

NEWS AND VIEWS

– Focus on challenges in HIV therapy

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New theory on HIV spread

Contrary to popular belief, people with high viral loads do not contribute the most to the spread of HIV in the long run, it is individuals with medium levels that do.

Viral load varies massively between HIV-infected people. Those with higher viral loads are more infectious but they also have a shorter life expectancy; thus, according to this study, they do not contribute the most to HIV spread.

The team of researchers found that it was individuals with a medium viral load that contributed the most to HIV spread because they are moderately infectious but normally remain asymptomatic for approximately 6–8 years before showing symptoms of AIDS. During this asymptomatic period many do not know they are infected and so do not receive treatment and may transmit the virus to a number of different sexual partners.

“Those with higher viral loads are more infectious but they also have a shorter life expectancy; thus, according to this study, they do not contribute the most to HIV spread.”

A reason for this finding, put forward by the researchers from Imperial College London (UK), is that the virus has evolved in such a way that it maximizes its chances of spreading by achieving the optimal balance between infectiousness and virulence.

Looking at a number of groups of HIV-infected people in Europe, the USA and sub-Saharan Africa, the team saw a pattern emerging whereby

those with the highest viral load were not contributing to the spread of the disease as much as those with medium viral loads.

“A reason for this finding ... is that the virus has evolved in such a way that it maximizes its chances of spreading by achieving the optimal balance between infectiousness and virulence.”

A common recommendation in sub-Saharan Africa, where effective treatment is not widely available, has been the targeting of the most infectious people to limit transmission. However, the results of the study suggest a rethink of this strategy may be necessary.

As summarized by study member Déirdre Hollingsworth: “Just being highly infectious isn’t enough, you have to live long enough to pass the virus on. This long-term view should inform public health policy.”

Lead author Christophe Fraser concluded: “We now want to see whether the virus has adapted in order to allow it to infect the most people, which seems plausible given the results of our study. This would have serious implications for public health policy, because if it is true then some strategies to prevent transmission could end up making the virus more virulent by accident. While it is too early to sound the alarm, more research to prove or disprove this theory is urgently needed. That is what we are focusing on now.”

Source: Fraser C, Hollingsworth TD, Chapman R, de Wolf F, Hanage WP: Variation in HIV-1 set-point viral load: epidemiological analysis and an evolutionary hypothesis. *Proc. Natl Acad. Sci. USA* DOI: 10.1073/pnas.0708559104 (2007).

Combination therapy key to saving HIV-infected children

With more than 2.3 million HIV-infected children worldwide, a study has been conducted to identify the best practice for treating HIV-infected children in Africa.

Led by Jeffrey Stringer, the team of researchers from the University of Alabama at Birmingham (AL, USA) found that the key factor in treating HIV-infected African children was the provision of combination antiretroviral drug therapy. In addition, using nurses and other healthcare workers is also an important factor in saving lives, particularly when doctors are in short supply. The study collected data by monitoring the health of 4975 children over a 3-year period at the Centre for Infectious Disease Research in Zambia (CIDRZ).

The team of researchers found that after 1 year of antiretroviral drug therapy there was a more than doubling of the children's CD4 count, from 12.9-

27%. A CD4 count test can identify a weakening immune system, which can put patients at increased risk of infections, including the development of AIDS. "We know from work in the US and Europe that children do well on antiretroviral drugs. But we were surprised in this study at just how high their CD4 counts went, and how quickly they went up," Stringer commented.

It was also revealed that children who received antiretrovirals noticeably increased their weight-for-age score, which is a measurement for monitoring the health of HIV-infected children, while HIV-infected children's weight-for-age score who were not receiving antiretrovirals actually worsened.

In addition, the decision by Zambian officials to allow pediatric care to be provided by nonphysicians, such as nurses and clinical officers, also contributed to saving children's lives.

Established in 1999, the CIDRZ is run by the University of Alabama faculty in conjunction with the Zambian government. It is a nonprofit clinical, research and training center that, with the help of funding from the President's Emergency Plan for AIDS Relief, the US CDC and the Elizabeth Glaser Pediatric AIDS Foundation, has enrolled thousands of patients on long-term HIV care in 50 clinics across Zambia.

“We were surprised in this study at just how high their CD4 counts went, and how quickly they went up”

Source: Bolton-Moore C, Mubiana-Mbewe M, Cantrell RA *et al.*: Clinical outcomes and CD4 cell response in children receiving antiretroviral therapy at primary health care facilities in Zambia. *JAMA* 298, 1888–1899 (2007).

Genes found to influence the speed of HIV–AIDS progression

A recently published study has increased our understanding of the genetic influence on the rate of HIV–AIDS progression

It was long thought that the viral load was the principal factor in the progression from HIV to AIDS; however, this study, led by Sunil Ahuja, adds weight to previous suggestions that there are a number of other factors influencing the disease progression rate.

By examining genetic information from over 3500 HIV-1 infected and uninfected people, the team of researchers from the University of Texas Health Science Center (TX, USA) discovered that the presence of two genes, *CCR5* and *CCL3L1*, in specific combinations affected the progression of HIV. *CCR5*

helps in facilitating HIV cell entry and *CCL3L1* is an immune response gene. Individuals who had these two genes in certain combinations showed features of HIV disease progression - reduced immune responses and greater decline in CD4 T cells.

“The presence of two genes, CCR5 and CCL3L1, in specific combinations affected the progression of HIV”

In addition, Ahuja and colleagues calculated the percentage variability in rate of progression to AIDS in HIV-infected patients for viral load and *CCR5* and *CCL3L1* variations, and found that their contributions to variability were 9 and 6%, respectively.

It is hoped that this finding will be able to more effectively predict the course of HIV disease, which would aid in the care for HIV-infected individuals.

Source: Dolan MJ, Kulkarni H, Camargo JF *et al.*: *CCL3L1* and *CCR5* influence cell-mediated immunity and affect HIV–AIDS pathogenesis via viral entry-independent mechanisms. *Nat. Immunol.* DOI: 10.1038/ni1521 (2007).

New drug factory raises hope of increased access to HIV therapy

Drug factory opens in Uganda to help in the fight against AIDS

Uganda is a relative success story when it comes to combating HIV/AIDS in Africa. Between 1990 and 2001 it cut its HIV infection rates from approximately 15 to 5%. However, the word relative is important here – there is evidence that not only is infection on the rise again in this country but it has also been stated by the WHO that only 41% of Ugandans who need antiretroviral therapy actually receive it.

“I expect the quality of life of people living with HIV to improve, and I expect the government to be able to buy more drugs than before.”

Hopefully, this may change in the near future thanks to an HIV/AIDS drug factory being opened in the country's capital, Kampala. A partnership between the Indian pharmaceutical giant Cipla, one of the world's leading producers of generic drugs, and the Ugandan-based Quality Chemicals company will produce generic antiretroviral HIV drugs and antimalaria drugs; it is hoped that these drugs will be available by January 2008.

Sam Okware, a spokesman for Uganda's health ministry commented: “Actually it is long overdue because you see these are generic drugs. This is epicenter of HIV/AIDS, East and Central Africa

are the epicenter, so it is very welcome. We are very happy as a country. I expect the quality of life of people living with HIV to improve, I expect now the government to be able to buy more drugs than before because now the drugs are available locally so the cost of transport will not be there. I also expect many of the people living with HIV/AIDS now to access this drug directly, not through the healthcare system, through the private system.”

He continued: “The only other fear we have is that as we move forward there may be newer drugs, which are coming and it is important that they integrate the new discoveries in what is existing right now. The whole science of HIV/AIDS, especially drugs, is always evolving, so we need to hope that they will be able to incorporate new remedies into their current plan.” This factor is a very real one owing to new Indian patent laws that have made it more difficult for generic drug producers to replicate the most up-to-date drugs.

A representative for ActionAid voiced another concern that will need to be overcome in Uganda's fight against HIV/AIDS: “The important thing is for the tablet to get on to the table. The challenge is to make sure that the production is followed by a good distribution system that makes sure that the drug can reach all corners of the country.”

Source: BBC News www.bbc.co.uk

HIV/AIDS cases in Korea top 5000

Between January and September 2007 there were 575 new HIV/AIDS cases in Korea, bringing the number of known infected individuals in the country to over 5000. The total figure reported by the Korea Center for Disease Control and Prevention (KCDC) of people who have tested positive for HIV/AIDS in the country is 5155, of which 686 have AIDS. There have been 938 deaths from the disease.

The KCDC also released the distribution of new cases in terms of age and gender. Most individuals of newly reported cases were between 20 and 49 years of age, with the 30–39 years bracket being the highest age group. In addition, 93% of the new cases were men.

The KCDC has identified and confirmed the route of infection for 354 of the 575 cases, of which all were a result of sexual intercourse – 35% being homosexual intercourse. The agency had stressed the importance of early diagnosis and treatment for this disease, and for the use of condoms.

Source: Digital Chosunilbo (English Edition); <http://english.chosun.com/w21data/html/news/200710/200710190027.html>

Urgent investment for HIV/AIDS prevention in Vietnam

It has been revealed that Vietnam is investing 1352 billion Vietnamese dong (US\$84.5 million) in HIV/AIDS prevention. To be spent between the years 2007 and 2010, the money is proposed to have a number of uses, including not only preventing infections among people in high-risk groups but also the spread of the disease from them to community, and intensifying training for health staff.

This investment is urgently needed because, as of the end of August this year, the Health Ministry in Vietnam reported that there were 128,367 HIV-infected people in the country, of which 25,219 were AIDS patients. Furthermore, from the total number of infected individuals, there were approximately 14,000 deaths. Some feel these figures are far too low and that the actual number of HIV-infected individuals has been estimated to be as high as 280,000, with 110,000 of them having AIDS.

Source: The Hindu News Update: www.hindu.com/the-hindu/holnus/003200710130346.htm

TRIAL WATCH

Shock at the ending of HIV vaccine trial

Company: Merck and Co.
Drug: HIV vaccine V520
Indication: HIV prevention
Trial: Phase II

The announcement at the end of September by Merck and Co. Inc. to stop their HIV vaccine V520 trial was a huge surprise for the HIV industry. The international Phase II clinical trial had been running for 3 years and the decision to pull it was because the vaccine did not appear to be working; in fact, more people in the vaccinated group became infected with the virus than those receiving a placebo.

The worrying problem for HIV-vaccine researchers was that, according to Mark B Feinberg, Merck's vice president for Medical Affairs for Vaccines & Infectious Diseases, approximately 90% of vaccine studies use major elements of Merck's approach. Thus, is it possible that all HIV vaccines are using the wrong theory?

"I must admit I was shocked when I saw the outcome. It was the most promising vaccine we had," said Hildegund CJ Ertl from the Wistar Institute (PE, USA).

However, while the community may be shocked, it is currently too early to know what Merck's study means. Light might be shed once the company collects its data and shares its results, which it does promise to do.

Researchers appear to be remaining optimistic, such as Gary J Nabel, the director of the Vaccine Research Center of the NIH who said: "To paraphrase some of my colleagues, the trial shows a failure of a specific product but not a failure of the concept."

Owing to lack of investment in the 1990s there have only been two completed HIV vaccine trials; however, the funding for a vaccine has risen since then, from US\$150 million to \$759 million, resulting in approximately 30 vaccines entering human trials in recent years.

Despite various people's hopes that the other vaccines will end in different, better results than the Merck trial, John W Shiver, who heads Merck's basic research in vaccines, said he did not think any current approach would work. He thought a new burst of creativity was needed.

Source: Merck Press release: www.merck.com/newsroom/press_releases/research_and_development/2007_0921.html

DRUG WATCH

Raltegravir approved by the US FDA

The US FDA has approved the use of raltegravir (Isentress™) for treating HIV-1 infected patients who are resistant to other antiretroviral drugs. They have approved the use of this drug in combination with other antiretroviral agents in treatment-experienced adults who have both evidence of viral replication and HIV-1 strains that are resistant to multiple antiretroviral agents.

Produced by Merck & Co., raltegravir is the first of a new class of HIV medicines, known as HIV integrase strand transfer inhibitors. The drug has been approved in a tablet form and works by interfering with an enzyme that is needed for the virus to multiply.

Based on data from two double-blind, placebo-controlled studies in 699 HIV-1 infected adults with histories of extensive antiretroviral use, the FDA found that the drug not only reduces blood levels of HIV but may also increase CD4 T cells.

The most common adverse events reported were diarrhea, nausea and headache. The FDA have issued a caution for people who either have muscle conditions or take other drugs that can contribute to muscle problems because some people in the clinical tests developed elevated levels of a muscle enzyme.

In addition, the agency warned that the drug's safety and effectiveness have not been assessed in pregnant women or in people less than 16 years of age; furthermore, its long-term effects are not known.

"This is an important new product for many HIV-infected patients whose infections are not being controlled by currently available medications," said Janet Woodcock, the FDA's deputy commissioner for scientific and medical programs, chief medical officer and acting director, Center for Drug Evaluation and Research.

Source: FDA News: www.fda.gov/bbs/topics/NEWS/2007/NEW01726.html