NEW INSIGHTS IN HIV-1 PATHOGENESIS: CLINICAL AND THERAPEUTIC IMPLICATIONS (SUMMARY)

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Mayor progress have occurred in the understanding of the pathogenesis of HIV-1 infection and its treatment. Some of these new developments have had direct impact in the approach and management of patients infected with HIV-1. The areas that have seen significant new insights are:

1. Replication kinetics of HIV-1, HIV infection is now viewed as a remarkably dynamic process in vivo. HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. Almost every untreated patient infected with HIV has measurable plasma levels of HIV RNA throughout the course of disease. $10^5$ to $10^7$ HIV RNA copies/ml are present in the initial burst associated with primary infection. Within 6 to 12 months after seroconversion a steady-state level ("set point") of HIV RNA is established between $10^2$ to $10^6$ HIV RNA copies/ml. This post-seroconversion "set point" is highly predictive of subsequent disease course; without treatment, 8% of patients with <5,000 HIV RNA copies/ml will develop AIDS 5 years after infection whereas 62% of patients with > 30,000 HIV RNA copies/ml will develop AIDS 5 years after infection. The striking association between HIV RNA copies/ml and disease stage, prognosis (and response to therapy as it will be discussed later) has no precedent in Infectious Diseases. No other infectious disease exhibit this remarkable association between the quantitation of the infectious disease process or correspondent immune response and its disease progression or response to therapeutic intervention. Examples of other infectious diseases in which quantitation may be used for clinical purposes include: hepatitis B, syphilis, brucellosis, coccidioidomycosis, paracoccidioidomycosis, cryptococcosis and urinary tract infections.

2. Standardization of assays to determine viral load individual patients. There are 2 assays to quantitate HIV-1 in peripheral blood: a PCR-based test (the "Roche test") and a non-PCR branched DNA test (the "Chiron test"). The 1st generation of these assays were able to measure down to only 10,000 HIV RNA copies/ml. With the advent of new more effective therapeutic agents a 2nd generation test was developed which is capable to detect down to 500 HIV RNA copies/ml.

Work is in progress to standardize 3d generation assays that will probably have a sensitivity down to 20 to 50 copies.

Clinical use of HIV RNA viral load

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<th>HIV RNA copies/ml</th>
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<td>Level to consider initiation of therapy</td>
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Level to initiate therapy: $> 30.000$

Target level: $< 5.000$

Indicates drug efficacy: $> 0.5$ log decrease

Indicates drug failure: return to pretreatment value (or within 0.3 to 0.5 log of pretreatment value)

3. Availability of several effective drugs has allowed to evaluate the clinical impact of the control of HIV-1 replication. There are now 9 drugs approved by the FDA to be used against HIV-1: five nucleoside reverse transcriptase inhibitors: zidovudine (ZDV or AZT), didanosine (ddl), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC); one non-nucleoside reverse transcriptase inhibitor, 3 protease inhibitors: saquinavir, ritonavir, indinavir.

4. Antiviral drug resistance: some genotypic changes have been associated with in clinical use of antiretroviral drugs. Some of these genotypic changes may be used in the near future for clinical purposes. However, as of January 1997 it is not clear if they provide more clinically relevant information than the viral load. At the reverse transcriptase gene, ZDV use has been associated with the following mutations: 41, 67, 70, 215, 219; ddl with 65, 74, 184; ddC with 65, 69, 184; 3TC with 184; d4T with 75; nevirapine with 103, 106, 108, 181, 188, 190. At the protease gene, saquinavir use has been associated with the following mutations: 10, 48, 63, 71, 90; ritonavir with 20, 33, 36, 46, 54, 71, 82, 84, 90; indinavir with 10, 20, 24, 46, 54, 63, 64, 82, 84, 90.