editorial

Stefan H.E. Kaufmann

Tuberculosis and AIDS – a devilish liaison

"We cannot fight AIDS unless we take on tuberculosis as well."

Nelson Mandela at the International AIDS Conference, Bangkok, 2004

One hundred and twenty-five years ago on 24 March, the tubercle bacillus was discovered. The pathogen is an acid-fast bacillus that is highly resistant to various adverse effects including host defense mechanisms, disinfectants and conventional antibiotics. In a host with a competent immune system, the bacillus persists long-term without apparent harm and absence of transmission; however, once the immune response is weakened, the protracted course of trench warfare is transformed into an aggressive assault allowing for massive growth of bacteria, exceeding a trillion (10^{12}) organisms, which are then transmitted through the air to other individuals [1].

Biomedical achievements between 1882 and 1952 have provided tools for diagnosis, prevention and therapy of tuberculosis leading to a remarkable decline of the 'White Plague' in the Western world. In addition, improved living conditions significantly contributed to this decline. Thus, European countries have seen a reduced morbidity and mortality of tuberculosis in the past 100 years.

Today, tuberculosis remains a poverty-related disease, which is most prevalent in developing countries. Although intervention measures for tuberculosis are far from satisfactory, it could have been expected that the end of the 20th century would have witnessed successful control of the White Plague. Yet, today, 9 million individuals still develop tuberculosis annually, of whom 2 millions die [2]. This is largely because of the introduction of another infectious agent 26 years ago, the Human Immunodeficiency Virus (HIV) [3,4]. Today HIV/AIDS is the number one killer amongst all infectious agents claiming 3 million deaths annually [5]. HIV is transmitted through body fluids, mostly through sexual intercourse. By infecting $CD4^+$ T cells, central regulators of the immune response, HIV causes immunodeficiency resulting in high susceptibility to opportunistic microbes such as *Pneumocystis jirovecii* and *Cryptococcus pneumoniae*, which rarely cause disease in immunocompetent individuals. Similarly, the immunodeficiency caused by HIV transforms the latent persistence of *Mycobacterium tuberculosis* in the immunocompetent individual into a horrifying assault [3,4]. Conversely, *M. tuberculosis* promotes development of AIDS because continuous activation of immune cells by latent infection increases replication of HIV.

Roughly 15 million people are already coinfected with HIV and *M. tuberculosis* worldwide and 2 million new cases of coinfection are added each year. HIV is the cause for the high mortality of tuberculosis in Sub-Saharan Africa. Due to HIV, infection with *M. tuberculosis* has reached a menacingly high level – one that would continue even if HIV would suddenly disappear, which unfortunately is unlikely in the near future. Moreover, incidences of tuberculosis are also becoming more frequent in Europe, notably in the East. Globally, the situation is worsening because of the increasing incidences of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis [6].

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A devilish liaison

Tuberculosis and AIDS have formed a devilish liaison in which HIV fuels tuberculosis outbreak that in turn acts as executioner. Unfortunately, this is not the end of the story. Although the current vaccine against tuberculosis, Bacille Calmette Guérin (BCG) does not protect against pulmonary tuberculosis, the most prevalent form of the disease in adults, it is protective against miliary tuberculosis in newborn [1]. Hence, BCG is routinely given to newborns as part of the expanded program of immunization. BCG is an attenuated live vaccine that can disseminate in immunocompromised individuals resulting in a disease sometimes termed BCGosis. Although there is no compelling evidence that HIV^+ newborns develop BCGosis more frequently than HIV^- newborns, BCG vaccination is not recommended. Therefore unfortunately, these babies suffer not only the risk of developing AIDS but also an increased risk of tuberculosis. Clearly, a vaccine is needed that is not only more efficacious than BCG but also safer [1].

Another burning issue is the increased incidence of the Immune Reconstitution Inflammatory Syndrome (IRIS) during antiretroviral therapy (ART) or highly active antiretroviral therapy (HAART) [7]. IRIS develops after reduction of the HIV burden through ART or HAART and can lead to a paradoxically strong restoration of the CD4 T cell response, frequently of antigen-specific T cells directed against *M. tuberculosis*. This often promotes outbreak of tuberculosis or exacerbates existing disease.

To this medical issue a social component must be added. Often HIV and tuberculosis are treated as separate diseases even when they occur in one patient. This practice of unhealthy separation should not be continued, particularly as IRIS is not the only complication of drug therapy of tuberculosis and AIDS [4,8]. Drug interactions and shared drug toxicities further added to this problem. Clearly novel combination therapies need to be developed that would avoid side effects because of treating tuberculosis and AIDS in patients as single entities. In this issue of *Drug Discovery Today*, Pepper *et al.* [8] describe the multiple challenges of novel combination therapies for treatment of AIDS and tuberculosis in a single patient.

What went wrong?

One hundred and twenty-five years after the discovery of the tubercle bacillus, we still use the diagnostics developed at that time, we still place our trust in a vaccine in use for more than 85 years and on drugs developed between 1945 and 1975 [9]. Today, these measures are insufficient. Current diagnoses miss a large proportion of tuberculosis cases, notably in patients coinfected with HIV; the BCG vaccine fails to protect against adult pulmonary tuberculosis and rising incidences of MDR and XDR tuberculosis reveal that our drug armamentarium has been largely exhausted [6]. Unfortunately, our failure to control tuberculosis adequately and hence allowing its exacerbation through HIV/AIDS is a story of ignorance. Of the ca. 1400 new drugs approved in the final quarter of the last century, only 3 were for tuberculosis [9]. Within a quarter of the century, state-of-the-art tools have become available for early diagnosis of HIV infection as well as sophisticated drugs for the prevention of AIDS, though not for sterile eradication of HIV. It has been through HIV/AIDS that the threat of infectious diseases in general has re-entered the radar screen of global health. Unfortunately, this awareness has not been translated into increased drug-discovery activities for tuberculosis, as yet.

What can be done?

Novel diagnostics, therapeutics and preventives are urgently needed for both HIV/AIDS and tuberculosis. At all levels, from basic research to drug discovery to field trials, researchers, clinicians and funding organizations alike must keep in mind the one patient who suffers from both diseases [3,4]. Intensive efforts in research and development have produced highly effective drugs to treat HIV/AIDS and these efforts must continue. At the same time, incentives are urgently required for tuberculosis research [10,11]. These should include earmarked funding for public/private partnerships such as the Global Alliance for TB Drug Development and a guaranteed market for drugs with an affordable price tag, probably accompanied by a two-tiered price system for developing and industrialized countries. In order to deliver drugs to those who need them most at an affordable price, stratagems are needed to avoid conflicts because of the unclear situation of compulsory licensing versus intellectual property rights in Trade Related Aspects of Intellectual Property Rights (TRIPS). Industry will have to reduce the price and governmental organizations (GO) and nongovernmental organizations (NGO) will have to provide financial support for drugs in order to find an affordable price in developing countries. This could be further supported by earmarked tax reduction for drugs needed most in developing countries as already practiced by some countries. We may also consider an extension of the current Orphan Drug Act: in addition to rare diseases, ignored diseases of global health dimension should be made eligible for the Orphan Drug Act. Similarly, a reformed patent law which not only considers the novelty of a product but also its importance for global health could be of help. Patents for drugs of the latter type could receive financial support from GO and NGO on the premise of global access to the newly developed compound. This would allow funding for the development of promising drug candidates and provide revenues for the inventor largely independent from sales income.

Five minutes before or after 12:00?

On 8 May 1980, the General Assembly of the World Health Organization officially declared the eradication of smallpox. Central to this success story was the unanimous support for global vaccination efforts. Only one year later the world was informed about a newly emerging peril – AIDS. Vaccinia, the vaccine central to eradication of smallpox is a live vaccine derived from cowpox with a relatively high risk of side effects, notably in immunocompromised patients. It is conceivable that a ten-year delay in smallpox eradication would have seriously jeopardized this effort, since smallpox vaccinations would have had to be abandoned in populations with high incidences of HIV/AIDS. In this case we were fortunate. We were not so fortunate, however, in the case of HIV/AIDS and tuberculosis, which became a cruel reality in Sub-Saharan Africa. The second wave of HIV/AIDS has arrived in China with 500,000 registered and 1.5 millions estimated tuberculosis cases as well as in India with 1.1 millions registered and 5 millions estimated tuberculosis cases. Clearly, further delays in the design of novel treatment schemes for the two diseases in one and the same patient cannot be afforded.

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Stefan H.E. Kaufmann
Max Planck Institute for Infection Biology,
Department of Immunology, Charitéplatz 1, 10117 Berlin, Germany
email: kaufmann@mpiib-berlin.mpg.de