New European HIV treatment guidelines

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Dear Readers,

The 13th European AIDS Conference, this year held in Belgrade, led to the publication of new HIV therapy guidelines, which will also be available online as from the middle of this month.

The conference demonstrated that these guidelines were the result of a heated discussion, which flared up again at some points, for example when it came to the relevance of neurocognitive disorders.

We present the new therapy guidelines, focusing on those points that are of special significance to HIV treatment. The complete guidelines are available for download on the Internet.

Enjoy reading!

Armin Schafberger, Steffen Taubert
There are no major changes; the innovations are in the details. At the 13th European AIDS Conference in Belgrade, the European umbrella organisation of physicians treating HIV, EACS, published an updated version of their HIV therapy guidelines. Furthermore, recommendations for the treatment of concomitant diseases and the political framework conditions under which HIV treatment takes place were also discussed in Belgrade. Because: The supply of HIV medication is not equally good in all European countries.

In mid-October, the European AIDS Conference of the European AIDS Clinical Society/EACS took place for the 13th time. With Belgrade, the capital city of Serbia, the organisers selected a place that demonstrates, more than any other, the big differences in medical care and social acceptance of HIV-positive people in Europe.

**Vice President of Serbia admits care deficits**

Whereas Western European researchers and community activists are discussing the application of combination preparations such as Truvada® for pre-exposition prophylaxis (PrEP), these new drugs are not even available for treatment in countries like Serbia. Božidar Đelić, Deputy Prime Minister of Serbia, admitted that there was still much room for development in his country, in particular regarding the social acceptance of the nearly 5,000 HIV-positive people in Serbia.

In order to attract the public attention to Central and Eastern European countries with lower HIV prevalence and poorer medical care, therapy activists met on the day before the conference to establish the NeLP network (Network of Low HIV Prevalence Countries). NeLP intends to contribute to remedying shortcomings in medical care – irrespective of the number of people affected. Moreover, discrimination against the groups that are most strongly affected by HIV is to be reduced. NeLP focuses on the discrimination of men who have sex with men, women, drug users, prostitutes and their clients, inmates, immigrants and ethnic minorities. “The epidemic in our country is of less prevalence, but it may nevertheless be fatal”, the activists stated in their "Budapest Declaration" entitled "Central and Southeast Europe Need More Positive Attention!".

**Guidelines presented in Belgrade**

At the congress in Belgrade, the EACS published the sixth issue of their HIV therapy Guidelines. The 80-page booklet in DIN A6 format contains recommendations on when treatment should be started, what combinations can be selected and what frequent side effects can occur, in addition to information about relevant concomitant diseases and a separate chapter presenting the diagnosis and treatment of viral hepatitis infections. Compared to the last issue, new topics include vitamin D, osteopathy, vaccinations, sexual dysfunction and information about antiretroviral therapy on long journeys. The compact and appealing booklet can be obtained from the EACS. The PDF is available for free download on the Internet.

**More situations to start treatment earlier**

The previous issue of the European therapy guidelines already recommended starting treatment as soon as the helper cell count is below 350 cells/mm³ and indicated several situations where treatment should be started even earlier (e.g. if hepatitis B/C co-infection is present).

The updated guidelines have been extended to incorporate recommendations for additional situations where treatment should be started immediately. These include, amongst others, HIV-associated neurocognitive disorders, HPV-associated cancer or pregnancy.
The treatment of the HIV infection during the primary infection, i.e. shortly after the infection, has also been added as a new subject. Irrespective of the helper cell count, the guidelines enable the application of antiretroviral therapy (“should be considered”).

The category “CD4 cell count between 201–350 cells/mm³”, where the previous guidelines had stated the additional information that treatment should be initiated “without delay”, has been removed completely. It has apparently become evident that HIV-positive patients with a helper cell count of less than 350 cells/mm³ should not defer the treatment either.

### Recommendations for starting treatment in HIV-positive patients without previous ART

1) At a CD4 cell count < 350 cells/mm³: starting treatment is recommended to all patients

2) At a CD4 cell count > 350 cells/mm³, the following applies:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Current CD4 count</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>350–500</td>
</tr>
<tr>
<td>Asymtomatic HIV infection</td>
<td>to be considered</td>
</tr>
<tr>
<td>Symptomatic HIV infection (CDC B or C conditions), incl tuberculosis</td>
<td>recommended</td>
</tr>
<tr>
<td>Primary HIV infection</td>
<td>to be considered</td>
</tr>
<tr>
<td>Pregnancy (before third trimester)</td>
<td>recommended</td>
</tr>
<tr>
<td>Conditions (likely or possibly) associated with HIV, other than CDC stage B or C disease:</td>
<td></td>
</tr>
<tr>
<td>HIV-associated kidney disease</td>
<td>recommended</td>
</tr>
<tr>
<td>HIV-associated neurocognitive impairment</td>
<td>recommended</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>recommended</td>
</tr>
<tr>
<td>HPV-associated cancers</td>
<td>recommended</td>
</tr>
<tr>
<td>Other non-AIDS-defining cancers requiring chemo- and/or radiotherapy</td>
<td>to be considered</td>
</tr>
<tr>
<td>Autoimmune disease - otherwise unexplained</td>
<td>to be considered</td>
</tr>
<tr>
<td>High risk for CVD (&gt;20% estimated 10-yr risk) or history of CVD</td>
<td>to be considered</td>
</tr>
<tr>
<td>Chronic viral hepatits</td>
<td></td>
</tr>
<tr>
<td>HBV requiring anti-HBV treatment</td>
<td>recommended</td>
</tr>
<tr>
<td>HBV not requiring anti-HBV treatment</td>
<td>to be considered, recommended in those who are HBeAg-positive</td>
</tr>
<tr>
<td>HCV for which anti-HCV treatment is being considered or given</td>
<td>recommended (to optimise the outcome of HCV treatment)</td>
</tr>
<tr>
<td>HCV for which anti-HCV treatment is not feasible</td>
<td>recommended</td>
</tr>
</tbody>
</table>

Source: Table from EACS. Guidelines. Version 6.0 – October 2011. p. 20–21
**Explanation of categories used:**

1) **Recommended** ("use of ART is recommended")

2) **To be considered** ("use of ART should be considered"). The benefits of known and unknown side effects of antiretroviral therapy need to be weighed up against the risks. Some experts recommend starting the treatment, others recommend deferring it.

3) **To be deferred** ("defer initiation of ART")

The therapy can also be started earlier, irrespective of the CD4 cell count and the viral load.

In their guidelines, the EACS states that the therapy could also be started earlier if desired by the patient. Furthermore, the preventive effect of the ART is pointed out. The authors of the guidelines recommend "actively discussing" the preventive benefits of starting the therapy at an early point with patients living in serodiscordant relationships.

Despite the clear trend towards starting the therapy at an early point, the EACS guidelines are generally somewhat more careful than the U.S. guidelines. The majority of experts in the expert body of the "U.S. Department of Health and Human Services" responsible for developing the guidelines now recommend starting the therapy as soon as the helper cell count is below 500 cells/mm³.

**Recommended medication for starting antiretroviral therapy**

As a "backbone therapy", the guidelines recommend the NRTI combinations emtricitabine/tenofovir (Truvada®) or lamivudine/abacavir (Kivexa®). Probably because of the still not quite clarified risk of possible heart attacks when using abacavir, the authors of the guidelines recommend applying this drug with utmost care in patients subject to increased cardiovascular risk. Care should also be taken if the patient has a particularly high viral load. According to the 2011 EACS Guidelines, the two drugs are combined with either the NNRTIs efavirenz or nevirapine, with boosted PIs (atazanavir, darunavir or lopinavir) or with the integrase inhibitor raltegravir/Isentress®.

Furthermore, alternative combination preparations are indicated if the recommended combination therapy cannot be applied for medical reasons or it is not available in the respective country.

tau/sch

A drug from column A should be combined with a (combination) drug from column B:

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTI-based</strong></td>
<td></td>
</tr>
<tr>
<td>Efavirenz (Sustiva®)</td>
<td>Abacavir/Lamivudine (Kivexa®) or Tenfovir/Emtricitabine (Truvada®)</td>
</tr>
<tr>
<td>Nevirapine (Viramune®)</td>
<td>Tenfovir/Emtricitabine (Truvada®)</td>
</tr>
<tr>
<td><strong>Protease inhibitors (boosted)</strong></td>
<td></td>
</tr>
<tr>
<td>Atazanavir/r (Reylaz®)</td>
<td>Abacavir/Lamivudine (Kivexa®) or Tenfovir/Emtricitabine (Truvada®)</td>
</tr>
<tr>
<td>Darunavir/r (Prezista®)</td>
<td></td>
</tr>
<tr>
<td>Lopinavir/r (1 × or 2 × daily) (Kaletra®)</td>
<td></td>
</tr>
<tr>
<td><strong>Integrase inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Raltegravir (Isentress®)</td>
<td>Tenfovir/Emtricitabine (Truvada®)</td>
</tr>
<tr>
<td><strong>Alternative combinations</strong></td>
<td></td>
</tr>
<tr>
<td>Saquinavir (Invirase®)</td>
<td>Zidovudine/Lamivudine (Combivir®)</td>
</tr>
<tr>
<td>Fosamprenavir (Telzir®)</td>
<td></td>
</tr>
<tr>
<td>Maraviroc (Celsentri®)</td>
<td>Didanosine/Lamivudine or emtricitabine (Emtriva®)</td>
</tr>
</tbody>
</table>

**HIV drug interactions**

A table containing information about interactions of ART with drugs frequently used for the treatment of concomitant diseases (e.g. cardiovascular diseases, infectious diseases, pulmonary dysfunction, mental disorders) or interactions with substances used for substitution therapy has been added to the therapy guidelines. Unfortunately, the table does not elaborate on interactions with illegal substances. Only the interactions with Viagra® are pointed out under the column of lifestyle drugs.

Anyone interested in detailed information on interactions should refer to the database of...
the University of Liverpool “hiv-druginteractions.org”, where a hepatitis interactions database has recently been added to the HIV drugs database.

**Recommendations for the treatment of co-morbidities**

The 2011 Guidelines contain a list of all examinations that are recommended following an HIV diagnosis and also later on. They describe the diagnostic procedure and briefly address the therapy. However, not all these recommendations were undisputed at the congress. The question of relevance of neurocognitive disorders led to an extended discussion.

**Neurocognitive disorders**

In order to recognise neurocognitive disorders, the EACS recommends conducting a specific test every two years. The attending physician should ask three questions:

1. **Do you experience frequent memory loss (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)?**

2. **Do you feel that you are slower when reasoning, planning activities or solving problems?**

3. **Do you have difficulties paying attention (e.g. to a conversation, a book, or a movie)?**

4. **Every question can be answered with:**
   a) Never
   b) Hardly ever
   c) Yes, definitely

If one of the questions is answered with “yes, often”, a specific diagnostic procedure should be initiated. It is recommended using an extensive questionnaire to identify practical impairments in everyday life (IADL = “Instrumental Activities of Daily Living Administration”). If the results are unusual, the patient should be referred to a neurologist or a detailed test and performance diagnosis should be conducted. Only when the neurological examination shows indications of neurocognitive deficits is it recommended that magnetic resonance imaging of the brain or liquor puncture be performed in order to determine the viral load and the possible presence of resistances in the central nervous system.

Some neurologists criticised this cautious approach to memory and concentration disorders. According to the German neurologist Professor Gabriele Ahrend, mild forms of changes in the memory would possibly not be recognised, as the patient himself notices hardly any change at this point.

![Extensive test battery. G. Ahrend, Belgrade, 2011. photo: tau](image)

**Clinical relevance of neuropsychological test results unclear**

At the congress in Belgrade, Alan Winston presented a current study investigating the relevance of neurocognitive disorders in England. 560 HIV-positive patients had been examined for motor functions, verbal memory, attention and executive functions. All study participants had a viral load of less than 50 copies/ml for at least six months. The tests revealed a fairly high prevalence of neurocognitive impairments. In half of the participants, the tests yielded unusual results. Unlike previous studies (e.g. Charter study, 2010), however, Winston et al. found no correlation between the number of existing helper cells and the stage of neurocognitive impairments in the study participants (skin colour: white). They explained this by the fact that all patients had been receiving antiretroviral therapy for a long time. The researchers emphasised that the clinical relevance of unusual neuropsychological test results was still unclear.

**Vitamin D insufficiency**
For the first time, the guidelines also address the issue of “vitamin D substitution”. Last year, there were an increased number of publications dealing with the relatively frequent vitamin D insufficiency in HIV-positive people. Sunlight is essential for the formation of vitamin D. For this reason, the amount of vitamin D stored in the body substantially decreases during the dark winter months. Epidemiological studies have now revealed numerous correlations between vitamin D insufficiency and the occurrence of certain diseases such as rachitis, osteoporosis, depression, chronic inflammatory intestinal diseases, diabetes, renal diseases or certain types of cancer. The epidemiological studies are not yet able to answer the questions whether there is a clear coherence between vitamin D insufficiency and these diseases. A higher vitamin D level could also be an indication of a more healthy way of life, e.g. spending more time outdoors/in the sun.

A study conducted in Sicily has demonstrated that vitamin D insufficiency in HIV-positive persons also occurs in sunny areas. The scientists examined 91 HIV-positive patients on the island. The result: 87.9% of all patients had a vitamin D level < 30 ng/ml (depending on the definition, this is said to be the threshold of vitamin D insufficiency). Vitamin D deficiency was found in 30.8% of the patients (< 10 ng/ml) (Nunnari, 2011).

An examination of 232 HIV-positive patients at the Ramón y Cajal Hospital (Madrid) yielded similar results: The vitamin D level of 2/3 of all persons examined was below 20 ng/ml (Tamarit, 2011).

The new EACS Guidelines recommend checking the vitamin D level in patients suffering from one of the following diseases:

- low bone mineral density
- high risk of bone fractures
- chronic liver disease

Vitamin D insufficiency is defined as the presence of less than 20 ng of vitamin D/ml; vitamin D deficiency occurs if less than 10 ng/ml is present. Some experts even regard a level below 30 ng/ml as vitamin D insufficiency.

Considering vitamin D substitution is recommended if osteoporosis, osteomalacia (increased bone softness) or an increased parathormone level is present. The efficacy of vitamin D substitution should be checked after six months of administration.

The experts’ recommendations for the amount of vitamin D substitution remain inconsistent. Some recommend a daily dose of 10,000 units over 8 – 10 weeks, followed by a maintenance dose of 800 – 1000 units.

A new Med-Info (publisher: AIDS Service Organisation Cologne & DAH) will comprehensively address the issue of “vitamin D and HIV infection” in January 2012.
Sexual dysfunction

By providing recommendations for the treatment of sexual dysfunction, the guidelines address an important aspect of quality of life during antiretroviral therapy.

According to the recommendations, the physician should at least once talk with the patient about his contentment with his sexual life, the possible presence of sexual dysfunction and, if necessary, also about contraception. If the patient indicates any problems in this respect, the guidelines prescribe a gradual diagnostic approach. Is there a lack of sexual appetite? Does the patient have difficulty becoming aroused or achieving an erection? Are there any difficulties achieving an orgasm or is there any pain during sexual intercourse? Depending on the causation of the disorder, the physician should refer the patient to an appropriate specialist (cardiologist, urologist, endocrinologist) or a psychotherapist.

Extended online version of the guidelines available as from mid-December 2011

An extended online version of the guidelines will be published in December 2011 der www.europeanaidsclinicalsociety.org. The online version will feature recommendations for handling antidepressants, adaptations of medication doses for the treatment of renal disorders and for the management of metabolic disorders as well as information on improving the quality of life during the treatment of HIV and other concomitant diseases.

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References


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