# AIDS, an epidemic in evolution

**Dr. P.H.J. Frissen**

## Etiology

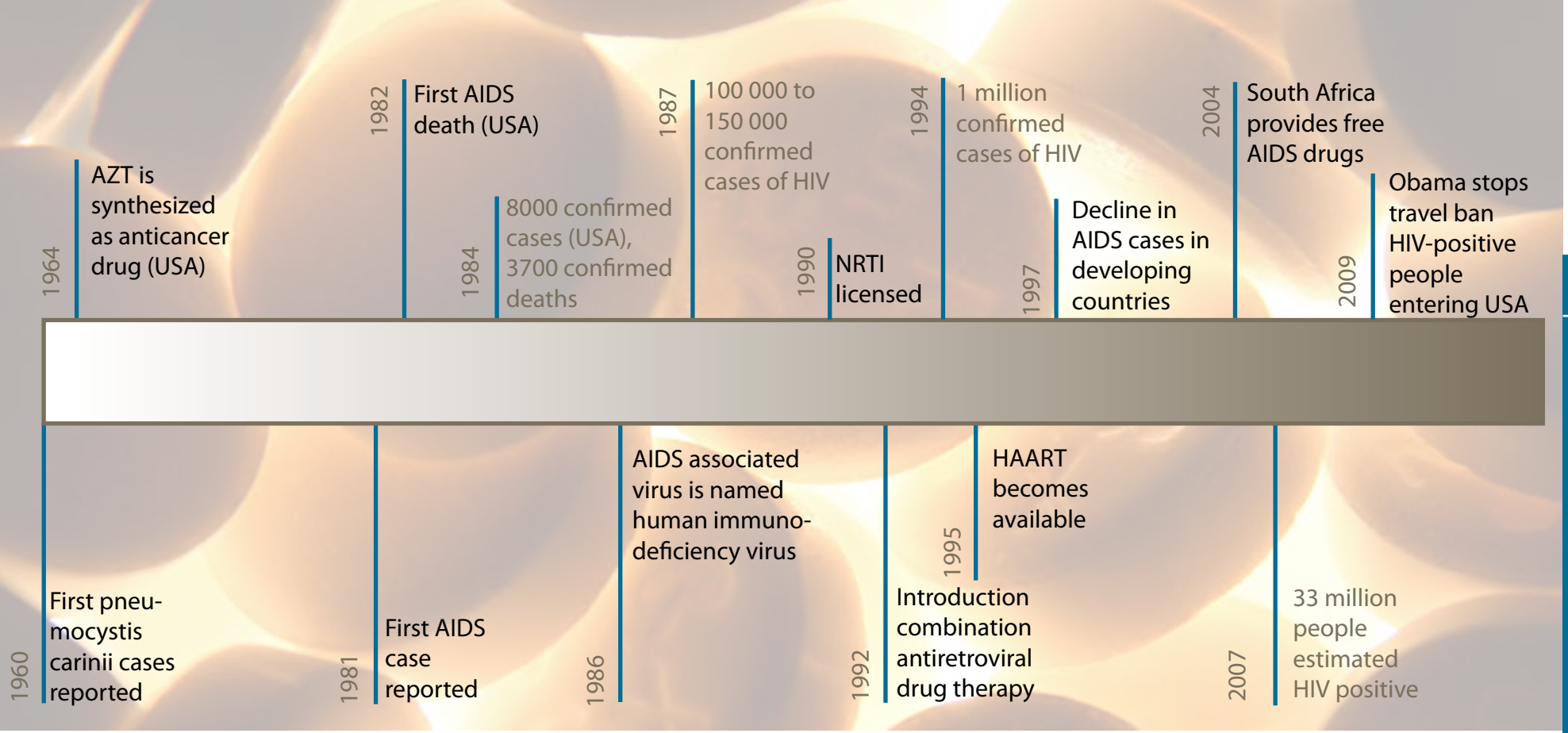
A new and distinct clinical entity, Acquired Immunodeficiency Syndrome (AIDS), was first reported in 1981. Various cases of Pneumocystis carinii pneumonia (PCP) and aggressive Kaposi's sarcoma were recognized in previously healthy homosexual men. An association with lifestyle habits was suggested such as frequent exposure to sperm, rectal exposure to sperm and to amyl of butyl nitrate (*poppers*). Soon, it appeared that other populations including intravenous drug users and recipients of blood products (e.g. haemophiliacs) were also affected, directing attention towards immunologic or infectious causes. Affected subjects had inverted CD4/CD8 T-cell ratios even before they had clinical overt AIDS. No other laboratory tests were able to identify infected patients.

In 1983, Montagnier (Nobel Prize) and Barré-Sinoussi detected a virus particle in a lymph node from an AIDS patient (lymphadenopathy-related virus or LAV). This virus was subsequently cultured by Gallo et al.. It was considered to be a retrovirus (human T-lymphotropic retrovirus type III or HTLV-III) because of its ability to infect T helper lymphocytes and the same routes of transmission as HTLV-I and II. In 1985, antibody assays became commercially available which was major progress in the detection of the disease. In 1986, LAV and HTLV-III, which appeared to be the same lentivirus, were renamed: human immunodeficiency virus (HIV). The most widespread variant is HIV type I while type II is mainly prevalent in Western Africa. HIV-1 and type 2 are both capable to cause AIDS but type 2 is less easily transmissible and less pathogenic.

The origin of HIV has been questioned by the scientific community but also by public organizations sometimes accusing authorities of deliberate spread of HIV. Researchers have demonstrated links to certain simian immunodeficiency viruses (SIV) in monkey populations in Central and Western Africa. HIV might have been transmitted to humans by eating bush meat or by bites from infected monkeys. HIV is possibly transmitted to man at the end of the 19th or early 20th century and spread after the mid-fifties by traveling, urbanization, sexual habits and vaccination campaigns. Retrospectively the first documented AIDS case was in 1959 in Manchester (UK). In 1994, one million HIV-infected patients were documented worldwide. This number rose dramatically thereafter.

## Treatment

During the early years (1981-1987) no antiviral therapy was available. Treatment was directed against opportunistic infections. Some of these infections, i.e. cryptosporidiosis and microsporidiosis, were untreatable. Treatment outcomes of AIDS-related malignancies (Kaposi's sarcoma, non-Hodgkin lymphoma) were very disappointing. A major progress was the use of daily low-dose cotrimoxazol as primary PCP prophylaxis in




patients with CD4 counts below $200.10^6$/l, which strongly reduced PCP (the most common opportunistic infection). 40-50% of the patients died every year of various concurrent HIV-related diseases. 25-30% developed AIDS-dementia-complex. Patients sometimes had widespread and mutilating Kaposi's sarcoma. The median survival after AIDS diagnosis was nine months.

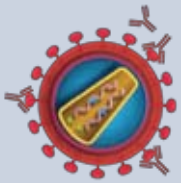
In 1987, the first antiretroviral agent zidovudine became rapidly available. This agent prevented AIDS-dementia complex and produced a survival benefit of about six months. In 1990, two other nucleoside HIV reverse transcriptase inhibitors (NRTI) were licensed, didanosine and zalcitabine. Zidovudine combined with either didanoside or zalcitabine offered about four to six months survival benefit compared with monotherapy, but no permanent success.

Major developments were made in the early nineties. By developing quantitative PCR of HIV in plasma, proper monitoring of the treatment effect was possible from 1995 onwards. Since then, the treatment goal is to achieve an undetectable plasma viral load (< 50 HIV-1 RNA copies/ml). Subsequently, CD4 T-cells show a natural recovery.

In 1996, the HAART (highly active antiretroviral therapy) era started. With a triple combination of two NRTIs and a new class of HIV-protease inhibitors sustained clinical, immunological and virological results were

**HIV might have been transmitted to humans by eating bushmeat or by bites from infected monkeys**

## AIDS facts



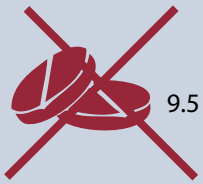
33.4 million people live with HIV worldwide

2 million people die from AIDS every year

430 000 children on antiretroviral prophylaxis

23 antiretroviral compounds are licensed

4 million people in developing countries receive treatment for HIV



9.5 million people are still in need of treatment

achieved. Initially, these regimens were very demanding: high pill burden, food restrictions and multiple dosing. The development of new compounds, drug classes (non-nucleoside RTI's, fusion inhibitors, HIV integrase inhibitors), fixed drug combinations and pharmacologic boosting of protease inhibitors by inhibiting their metabolization in the liver have led a major simplification of the drug regimens. The current first-line regimen consists of once daily one triple-drug tablet (Atripla®). Nowadays, a total of 23 antiretroviral compounds are licensed.

The life expectancy and quality of life of AIDS-patients have improved dramatically. Still, there are some drawbacks. Treated patients may develop stigmatising lipodystrophy due to the treatment. The causative drugs (e.g. stavudine, indinavir) are now avoided. Recently, an increase in morbidity and mortality from cardiovascular disease, diabetes, osteoporosis, hepatitis and malignancies is noted. This may be prevented by starting HAART at higher T-cell counts (currently > $350.10^6$/l). Special attention should be paid to drug interactions, e.g. tuberculostatics, statins, and St. Johns wort. Finally, HAART has to be taken lifelong and continuously and requires optimal adherence (>95%) to prevent development of resistance.

Stichting Wetenschap en Onderzoek Interne Geneeskunde (SWOIG) is a dutch foundation established by the department of Internal Medicine in the Onze Lieve Vrouwe Gasthuis (OLVG) in Amsterdam. It supports scientific related projects, education programmes, as for HIV consulents, and scientific meetings, financially. Global Medicine 10 is supported by SWOIG.

## Challenges

At present, vaccine trials were very disappointing and research is halted. In the western world, the aging of HIV patients will pose new challenges. However, the greatest challenge is to provide medication and monitoring facilities to resource-limited settings.

## About the author

Dr. P.H.J. Frissen is internist in the Onze Lieve Vrouwe Gasthuis Amsterdam and specialized in infectious diseases.

## Further reading


- Gottlieb MS, et al. PCP and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired immunodeficiency. N Engl J Med 1981: 305: 1425-30.
- Barré-Sinoussi F, et al. Isolation of a T-lymphotropic virus from a patient at risk for acquired immunodeficiency syndrome. Science 1983: 220: 868-71.
- Fischl M,et al. The AZT Collaborative Working Group. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex: a double-blind placebo-controlled trial. N Engl J Med 1987; 317: 185–191.