



# The transparent virus

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HIV test

Medicine for the future

New HIV test allows individualized therapy

**HIV has many faces. The AIDS-triggering virus is able to reproduce itself, making numerous changes to its genetic code in the process. As a result, it renders medicines ineffective. Bayer's Trugene® HIV-1 Genotyping Test decodes the genetic material of the virus and shows up resistances, thus providing a basis for individualized HIV therapy.**

Every patient has his or her very own form of a disease, even if the initial diagnosis is the same. This is particularly true when it comes to HIV infections. A patient's personal and medical history often plays a major role and has to be taken into account as far as possible when deciding on the best course of treatment. In each individual case of infection, HIV (human immunodeficiency virus) represents a new unknown quantity.

This is because the virus is forever reinventing itself on a molecular level. All organisms, including viruses, comprise genetic material which provides the blueprint – a type of construction manual – for the corresponding proteins. Changes to the genetic material



HIV test:  
Diana Pabilona  
prepares samples  
for the new  
Trugene® HIV-1  
Genotyping Test.

are known as mutations and can alter the protein structure.

HIV has one of the highest known mutation rates. The virus invades certain human immune cells and settles there by incorporating its genetic material into the genetic code of the infected cell. This sequence is then used as a pattern for the production of new viruses. Two of the enzymes that are directly involved in the replication of the pathogen work very imprecisely, and as a result the virus mutates. On average, the genetic material of each newly created virus differs from the original one that infected the cell by at least one position.

"With this type of infection, new viruses are being generated all the time,"

says Dr. Peter Knüppel, Senior Vice President of Bayer's Diagnostics Division in Berkeley, California. "The pathogen tries to evade the effect of drug therapy by mutating." Generation after generation of viruses self-replicates, leading to considerable genetic diversity. If treatment is continued, the severe pressure of selection means that only the immune pathogens survive. In some cases, it only takes a few weeks before the original type of virus is replaced by a resistant strain.

**Active ingredients that cannot find the target are ineffective**

"It is estimated that around ten percent of new infections are now caused

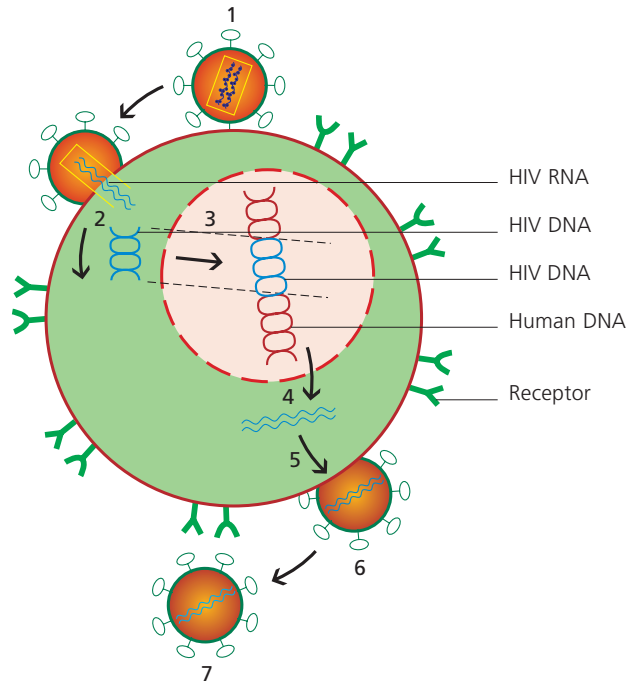
by viruses that already have resistances," reports Dr. Rainer Ziermann, Head of the HIV Scientific Affairs Department at Bayer HealthCare's Diagnostics Division in Berkeley.

AIDS – the final stage of HIV infection – is still an incurable disease and, in nearly all cases, ends fatally. However, there are now more than 20 products available to treat HIV.

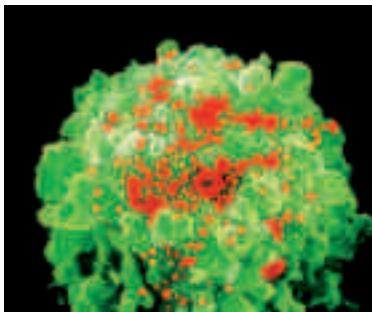
Virtually all of these products very specifically target one of the two main enzymes of the virus: reverse transcriptase and protease. Just like a lock and key, the active ingredients have to interact with the enzymes in order to inhibit or block their function. This complex interplay is often disrupted by even the most minor changes to the enzyme

## The HIV life cycle

All viruses have to invade host cells in order to be able to produce more viruses. In the case of HIV, the pathogen docks onto certain immune cells (1) and injects its genetic material (2). This is incorporated, via an intermediate stage, into the human genetic material in the cell (3). The viral genetic material is read together with that of the cell so that the corresponding proteins can be produced (4, 5). The new viral particles bud off from the cell (6, 7).



Deadly: the human immunodeficiency virus (HIV) viewed through an electron microscope.



structure. If an active ingredient can no longer find its target molecule, it loses its therapeutic effect.

In view of the high mutation rate of HIV, conventional therapy relies on at least two products from different categories of drugs. This combination therapy is based on the assumption that the virus is more likely to become resistant to one drug than to two or more at the same time. "If, however, the viral load continues to grow, the combination of medicines has to be changed," explains Knüppel.

It was this predicament that prompted scientists to develop a viral test that would allow them not just to determine the amount of virus in the blood but also to assess the type of muta-

tions that may have occurred. The Trugene® HIV-Genotyping Test is one of the molecular tests that have only quite recently become available on the market but have already revolutionized the diagnosis of some diseases: they allow doctors to come up with a tailor-made therapy, or change a course of treatment that is no longer effective. This type of detection method is currently the fastest-growing segment in the diagnostics market.

The Trugene® HIV-Genotyping Test is now being recommended more and more for new HIV patients who have not yet undergone a course of antiviral treatment. The technical procedure is very simple for doctors. All they have to do is send their HIV patients' plas-

ma samples – blood without proteins – to a laboratory.

### The Trugene® HIV Test identifies mutated viruses

"Lab technicians have to attend a course held over several days at a training center," explains Dr. Susan Bromley, Product Development Director for Molecular Products at Bayer HealthCare's U.S. Diagnostics Division in Walpole, Massachusetts. "Then they analyze a few samples in their own lab in order to acquire their accreditation. Only then are they permitted to offer evaluation of the Trugene® HIV-Genotyping Test." There is usually no problem at all with the procedure:

Diagnostics expert: Dr. Peter Knüppel from Bayer HealthCare.





Fiberglass capillaries are used for fragment analysis and also, for example, for separation during DNA sequencing.

"All important reagents are already included and the materials are handled according to a standard protocol." Lab workers isolate the HIV genetic material from the plasma sample and decipher certain parts of it. The DNA sequence that encodes protease and a section of the reverse transcriptase enzyme is thus available in its decoded form for each component part. These sequences are compared with a segment of the viral genome without mutations, the "gold standard". Any deviations in the genetic code, as regards the sequence of its molecular letters, are then documented.

### The resistance report facilitates the choice of drugs

Special Bayer software then checks whether these are known mutations and whether they are already associated with resistance to drugs. The results of this evaluation are set out in detail in a resistance report, which is sent to the attending doctor. In addition to the most important mutations, this report also lists all HIV medicines. Although this document does not provide the doctor with a ready-made treatment plan, it does contain essential information for the start or continuation of a patient's therapy. Experts have also been drafted in to form a committee especially for the Tru-

gene® HIV-Genotyping Test. Their job is to define what is called the algorithm and compile a list of mutations with their corresponding drug resistances. "This 'consensus panel' composed of 14 international experts works completely independently of Bayer," reports Ziermann. "They usually meet after major HIV conferences and pool their latest findings." Their work feeds into a final report which requires the approval of the U.S. Food And Drug Administration (FDA). "An extraordinary amount of work goes into this process," says Ziermann. But it is worth it: thanks to the panel and the regularly updated algorithm, viral sequences can be evaluated according to the very latest research. And this in turn means that Bayer's HIV test occupies an important position in the market. It has also achieved a very special accolade: the Trugene® HIV-Genotyping Test is the first diagnostic test of its kind to have gained the approval of the FDA. And it has not even reached its full potential. "We're currently adding more genomic regions, so that in future we'll be able to sequence more of the HIV genome," says Bromley. "There are still so many ways this technology can improve therapy for patients."

[www.unaids.org](http://www.unaids.org)

The United Nations reports on the global HIV situation.

### Rising death toll

Today more and more people across the globe are living with HIV or AIDS. But the number of patients dying of the infection is also on the increase.

