

MICE TIMES

Significantly fewer AIDS deaths thanks to research Animal models are indispensable

Thirty-three million people infected worldwide, 2 million deaths every year and around 2.7 million new infections every year: the spread of the human immunodeficiency virus (HIV) remains dramatic.

Nevertheless, experience with the virus that causes acquired immune deficiency disease (AIDS) shows what medical research can achieve within a short time. While the life expectancy of an infected person was about 12 months before the introduction of the first HIV medicine in 1987, HIV infection today has become a treatable chronic disease thanks to numerous different medicines, at least in countries with a financially strong health system.

Research must be continued

Yet this virus, which was discovered at the start of the 1980s, is fiendishly clever: in a hitherto unparalleled manner it knocks out the body's immunological defense system that is responsible for eliminating disease pathogens.

To develop a protective vaccine or cure the disease and finally drive the virus out of the body for good - which treatments to date do not do - further research is needed to establish exactly what the versatile virus does in the human body.

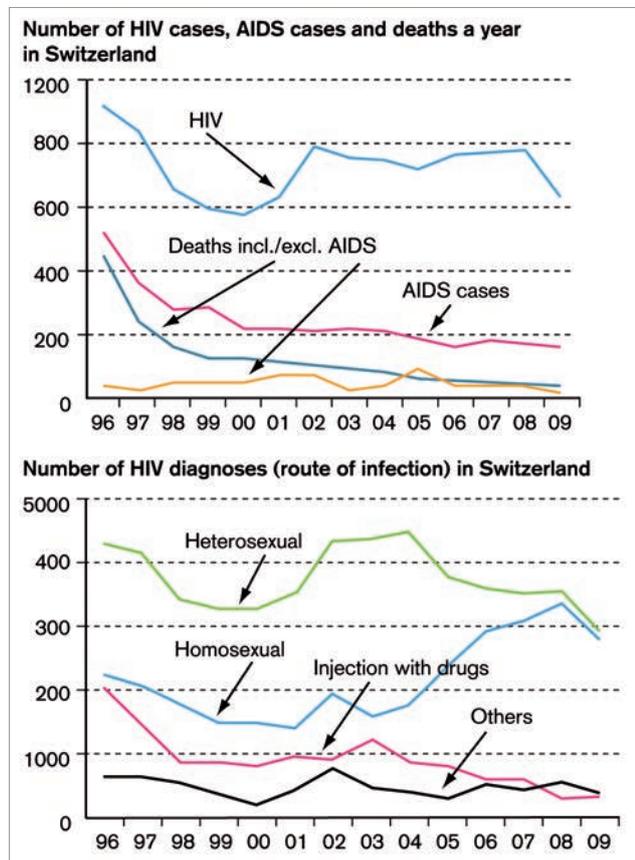


Fig. 1: BVG statistics

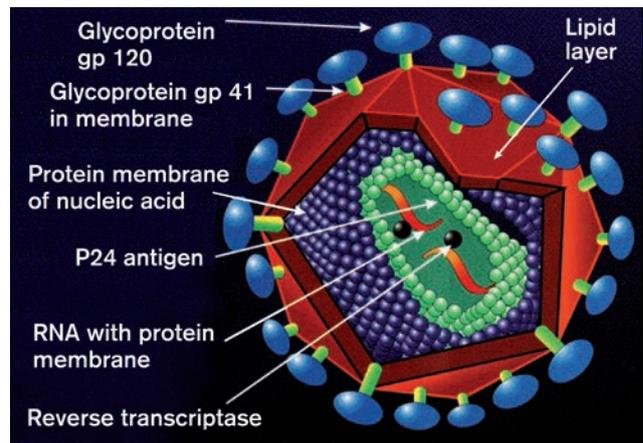


Fig. 2: Model of HIV



Fig. 3: Mature HIV particle immediately after release from human cells

Animal models are indispensable in basic virological research

HIV research can be seen as like working on a gigantic jigsaw puzzle: to create a complete picture you are reliant on cooperation with different research disciplines and methods. Studies in patients are just as important as studies with cell cultures or experiments in different animal models. «Basic virological research without animal models is not possible», says Roberto Speck, doctor and HIV researcher at the Clinic for Infectious Diseases and Hospital Hygiene in the University Hospital Zurich.

Although a great deal of knowledge about virus replication and the interplay with building blocks in the host cell could also be obtained in cell cultures, «real life» and thus also the events during a virus infection take place in the interplay of various cell types in body tissues and organs, says Roberto Speck. In the case of HIV, studies in monkeys immediately suggest themselves, because the AIDS pathogen was originally transmitted to humans from African chimpanzees. Many primate species are naturally often infected with a virus that is closely related to HIV, namely the simian immunodeficiency virus (SIV), but without showing any signs of disease.

Studies in macaques have yielded little in the way of findings

However, it has been known since the mid-1980s that SIV infection in a non-natural host, such as the macaque monkey, induces an AIDS-like disease. As a survey by the science journal *Nature* revealed last year, the overwhelming majority of HIV researchers also consider that the «macaque model» will also be indispensable in the future for studying the development of the disease and developing possible candidates for vaccines or vaginal microbicides.

What exactly takes place during the transmission of the virus in the female genital tract and how the virus can be therapeutically stopped here are questions that cannot be answered in cell culture but only through studies in an organism, says Thomas Klimkait from the Institute for Medical Microbiology at the University of Basel. Important findings on how and when HIV is transmitted from mother to child during pregnancy and what treatment should follow as a result were obtained with monkey infection models, amongst other things. Starting the present treatment strategy as early as possible with an antiviral therapy was also established partly on the basis of studies in macaques.

One of the first HIV researchers, Françoise Barré-Sinoussi, described in the lecture she gave at the Nobel Prize ceremony for her and Luc Montagnier two years ago a further enormous opportunity offered by monkey studies: «Most naturally infected African primates do not develop AIDS; they are therefore a unique model for studying endogenous protective mechanisms against AIDS.»



Fig. 4: Vervet monkeys do not develop AIDS

«Without research in mice we would know much less today about the various immune cells and the complicated way in which they interact.»

Mice are also helpful

HIV research is also unthinkable today without the mouse, although at first glance it appears highly unsuitable – since it is not even susceptible to the virus. «With the help of mouse experiments we can exactly study the function of molecules, such as those considered to be suitable targets for therapeutic strategies», explains Huldrych Günthard from the Clinic for Infectious Diseases and Hospital Hygiene at the University Hospital Zurich. Nature does not always play into the hands of researchers as it has with the development of the HIV medicine Maraviroc.

As a result of a genetic mutation, about one percent of Europeans does not carry an intact CCR5 molecule. This molecule is actually involved in the communication of cells, but also serves as a co-receptor for a certain HIV strain, as an additional doorway, so to speak, through which immune cells can enter. Humans without a functioning CCR5 are healthy and cannot be infected with R5 viruses, which make up a large proportion of the circulating human immunodeficiency viruses. For this reason, CCR5 was selected as a pharmaceutical target for blockade.

Studies directly in humans would be ethically unacceptable

In addition, however, studies in mice also played a part in the approval of Maraviroc three years ago for HIV therapy. Mice whose CCR5 gene has been experimentally switched off also showed completely normal development and remained healthy. Additional evidence that CCR5 blockade by a medicine would not induce any serious side effects.

«There are things, such as knocking out a gene, that cannot be done in humans», says Günthard, who is engaged in HIV research himself, albeit with

human sample material from day-to-day clinical practice, but nevertheless he would not be without the synergy effects that come from animal models.

Other research disciplines also benefit

The last 20 years have seen a boom in knowledge in the field of immunology thanks to HIV research.

Without research in mice we would know much less today about the various immune cells and the complicated way in which they interact. HIV research has therefore been of benefit to other areas, such as transplantation medicine, says Huldrych Günthard. After all, the immune deficiency and hence susceptibility to essentially harmless infectious pathogens in AIDS patients is similar to the situation in humans who live with a transplanted organ and whose immune defense mechanisms are therefore suppressed with medicines.

In the field of basic research on HIV Annette Oxenius from the Institute of Microbiology at the Swiss Federal Institute of Technology (ETH) Zurich actually feels the time of the mouse model is only just arriving. «Today we are able to incorporate human blood-forming cells into a mouse body so that the animal can form a human immune system», says Oxenius.

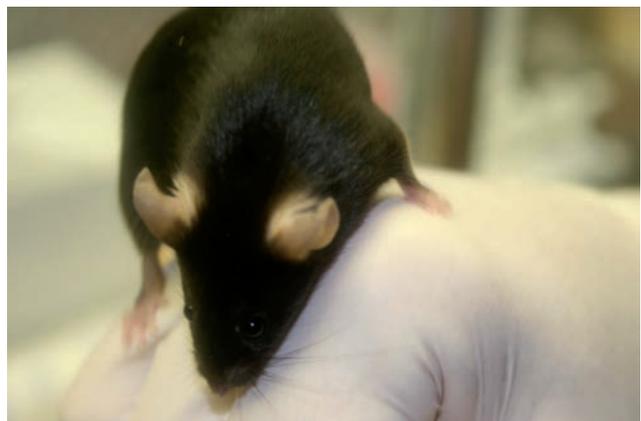


Fig. 5: Black laboratory mouse

«There is no ideal animal model for HIV – each one has its possibilities, but also its limits.»

The mice can then be easily infected with HIV. In Zurich the working group headed by Roberto Speck is working with this mouse model. The researchers want to use it to find out, amongst other things, in which cells the virus hides, for example, when it is prevented by antiviral therapy from actively multiplying.

Only many diverse paths will lead to the goal

If we manage to lure viruses out of their hiding place and then remove them, the disease could be not only suppressed but also cured. To achieve our goal, however, we have to go down diverse paths. There is no ideal animal model for HIV – each one has its possibilities, but also its limits.

«In HIV research we have to be open to different research disciplines and to respect one another», says Roberto Speck. It is not an «either/or», but only different ways of looking at the extraordinary phenomenon of HIV that have brought success in the past and will do so in the future. «We must not become immersed here in a parallel world that loses sight of the actual concerns of research, but must keep asking: what is really important for the disease in humans», says Huldrych Günthard.

It would be ideal if we could understand the complicated mechanisms of a body without stressful animal experiment. Unfortunately that is not yet possible today, although researchers have for a long time conducted countless experiments with cells and tissues and, in the age of system biology, are also increasing our knowledge by means of computer simulation. But the dilemma will remain for a long time to come: basic research without experiments in animals would mean abandoning any medical progress. Mausblick aims to explain why and therefore reports on medical success stories that were only possible thanks to animal experiments.

Mausblick is published in collaboration with the Basel Declaration. www.basel-declaration.org

Sources:

Fig. 1: Swiss Federal Office of Public Health (FOPH)

Fig. 2: http://biology.kenyon.edu/slonc/gene-web/Lentiviral/hiv_image.jpg

Fig. 3: Photo Prof. Thomas Klimakati and Dr. Jan Orenstein

Fig. 4: http://www.herz-fuer-tiere.de/uploads/pics/Gruene_Meerkatze_Brodmann.jpg

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