Netherlands
The Journal of Medicine

EDITORIAL

Highly active antiretroviral therapy for HIV infection: lessons for the future

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ABSTRACT

HIV-related morbidity and mortality has been greatly reduced since the introduction of highly active antiretroviral therapy. Issues regarding the patient, the virus, the drugs and the treatment team are discussed. HIV treatment remains complex with a rapidly changing field of possibilities and views, and should therefore be limited to specialised centres.

In this issue of *the Netherlands Journal of Medicine*, Lowe, Prins and Lange from the International Antiviral Therapy Evaluation Treatment Centre (IATEC) review the studies on efficacy of HAART for the treatment of HIV infection. When all regimens are compared according to the outcome of a plasma viral load of HIV-1 RNA below the detection limit of 50 copies/ml after 48 weeks of therapy, an average value of 50% can be calculated with a wide range from 20 to 88%. The authors describe four factors that determine this wide range: the patient, the virus, the drug, and the treatment team. How can the lessons from this review be applied in daily clinical practice?

THE PATIENT

Several factors related to the patient may determine treatment outcome. First of all, adherence to this therapy is the most important factor associated with success of therapy. A plethora of studies has been conducted to evaluate which factors determine adherence, and many factors have been found in at least one study to be predictive of adherence. However, only a few patient factors have consistently been associated with good adherence: the absence of depressive symptoms, the ability to implement HAART regimens in daily life, and a good patient-physician (or nurse) relationship.

Depression may occur in at least 20% of HIV-positive patients, which is at least double the incidence in non-HIV-infected individuals. Having a potentially fatal disease, social isolation, and having lost friends due to AIDS may all contribute. The presence of depressive symptoms may be associated with a negative view on treatment possibilities, and adverse effects are possibly less well accepted. Therefore, the diagnosis of depression is of utmost importance before starting HAART. If pharmacological treatment of depressive symptoms is indicated, one should of course be aware of the potential drug-drug interactions with HAART regimens. Unfortunately, many interactions exist between antidepressants and HAART, and consultation of a clinical pharmacologist may be wise.

When HAART was introduced around 1996, many drug combinations existed of three times daily intake, food instructions and a high tablet count (>10 tablets/day was not unusual). In recent years, much has improved, and nowadays regimens are always twice daily or once daily, food restrictions have become less important, and the number of tablets per day is usually less than six to eight. In the near future, HAART regimens consisting of one to two tablets taken once daily will become available.

Although obvious, a good patient-physician (or nurse) relationship may not always be present. Within a medical team, several types of professionals need to be present to deal with the heterogeneous patient population (IV drug addicts, immigrants, etc). The role of dedicated HIV nurses

should not be underestimated. They usually have more time to discuss social aspects of therapy, barriers for 100% adherence, etc. For that reason, the Dutch government has required the presence of at least one HIV nurse at every HIV treatment centre in the Netherlands.

THE VIRUS

Two aspects of the virus may be relevant here: (1) the magnitude of the plasma viral load, and (2) the presence of primary mutations. As Lowe *et al*. describe, there are conflicting data on the effect of a high baseline viral load (i.e. >100,000 or >1,000,000 copies/ml) on treatment outcome. It is beyond doubt, that it takes longer to achieve an undetectable viral load when the baseline value is high. This may increase development of resistance, although the evidence for this is not strong. Four drug regimens have been tried to achieve a faster and more durable virological response in patients with very high baseline viral load. However, the results were disappointing; in particular the side effects did not balance the effect. At the moment, three drugs should therefore remain the mainstay of HAART until more data are available.
So far, the presence of primary resistance has been documented to be less than 10% in most of the cohort studies. It can be expected, however, that this figure will rise, especially against agents with a low barrier against resistance, such as lamivudine, efavirenz and nevirapine. Unfortunately, the mutations selected by these agents may disappear from the plasma after some time, but remain present in other compartments. Therefore, a negative result of a resistance test on a plasma sample before starting treatment may give false information. Nevertheless, response to HAART may be suboptimal in the case of primary resistance. Recommendations for testing for primary resistance vary within the literature, but Dutch guidelines recommend testing in selected groups of patients.

THE DRUG(S)

Lowe *et al*. pay relatively little attention to the selection of drugs for the initial HAART regimen while this may be the most important influence a physician may have in assuring treatment response. With the availability of more than 15 different drugs for initial treatment of HIV infection, there is an urgent need for standardisation of first-line treatment both within centres and within the country. Unlike regionalised treatment guidelines for treatment of malignancies, a patient may receive three different first-line regimens in three different HIV treatment centres in the same city. National guidelines for the treatment of HIV infection have therefore been developed recently. Of even more concern is the use of unapproved treatment combinations in the absence of evidence-based criteria. For instance, a number of physicians have started to use triple nucleoside therapy as initial or maintenance treatment while there were no data available about the efficacy and safety of these approaches. Later, data from clinical and cohort studies indicated inferior efficacy of these triple nucleoside therapies, and they are now no longer in use. Some patients, however, have been treated with these inferior regimens while there was no urgent reason for not selecting the recommended regimens. We advocate the use of regional or national treatment guidelines, and that choices for individual patients are made in multidisciplinary teams so that convenience of the regimen, drug-drug interactions, toxicity, comorbidity and potential salvage ability can be taken into account.

THE TREATMENT TEAM

Very limited data are available on what knowledge is needed to treat HIV-infected patients. Daily practice teaches, however, that extensive knowledge on (new) drugs, changes in toxicity profiles, and (new) drug combinations are a prerequisite for treating HIV infection. Patients frequently interrupt or change their initial regimen because of drug toxicity, while therapy changes as well as interruptions are associated with a less favourable treatment outcome. As Lowe *et al*. indicate, one study has related greater HIV-treatment experience with better survival. In most European countries, HIV care is restricted to specialised centres. In the Netherlands, the Dutch government has selected 22 treatment centres for approximately 8000 to 10,000 HIV-infected adults and children. These treatment centres are selected based on historical arguments and have to fulfil a number of quality criteria. We are awaiting peer review of these treatment centres. In addition, it is well known that there are patients still being treated in hospitals not listed as HIV-treatment centres. Apparently, there is no mechanism to protect patients against this practice. We plead for adherence to the guidelines for treating these patients in specialised centres only and for self-control among the group of medical specialists.

CONCLUSIONS

Great improvements have been made in the treatment of HIV infections. Mortality has been reduced to less than 5%, and according to current knowledge a newly infected patient may have the same life expectancy as a non-HIV-infected subject, assuming good adherence and tolerability to the drugs. Nevertheless, HIV treatment is remains complex, is a rapid changing field of possibilities and views, and should therefore be limited to specialised centres.