondras: How did you think that antibodies could play an important role anyway?

Ruprecht: I knew that antibodies help prevent hepatitis B virus infection. I also knew that the hepatitis B virus has some similarities to HIV. So I decided to focus on finding potent antibodies from HIV-infected people. Other investigators have succeeded in engineering cultured cells to produce just

a single antibody, called monoclonal antibody. My colleagues kept isolating B cells [the cells in the blood that produce antibodies], and kept screening until they found cells that produced antibodies that successfully neutralized HIV. Then we could learn to mass produce the monoclonal antibodies. Today this is possible; in fact, tobacco plants can be engineered to produce these antibodies.

The Animal Tests

Ruprecht: We decided to combine antibodies that worked against HIV, in the hope that a cocktail of antibodies would be more effective than one antibody alone. We looked for overall potency of triple combinations, picked a combination that stopped HIV in the test tube, and then tested if that combination would stop a virus similar to HIV that can grow in animals.

The three antibodies that we picked are human monoclonal antibodies, targeting conserved epitopes of the envelope of HIV. [The "envelope" is the outside part of the virus, that antibodies can get to. "Epitopes" are particular shapes of parts of HIV; antibodies target foreign substances by being shaped just right to fit them. "Conserved" epitopes means ones that do not change much from one strain of HIV to another (probably because when they do change as a result of mutations, the virus is not able to survive).]

This kind of therapy that uses antibodies is called "passive immunotherapy." It is important for babies, in particular, because it may be able to protect babies from getting HIV from their mothers, and also protect them from getting HIV from breast milk from the infected mother. Antibodies stay in the blood for a fairly long time [so it might be possible to protect babies with only a few injections, instead of shots or pills every day].

Scondras: Is there any connection between this and developing a vaccine to protect people from HIV?

Ruprecht: Yes. We have antibodies now that are completely characterized [meaning that we know to what part of HIV they bind]. If these antibodies can provide complete protection from HIV transmission, then a vaccine that elicits these antibodies should be protective.

Scondras: Is it possible that these antibodies could be a therapy for people who have HIV?

Ruprecht: We just do not know yet -- no experiments have been conducted to test this approach.

Scondras: Why do you think you may have found the right antibodies?

Ruprecht: We have data showing that these three antibodies can completely protect against SHIV challenge in adult rhesus monkeys. [SHIV is a virus which combines parts of SIV, which infects monkeys, and parts of human HIV.] We have also shown that newborn monkeys could be protected completely with the triple combination of antibodies against mucosal SHIV infection. Then we tried a much more aggressive SHIV strain, and it was stopped in some newborn animals. We purposely infected these monkeys with much, much more virus than is usually transmitted from mothers to babies, and the antibodies worked well.

One other point: The antibodies we have identified are of the IgG subtype, not IgA, the typical mucosal antibodies. This implies that you do not need mucosal immunity to HIV to protect people from HIV.

Scondras: Dr. *Ruprecht:* How did you get started in AIDS research ?

Ruprecht: I was about to start a thesis in physical chemistry in Switzerland, my native country, but my real love was molecular biology. When I was in the U.S. as a summer intern in chemistry, I discovered that the U.S. graduate-school system would allow me to make this change of fields, unlike my school in Europe. So I decided on the spur of the moment to stay in the US, and went to Columbia University. I worked on cancer-causing retroviruses and studied the mechanism of reverse transcriptase.

After getting my Ph.D., I attended a two-year medical school at the University of Miami, and then completed my residency in internal medicine at UCLA. I was there when the first HIV patients came to the hospital. I started a fellowship, moved back to New York City, then got an academic position in 1984 at the Dana-Farber Cancer Institute, and have worked in AIDS research ever since.

References

(1) M. Gupta, S. Mahanty, M. Bray, R. Ahmed and P.E. Rollin. Passive transfer of antibodies protects immunocompetent and immunodeficient mice against lethal Ebola virus infection without complete inhibition of viral replication. *Journal of Virology*. May 2001; volume 75, pages 4649-4654.

Danger: Counterfeit Neupogen® (Filgrastim)

On May 10 Amgen Inc. warned medical professionals that counterfeit vials labeled as Neupogen (filgrastim) have been found in the United States (but not in other countries at that time). These vials contain a clear liquid, but no active ingredient -- a fraud that could be life-threatening to patients.

The Amgen Web site has detailed instructions for distinguishing the counterfeit product, which is easy to do, because there are differences in the lot number, packaging, and labeling. For example, lot number P000948 is counterfeit; while lot number P000890 with one expiration date is counterfeit, but the same lot number with another expiration date is probably authentic. Since other fake labels may be printed, check the Amgen Web site,
http://www.amgen.com

(Try clicking Corporate Center, then Amgen News -- check the May 10 or 11 press release, which has photos showing the differences, and see if there are any later press releases.)

Danger: Counterfeit Serostim® (Human Growth Hormone)

On May 17 Serono, Inc. and the U.S. FDA warned that new counterfeit drug labeled Serostim had been found. There had been a warning of a previous case of counterfeit Serostim in January of this year. From the press release:

"Serono, Inc. and the U.S. Food and Drug Administration (FDA) are informing distributors, pharmacies, physicians and patients of the existence of a new counterfeit lot of Serono's Serostim® 6 mg [somatropin (rDNA origin) for injection]. The counterfeit material, which is made to resemble Serostim®, bears lot number MNH605A. Any product labeled as Serostim® and carrying this lot number should be considered to be counterfeit.

"Patients in possession of the counterfeit lot should return it immediately to their pharmacy for a replacement. Patients seeking additional information may also call Serono's product information line at 1-888-275-7376.

"Serono is sending a 'Notification of Counterfeit Product' letter to wholesale distributors, pharmacies, physicians and AIDS service organizations to alert them. The counterfeit material was neither manufactured nor distributed by Serono and is definitely not Serostim®. Therefore, it cannot be assumed that the counterfeit product is either safe or effective.

"Serono is cooperating fully with the FDA in its effort to stop the distribution of the counterfeit product and to prosecute those responsible for it.

"Serostim® (SEHR'-uh-stihm) is approved in the U.S. for the treatment of AIDS wasting."

June 23: New York March and Rally Before United Nations AIDS Session

Dozens of organizations have called for a march and rally in New York on June 23, just before the United Nations General Assembly Special Session on AIDS (UNGASS). Some international delegates and organizers who have traveled to New York for the United Nations session are planning to join the march.

Sponsors include the African Services Committee, Bailey House, Global AIDS Alliance (GAA), Health GAP Coalition, and ACT UP New York -- in cooperation with NAPWA South Africa, and the Treatment Action Campaign (TAC) in South Africa. Endorsers include many other AIDS, international, and social-justice organizations. [Note: This is not to be confused with the June 3 march on the 20th year since the discovery of AIDS, which takes place in Washington.]

This event is the same day as the NYC Dyke March, and one day before New York's Lesbian/Gay Pride parade.

For more information, see
http://www.stopglobalaidsnow.org

United Nations: Civil Society Snubbed at Final Preparatory Meetings on AIDS

by John S. James

On June 25 - June 27 the United Nations will hold an historic special session on AIDS, often called UNGASS (United Nations General Assembly Special Session). Two preparatory sessions were scheduled to allow official delegates and civil society to interact; the last one was May 21-25. The United Nations also set up an email discussion list, Break the Silence, for organizations and individuals throughout the world to have their voices heard during the preparation for the Special Session. (At the June 25-27 official meeting it will be too late for significant changes and initiatives, as most of the outcome will have been set up in advance.)

The preparation process uses the well-known "single text" method of negotiation. A document is drafted, put out for comment, and then changed periodically in the attempt to reach agreement. The second version of this document (May 28, 2001) is now being circulated; it is on the UNAIDS Web site, at http://unaids.org

The email discussion list is working well. Readers may want to subscribe by sending email to:
join-break-the-silence@hdnet.org

The first session set up for meetings between official United Nations delegates and civil society also went very well, although perhaps by accident. Due to glitches in the agenda, there were entirely unexpected opportunities for official delegates and civil society members to meet and discuss AIDS.

The May 21-25 preparatory session was different. According to a May 24 press release by 12 organizations from the U.S., Canada, Venezuela, Ukraine, Brazil, UK, India, and Norway:

"Many NGOs [non-governmental organizations, usually called nonprofits in the U.S.] traveled to New York from around the world, responding to the invitation of the President of the General Assembly, but found themselves unable to participate meaningfully or share their expertise with delegates, contrary to the General Assembly's own resolution which called for involvement of civil society in the development of a Declaration of Commitment to be signed by all 189 UN member states in June. While a handful of countries strongly supported civil society's contributions, two brief "dialogue" sessions - scheduled during the lunch and evening hours - went unattended by the majority of countries. Anand Grover from the Lawyers Collective HIV/AIDS Unit, Mumbai, India, said 'I am very disappointed at the absence of the delegates from countries who are most affected, their short attention span, and the lack of meaningful government participation.'

"Yesterday the United States went so far as to ask all NGO representatives to leave the room, including those with ECOSOC accreditation who are normally entitled to observe country delegation negotiations. Since the US made a formal complaint, the Chair was forced to take the action, although he was perfectly willing to have the NGOs stay in room. 'This is a very bad precedent for the future and makes NGOs worry as to what will happen at the General Assembly itself,' said Carol Lubin, one of those who was ejected."

The NGOs called on the United Nations to encourage member nations to include civil society and especially people with HIV or AIDS in their delegations, encourage member states to attend sessions they set up for dialog with civil society, and otherwise ensure that civil society can participate meaningfully in the process of developing worldwide programs for controlling AIDS.

There is particular concern that some countries want to roll back human rights in general, and some do not want to acknowledge or even name vulnerable groups (such as men who have sex with men, injecting drug users, transgenered individuals, and sex workers) because of prevailing attitudes.

Comment

The fundamental problem, we suspect, is that any successful global AIDS program is likely to threaten powerful interests: big pharmaceutical companies (fearful about patent rights), some conservative religions (threatened by sex), and even part of "AIDS Inc." (concerned that momentum for other AIDS programs might damage theirs). We suspect that political problems like these are what has kept the world from dealing successfully with AIDS so far. It will be hard to negotiate among all the special interests that hold some degree of veto power over global progress against disease.

Global AIDS: Back to the Past?

Comment by John S. James

Summary: The new affordability of treatment in poor countries made possible the unprecedented high-level mobilization against global AIDS earlier this year, by transforming AIDS in poor regions from an unsolvable tragedy to a moral issue and chance to save lives. But then a backlash turned funders against treatment -- transforming AIDS again, from a chance to save lives to a chance to sit by and watch tens of millions die. As a result, AIDS lost some political support and momentum -- not only for treatment, but for prevention as well. If treatment is a key to mobilization, we need to recognize that.

* * * * *

Just weeks ago, governments of rich and poor countries alike seemed more likely than ever before to mobilize serious commitment to controlling the global AIDS epidemic. There was growing consensus that 7 to 10 billion dollars per year -- the amount proposed by United Nations Secretary General Kofi Annan, about 1% of world military spending -- would be enough to greatly reduce the spread of AIDS, treat many of those who are ill, do operational research to make sure the programs are effective, speed the development of vaccines and new treatments, and greatly reduce the burden of tuberculosis, malaria, and other infectious diseases.

But suddenly rich-country governments in the U.S. and Europe pulled back. The U.S. contributed $200,000,000 to the United Nations fund -- about 2% of the need, about a tenth of what would have been regarded as serious. European governments so far have not contributed anything. And in the recently concluded World Health Assembly, the U.S. and European governments actively blocked proposals to help poor countries buy low-cost medicines -- on behalf of the proprietary pharmaceutical industry, which seems to fear that any plan to make patented medicines permanently affordable in poor areas would threaten its patents or ability to charge high prices in the U.S. and other rich countries.

What happened?

We suspect that one key cause of the loss of momentum on global AIDS is something that has not been discussed or recognized even by the participants.

For years it was an article of faith that public money for AIDS control in poor countries should go to prevention, never to treatment. Few said otherwise, because at $10,000 per year for drugs alone (or even $2000), HIV treatment was not going to become widely available in poor areas no matter what anyone said or did.

Some prevention advocates have long feared that treatment would out-compete prevention politically (probably because it saves the lives of identifiable people, unlike prevention), resulting in resources being misdirected to treatment of the terminally ill instead of to stopping the epidemic. But in fact, treatment gives people reason to be tested, reason to mobilize to save their own lives or their family members or friends, reason to become involved in comprehensive AIDS-control programs. It also motivates the fight against AIDS stigma, by transforming it from something unpleasant but only rarely life-threatening, to a direct threat to the lives of specific people. Some professionals have missed the fact that treatment access is a strategic cause to improve prevention and reduce the spread of HIV, as well as a humanitarian cause to save lives because it is the right thing to do.

These arguments had no consequences until recently, when generic pharmaceutical manufacturers started offering some modern combination antiretrovirals at under $500 per year. At this price widespread treatment in Africa became thinkable for the first time.

We believe this new possibility of treatment in poor regions fundamentally transformed world thinking about AIDS. Before, most of the public in the U.S., and probably other rich countries as well, basically saw the global epidemic as an unsolvable tragedy (or as a bottomless resource pit) in Africa. Tens of millions of people already infected were doomed, and nothing could be done to change that, nothing anyone did could make any meaningful difference.

But with drugs less than $500 per year, the perception of global AIDS changed from a hopeless cause to a moral issue and chance to save lives. Now people could get involved. The result was the first-ever move toward serious government commitment to control the epidemic, and other major infectious diseases -- not just through treatment, but through prevention, research, treatment, whatever was needed.

The "Harvard plan" -- a widely discussed analysis of how to provide treatment in developing countries, released in early April -- also helped to show it was doable, and at a cost amounting to "small change" in

the global economy.

But then a backlash occurred. Some prevention experts became alarmed and upset by the new momentum behind treatment. As one "international health official who asked not to be identified" told *The Washington Post*:

"It's so politically incorrect to say, but we may have to sit by and just see these millions of [already infected] people die," he said, acknowledging that this was an option that would be considered unacceptable in the developed world. "Very few public health professionals are willing to take on the wrath of AIDS activists by saying that. But a whole lot of them talk about this in private." (Global AIDS Strategy May Prove Elusive: More Funds Available, but Consensus Lacking, *Washington Post*, April 23, 2001, page A01).

We do not know to what extent anyone went to the major funders -- the handful of key staff people involved in AIDS funding in the U.S. and European governments, and major foundations -- and soured them on treatment. AIDS activists were surprised to find unexpected lack of support in Congressional offices, and to hear international-development experts new to AIDS saying the fight was to save *future* generations. One Congressional bill earmarked 10% or less for treatment, vs. 70% for prevention. Overall, there was a sudden surge in official sentiment for abandoning those in poor countries who are already infected -- and the millions more who will become infected there.

One might think that pharmaceutical companies would lobby for global treatment, providing balance. If anything, the opposite was true. Widespread treatment in poor countries might threaten their patents and high prices in rich countries -- the cash cow that supports the entire industry.

Potential donor governments seem to have responded mainly not by shifting future money from treatment to prevention, but by losing interest in AIDS. Why?

We believe that what happened is that with treatment marginalized, AIDS was transformed again -- from a moral issue and chance to save lives, to a chance to sit by and let tens of millions of people die. Government officials and their staffs are people, too; and when this happened, they lost enthusiasm for the whole project of controlling global AIDS. Other world issues are always available.

Many have said (correctly, we believe) that without hope of treatment, prevention will not work well. What has been overlooked is that without hope of treatment in poor countries, it becomes very difficult to mobilize against global AIDS in rich countries. The triple track of advocating funding for research, prevention, and treatment -- long successful for U.S. domestic AIDS programs -- should be considered for international funding advocacy as well.

As one activist put it, treatment is easier to sell than condoms. Of course the point is not to substitute treatment for prevention, but to facilitate widespread mobilization to do whatever is necessary to stop the epidemic.

We suspect that hope of treatment was the key that transformed the meaning of the global epidemic, and made possible the beginnings of the unprecedented mobilization earlier this year. When this hope was removed, the movement stalled. Rich-country governments, which had never made a commitment to a properly funded campaign against global AIDS and other infectious diseases, reverted to business as usual.

This is only a theory -- that the possibility of treatment in developing countries was central to the rise and then a sudden fall in high-level interest in global AIDS. Many theories are wrong. We urge those involved to consider this one, and see if it holds true.

If hope of treatment is key to effective political mobilization against the global epidemic -- critical to involving people in rich countries even though they are not directly affected (as they already have access), as well as people in poor ones who are directly affected -- we need to recognize that fact and design comprehensive research, prevention, and treatment programs that do not abandon those already infected.