Improved survival in HIV-infected persons: consequences and perspectives

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A human immunodeficiency virus (HIV) patient in 2007 has the option to commence an antiretroviral regimen that is extremely efficacious in suppressing the virus and has few side effects. In a recent study, we estimated the median remaining lifetime of a newly diagnosed 25-year-old HIV-infected individual to be 39 years. The prospect of a near-normal life expectancy has implications for the HIV-infected persons as well as for the handling of the disease in the healthcare system. The patients can now on a long-term perspective plan their professional career, join a pension plan and start a family. Further, they may expect to be treated equally with other members of society with respect to access to mortgage, health insurance and life insurance. As the infected population ages, more patients will contract age-related diseases, and the disease burden on some individuals may even come to be dominated by non-HIV-related conditions that may have a worse prognosis and therefore become more important than HIV-related conditions. Despite the improvements in antiretroviral therapy, there is still an excess mortality among HIV patients, which appears to be only partially attributable to immunodeficiency, with lifestyle factors potentially playing a pronounced role. Consequently, an effort to further increase survival must target risk factors for both HIV-related and -unrelated mortality. The continuation of the positive trend may be achieved by increased HIV testing, earlier initiation of antiretroviral therapy, improved drug adherence, prevention and treatment of HIV-unrelated co-morbidity and collaboration with other medical specialists to treat an ageing co-morbidity-acquiring HIV population.

Keywords: prognosis, treatment strategies, co-morbidity, mortality

Background

The effectiveness of highly active antiretroviral therapy (HAART) against the human immunodeficiency virus (HIV) has been a medical success story. For those fortunate enough to have access to HAART, an inevitably deadly disease has turned into a chronic condition. In the 1980s, simply finding a drug or drug combination that could delay AIDS or death was the main clinical goal. In the mid-1990s, triple-combination therapy was introduced, leading to substantially prolonged survival. Simultaneously, it was shown that the substrate for the clinical effectiveness was suppression of HIV replication.1 Many patients experienced the comfort of a rising CD4 cell count and reversal of their AIDS-defining conditions. However, short-term and long-term side effects of the drugs became increasingly concerning, whereas episodes of virological failure led to the development of drug resistance, forcing patients to resort to often less efficacious second- or third-line regimens. Pharmaceutical companies began competing to develop new drugs with fewer side effects, lower pill burden and a better tolerance to non-compliance. Patients and physicians speculated whether controlled treatment interruptions could bring about a clinical success by delaying the potential exhaustion of available drug combinations and reducing the harm due to side effects. The intensive drug development and the massive research into mechanisms of resistance and side effects have paid off. An HIV patient in 2007 has the option to commence a drug combination that is both efficacious in suppressing the virus and has few side effects. Despite HIV’s ability to escape antiviral pressure, the rate of resistance to the antiviral drugs—a major problem in the early years when the regimens were suboptimal—is declining in a number of settings and may be <1% annually. Thus, there is growing optimism among HIV experts.
that a large proportion of their patients will be able to remain on their initial regimens and survive for many years. The big question has been, though, how long?

**Survival of HIV-infected persons**

Our group has addressed this question in the Danish HIV Cohort Study, using data from a population-based cohort of all HIV-infected persons in Denmark, a country with free tax-supported medical care, including universal, income-independent access to HAART. The high quality of the Danish Civil Registration System enabled us to compare, with little attrition, the survival of HIV patients with that of a matched cohort from the general population. Life-table methods were used to estimate survival of a 25-year-old HIV-infected person, regardless of whether the person had started HAART. The estimated median remaining lifetime has increased from 8 years in 1995–96 to 23 years in 1997–99 to 33 years in 2000–05. Among persons not co-infected with the hepatitis C virus (HCV), the median remaining lifetime in 2000–05 was 39 years (95% CI: 35–40 years), similar to that of a young person with diabetes. In comparison, the median remaining lifetime for a 25-year-old HIV-uninfected person was 51 years. Furthermore, we found that neither time since diagnosis nor duration of HAART was associated with an increased mortality. Importantly, the highest mortality was observed in the first year after the initiation of treatment.

**Immediate implications of the improved prognosis**

As clinicians know, the prognosis for individual HIV patients depends on many determinants, including immune status at the time of diagnosis, harbouring of a drug-resistant virus strain, adherence to treatment and concomitant infection with HCV. Nevertheless, the overall improved prognosis, with the prospect of a near-normal life, has implications for the HIV-infected persons as well as for their physicians. The patients may now plan their professional career, join a pension plan, start a family—things that just a few years ago seemed to be irrelevant luxuries. They may expect to be treated equally with other members of society and to have easy access to mortgage, health insurance and life insurance. They also expect to receive high-quality healthcare for non-HIV-related conditions, including fertility treatment. As the patients now get older, they will contract age-related diseases, and the disease burden on some individuals may even come to be dominated by non-HIV-related conditions. Some of these diseases may have a worse prognosis and therefore become more important than HIV for some patients. It would be important to know when an HIV-infected person needs a hip replacement, a bypass operation or even a cardiac transplantation. Elements of healthy lifestyle—smoking cessation, weight loss and regular physical exercise—that take 10 years or more to yield full benefits are becoming increasingly relevant for HIV patients. Furthermore, they should be offered prophylactic treatments, such as cholesterol-lowering therapy and antihypertensive treatment, just as their non-HIV-infected counterparts do.

**Why do HIV patients still have a higher risk of death?**

Even though survival has increased markedly, HIV-infected persons still die at rates that are 3–15 times higher than the general population. Cause-specific rates have decreased for both HIV-related and non-HIV-related mortality, but the decreased risk of AIDS has led to a change in patterns of co-morbidity and causes of death, and most deaths (50% to 70% of all deaths) are now non-HIV-related.

Common causes of non-HIV-related death are non-AIDS-defining cancers (~10% of all deaths), cardiovascular diseases (~7%), substance abuse-related death (~7%), liver-related death (up to 15% reported) and bacterial infections (~6%). The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study found mortality rates of non-AIDS-defining cancers to be related to the degree of immunodeficiency. Some cancers are known to be associated with lifestyle-related viral infections, such as hepatitis B virus (hepatocellular carcinoma), HCV (hepatocellular carcinoma and lymphoma) or human papilloma virus (anal, mouth and throat cancer), whereas others may be associated with smoking (cancer of lung, mouth and throat).

Liver-related deaths are mainly seen in hepatits C or B co-infected patients and the actual risk varies with the prevalence of these co-infections. We have found that a large part of the increased mortality seen in HIV/HCV co-infected individuals is associated with family-related risk behaviours—mainly drug abuse—and to a lesser extent, with the HCV infection itself. Behavioural risk factors for disease and death, such as cigarette smoking and excessive alcohol consumption, are common in many HIV-infected populations. Thus, the excess mortality among HIV patients appears to be only partially attributable to immunodeficiency, with lifestyle factors potentially playing a pronounced role. Consequently, an effort to further reduce mortality and increase survival must target risk factors for both HIV-related and HIV-unrelated mortality.

**How can we provide better care for the patients?**

A reduction in HIV-related mortality requires improved virological suppression, and research has shown that adherence to therapy is the key to success. The first step is easy and free access to drugs and healthcare, which should be supplemented by a coordinated effort of experienced care teams—physicians, nurses and social workers—in order to adequately address each individual’s needs, problems and taboos. Further, and in line with current CDC recommendations, test frequency must be increased for individuals at risk of being HIV-infected, including all adults in healthcare settings. This may help identify HIV-infected patients at an earlier stage of the disease and thereby enable timely therapy initiation. Reducing non-HIV-related mortality calls for a multifaceted approach whose success partly depends on behavioural changes that physicians can merely encourage, but not enforce. In addition, physicians must be aware that the HIV-infected population is getting older and therefore becomes increasingly affected by the diseases common in the general population. Optimal treatment and prevention therefore require the expertise of other medical specialists.

**What can be done to stem the epidemic?**

In order to optimize the benefit of the highly efficacious antiretroviral drugs that are available today, we must understand how the new treatment strategies may affect the spread of the disease on the population level. The improved survival increases the prevalence of persons who carry HIV and are thus at risk for
transmitting the virus to others. In addition, the awareness of improved prognosis may cause people to be less afraid of getting infected and cause them to become less vigilant. Furthermore, increased use of HAART may lead to resurgence of drug resistance. In contrast, a combination of high adherence and efficacious regimens will maintain viral suppression in the population and prevent the development of resistance. In support of the optimistic view, a recent population-based study from our group showed an increase in viral suppression and a decreasing incidence of potential resistance. Finally, there are persons who are unaware of their HIV infection; most of them have high viral loads and are more likely to engage in high-risk behaviours than they would if they were aware of being infected. The prevalence of these persons is unknown, and thus the extent of the problem is difficult to estimate.

Hence, the following needs to be considered. First, controlled treatment interruptions have been shown to do more harm than good in the individual, nor are they justifiable from a population perspective, because of the increased risk of transmission during periods of interruption. Secondly, initiating HAART at an earlier stage—possibly treating all patients—is an intervention that may restrain the spread of the epidemic. Thirdly, intensified testing will help reduce the prevalence of risk behaviours and improve viral suppression on the population level.

Other research questions are pending: What is the long-term impact of HIV and HAART on the risk of non-HIV diseases? How do antiretroviral drugs interact with other drugs in older individuals? Can we tailor individual regimens based on genetic markers for drug susceptibility and on individual risks for adverse drug reactions? What are the social and economic consequences of a growing population of HIV-infected persons? Some will require intensive medical care and receive financial support from the state, but many will contribute to the economy through work and tax payments. Ultimately, how can we transfer the success in the Western world to resource-poor settings, where poverty may force patients into antiretroviral drug-sharing and treatment interruptions? A requisite, contributory step forward will be the development of a preventive and/or therapeutic HIV vaccine.

Conclusion

Many HIV-infected persons with access to antiretroviral therapy have a near-normal life expectancy, but mortality among them is still higher than that in the general population. The continuation of the positive trend may be achieved by vaccine development, increased HIV testing, earlier HAART initiation, individually tailored regimens, improved drug adherence, prevention and treatment of HIV-unrelated co-morbidity and collaboration with other medical specialists to treat an ageing co-morbidity-acquiring HIV population.

Transparency declarations

None to declare.

References