Panorama actual de la Terapia Antirretroviral y utilidad práctica de las Pruebas de Resistencia.

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Although AIDS-related morbidity and mortality have been significantly improved with the use of chemoprophylactic and antiretroviral drugs, new cases of HIV infection continue to be diagnosed in the United States and worldwide.

An increasing percentage of the new cases in the US is being observed in women, African-Americans, Hispanics, injecting drug users, young gay males, and individuals from smaller cities and towns. Most of these patients are not aware of their HIV infection. Worldwide, the vast majority of humans infected with HIV do not have access to antiretroviral drugs.

Initial Approach to and Staging of the HIV-infected Patient

Patients infected with HIV should be followed by a primary care provider with experience in taking care of these patients or in its absence by a primary care physician who has easy access to an HIV clinician for ongoing consultation. The complex care of these patients requires a comprehensive approach in the setting of a multidisciplinary team or network (i.e. primary care physicians, specialists, nurses, social workers, nutritionists, psychologists, psychiatrists, and benefits counselors).

The peripheral blood T cell CD4+ lymphocyte count ("T" cell or CD4 count, normal range = 600 - 1600 cells/dL) and HIV RNA copy number [viral load (VL), normal = 0 / ml] are the two most important laboratory tests for staging HIV infection. AIDS will develop within five years in approximately 60% and 8% of untreated patients with a VL of >100,000 and > 5000, respectively. Most of the opportunistic infections (OI's) occur in untreated patients when their CD4 count is < 200. Additional important laboratory/radiological tests in the initial evaluation of HIV-infected patients include: complete blood cell count; comprehensive chemistry (including glucose, electrolytes, creatinine, liver function tests, LDH); G6PD screening; hepatitis (A, B and C), toxoplasma, syphilis, varicella zoster, measles and rubella serologies; PPD testing, baseline chest-X-ray and cervical Pap smear for women. Consider lipid panel in elderly patients or those with risk factors for coronary artery disease and/or candidates for treatment with protease inhibitors.

Antiretroviral therapy

Currently there are 14 drugs approved by the FDA for the treatment of HIV infection in the United States (Table 1). Regimens containing these agents (anti-HIV "cocktails") have been mostly responsible for the decrease in the incidence of OI's and mortality observed in patients with AIDS since 1996. These drugs target 2 key enzymes in the life cycle of the virus, a reverse transcriptase (shortly after penetration of the virus into the CD4 positive

cell, this enzyme is required for the conversion of viral RNA into DNA) and a protease (shortly before exit of the virus from the infected cell, this enzyme is required for "trimming" the virus from excessive coating proteins). Most effective combination regimens [highly active antiretroviral therapy (HAART)] usually include 2 nucleoside reverse transcriptase inhibitors (NRTI) PLUS either 1 (or two) protease inhibitor(s) (PI) or 1 non-nucleoside reverse transcriptase inhibitor (NNRTI). Most clinicians in the United States will consider initiation of HAART in patients whose CD4 count is less than 500 (some will wait until is 400) and/or the viral load is > 5,000 (or > 10,000). HAART must be offered to all patients whose CD4 count is < 200 and/or viral load is > 100,000 and those who appear to be in the phase of acute or primary infection (i.e. infectious mononucleosis-like syndrome accompanied by an initial negative or indeterminate HIV ELISA antibody and positive HIV RNA in peripheral blood).

It is not unusual for 60 to 80% of previously untreated patients (those who have not received any of the anti-HIV drugs) to achieve a non-detectable viral load (< 50) within 3 months of initiation of HAART. It appears that the lower the initial nadir in viral load that is achieved, the longer the efficacy that can be obtained with a particular HAART regimen. Significant suppression in HIV viral replication is usually followed by significant rises in the CD4 count. There is a lag of weeks to months between viral load reductions and this CD4 count increase. Both, memory and naive CD4 lymphocytes reconstitute the pool of T cells in peripheral blood and lymph nodes. It is becoming evident that this secondary immune reconstitution is translated in substantial clinical benefits and results in the control of several OI's that previously were only amenable to chemoprophylactic drugs. It is important to emphasize that despite non-detectable viral loads that can be achieved with HAART, several investigators have demonstrated that low-level viral replication continues to occur in these patients and thus it has been well established that HAART does not eradicate HIV. At the present time, HAART should not be discontinued in any patient with the hope that the virus has been eliminated (this also applies to patients who have been non-detectable for several years).

From the currently available data, it is not possible to establish which particular HAART regimen(s) is(are) most effective or should be chosen as first line combination therapy. Studies are underway to address this question.

Side effects from HAART may be significant and result in discontinuation of the drugs (for most common side effects of each drug see Table 1). The use of HAART (particularly PI-containing regimens) has also been associated with the development of diabetes mellitus (it may require treatment with insulin and/or oral hypoglycemic agents), hyperlipidemia (treatment may be indicated with lipid-lowering agents) and lipodystrophy (no proven treatment is currently available). The latter adverse events may be significant and lead the clinician to change HAART to a regimen without PI's.

Major caution, good clinical judgment, and consultation with a pharmacist (familiar with HAART) should be frequently exercised in the care of patients on HAART. Significant

drug interactions may occur in patients treated with HAART and other drugs usually used in the care of HIV-infected patients.

Once three or four regimens have been identified as potentially beneficial for a particular patient, the most important next step is to allow her/him to make the choice of the regimen that will best fit her/his lifestyle.

Resistance Testing

The role of antiviral drug resistance in the current treatment of HIV infection will be discussed.

The pros and cons of both genotyiping and phenotyping methods to characterize HIV resistance will also be discussed.