Corporación de Lucha contra el Sida

VI CURSO INTERNACIONAL DE ENFERMEDADES INFECCIOSAS
VII SEMINARIO INTEGRAL DEL SIDA
Santiago de Cali , Colombia, 4 al 7 de Abril del 2001

Terapia antirretroviral inicial y de rescate: Utilidad actual y futura de nuevos medicamentos

(Antiretroviral Therapy – Present and Future Prospects of Antiretroviral Drugs in Initial and Salvage Therapy)

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The person diagnosed with HIV infection today can take comfort in the knowledge that there are multiple therapeutic options available to control his or her infection. The spector of an inevitable downward spiral in health punctuated by increasingly debilatating opportunistic infections and finally in death can be postponed indefinitely if not avoided altogether. But it comes at a price – a price in dollars, a price in personal priorities, and a price in health as the long term adverse effects of these new drugs emerge. There are several important decisions in treatment of a person with HIV infection. The first - when to initiate antiretroviral therapy. The second is what therapy to begin. The third, what drugs to use should the initial therapy need to be changed. The topic of this presentation concerns primarily the second and third issues.

Shortly after the success of combination antiretroviral therapy was recognized, the theme of "Hit hard, hit early" became the mantra for HIV specialists. The recognition that even our best regimen is unlikely to ever be curative, and that these wonder drugs have serious consequences over the long term has tempered our enthusiasm for starting therapy during the early **asymptomatic** stages of infection. All persons with symptomatic HIV infection or AIDS by virtue of T-helper lymphocyte counts < 200 cells/ml, however, should be treated. Last year's recommendations of various "expert" groups had been to consider therapy with T-helper lymphocyte counts of less than 500 cells/ml, or even earlier if the HIV quantitative load is greater than 30,000. The most recent recommendations from the United States DHHS/Kaiser Foundation have become more cautious. These recommendations suggest starting only when the T-helper lymphocyte count falls below 350 cells/ml, or if the T-helper lymphocyte count is between 350-500 cells/ml, only if the viral load of > 30,000 copies/ml.

The antiretrovirals now available number 15 - 17 if one includes two combination formulations- in three classes (Table).

Table 1. ANTIRETROVIRAL DRUGS, APRIL 2001

Nucleoside Reverse Transcriptase Inhibitors

- Abacavir (Ziagen®)
- Cytabine (Hivid®)
- Didanosine (Videx®)
- Lamivudine (Epivir®)
- Stavudine (Zerit®)
- Zidovudine (Retrovir®)
- Zidovudine/Lamivudine (Combivir®)
- Zidovudine/Lamivudine/Abacavir (Trizivir®)

Non-Nucleoside Reverse Transcriptase Inhibitors

- Delavirdine (Rescriptor®)
- Efavirenz (Sustiva®)
- Nevirapine (Viramune®)

Protease Inhibitors

- Amprenavir (Agenerase®)
- Indinavir (Crixivan®)
- Lopinavir/ritonavir (Kaletra®)
- Nelfinavir (Viracept®)
- Ritonavir (Norvir®)
- Saquinavir (Fortavase®)

The treatment of HIV infection with antiretrovirals is optimized by the thorough education of the patient before initiation of medications. Points that should be emphasized include: the necessity of strict adherance to the dosage schedule; the importance of avoiding interruptions of therapy; the extent of potential adverse effects and how they can be managed; the danger of drug interaction; the reality of life-long therapy; and patient's ability to secure funding for the therapy. The pros and cons of various regimens should be discussed and the patient included in the selection of the initial regimen. For example, a patient in a high profile position may not be able to take a handful of pills three times a day in private, but on a twice daily regimen he could take his medication in the privacy of his own home. Another patient might also want to take a simple regimen, but because of his extremely high HIV load, medically the more appropriate choice would be to maximize antiviral activity until control of his infection is achieved.

Table 2: Recommended Antiretroviral Agents for the Initial Treatment of Established HIV Infection. (Adapted from DHHS/Kaiser Found. guidelines, 2001)

Strongly Recommended (one from column A and one from column B

Column A	Column B
Efavirenz	Stavudine and Didanosine
Indinavir	Stavudine and Lamivudine
Nelfinavir	Zidovudine and Didanosine
Ritonavir and Indinavir	Zidovudine and Lamivudine
Ritonavir and Lopinavir	
Ritonavir and Saquinavir	

Recommended as Alternatives

Abacavir	Didanosine and Lamivudine
Amprenavir	Zidovudine and Zalcitabine
Delavirdine	
Nelfinavir and Saquinavir –(soft gel)	
Nevirapine	
Ritonavir	
Saquinavir –(soft gel)	

No Recommendations (Insufficient data)

Hydroxyurea in combination with antiretroviral drugs
Ritonavir and Amprenavir
Ritonavir and Nelfinavir

Not Recommended (should not be offered)

Saquinavir – hard gel capsules	Stavudine and Zidovudine
	Zalcitabine and Didanosine
	Zalcitabine and Lamivudine
	Zalcitabine and Stavudine

Are there differences in potency among initial regimens? This is a difficult question to answer, since the clinical trials that provide the direction to therapy all have unique characteristics that make direct comparisons an imprecise matter. The most recent guidelines regarding preferred regimens consider those recommended to be comparable in potency with certain qualifications. Aside from patient acceptance and toxicity profiles, little is known about the durability of these regimens. The greatest experience has been collected with protease inhibitor based regimens,

but this may be due simply to the fact that we have the greatest experience with these, not that they truly produce a more lasting suppression of HIV. On the other hand, the protease inhibitors are the most potent of the antiretrovirals as a class and resistance occurs gradually with the accumulation of multiple mutations. Some physicians suggest choosing the initial therapy in anticipation of the inevitable emergence of resistance and need for salvage regimens. This has given rise to the terms "protease sparing"and "non-nucleoside sparing" regimens. On the other hand, salvage regimens have a lower rate of response than initial therapy and one should not lead with a suboptimal regimen because it makes choosing subsequent regimens easier.

Second regimens or "salvage therapy" will depend upon the initial regimen and eventually on the resistance profile as determined by genotypic or phenotypic assay. Resistance testing will be increasingly important, especially for patient's failing their first or subsequent regimens. The inhibition of the P450 cytochrome enzyme, 3A4, by ritonavir (most PIs inhibit these enzymes) has been turned to good advantage by administering low dose ritonavir with a second protease. The serum half life of the second PI (all but nelfinavir) is significantly prolonged and the AUC (area under the curve) increased. Not only does this allow b.i.d. or q.d. dosing, it also may raise the drug concentration suficiently to overcome low and moderate resistance. A change in therapy because of toxicity does not require the introduction of multiple new agents if the initial regimen was effective.

There are several drugs in various stages of development. They include several NRTIs, NNRTIs, new PIs, as well as drugs which block attachment of HIV to CD4 cells (dextran sulfate, T-20). Improved formulations of drugs have been introduced and make antiretroviral therapy more users friendly. Combivir (zidovudine and lamivudine) has been joined by Trizivir (zidovudine, lamivudine and abacavir), Kaletra (ritonavir and loprinavir). Didanosine is available as an enteric coated capsule, and other agents have new dosage formulations to decrease pill burden. Further antiretroviral drug development is to be expected, although the hope for a curative therapy remains elusive.

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