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MONITORING OF HIV INFECTION INFORMATION SHEET

INTRODUCTION

Once the diagnosis of HIV infection is made, two tests are used to monitor disease progression. These same two tests are used to monitor response to therapy: HIV plasma viral load and CD4+ T cell count.

HIV plasma viral load quantitates the amount of virus circulating in the blood. The level of plasma viraemia has been shown to correlate with long term outcome and the rate of disease progression. Currently, the assay employed by the NSW Reference Laboratory at St Vincent's is a quantitative polymerase chain reaction (PCR) assay.

CD4+ T cells are the major target of HIV. The peripheral blood CD4+ T cell count is a good correlate of the intactness of the immune system. It guides the timing for commencement of anti-retroviral therapy and the use of chemo-prophylaxis for opportunistic infections that characterise the later stages of the disease. In established HIV infection CD4+ T cells decline at a mean rate of 50 cells/µL/ year. CD4+ T cells are measured using flow cytometry. This allows the determination of the percentage of lymphocytes that are CD4+ T cells. Using the lymphocyte count from a concomitantly performed full blood count an absolute count of CD4+ T cells/µL of blood can be determined. For this reason, a FBC with white cell differential should always be ordered with the request for CD4+ T cell count.

In addition, an HIV genotype resistance test should be ordered to determine if the circulating HIV is resistant to any antiretroviral drugs. This test sequences regions of HIV reverse transcriptase, HIV protease and HIV integrase that encode for protein sequences at which antiretroviral drugs in these drugs classes bind. The test only detects resistance when 20% or more of the circulating HIV is drug resistant. Therefore, a result detecting sensitive HIV cannot exclude the possibility of low-level drug resistance – this is more likely in patients who are tested many months or years after infection or after cessation of antiretroviral therapy.

MONITORING HIV INFECTION

PLASMA VIRAL LOAD

Plasma viral load is expressed as RNA copies/ml. Currently, the routinely conducted assay has a lower limit of detection of 20 copies/mL and an upper limit of detection of 1,000,000 copies/mL. During primary HIV infection, peak viral loads are usually in excess of 106 copies /mL and are often in excess of 108 copies/mL. During the asymptomatic phase of infection viral loads stabilise at levels that vary markedly between individuals but are usually in the range of 104 -105 copies/mL. With disease progression viral load often rises to greater than 106 copies/mL. The large dynamic range of the test has meant that results are also expressed as the log10 of the copy number (for example 10,000 copies/mL is also expressed as 4.00 log10 copies/mL). The test depends on massive amplification of viral plasma RNA.

This amplification unavoidably limits the reproducibility of the test. This means that changes of less than 3 fold or 0.5 log10 copies/mL may be due to test to test variation rather than having clinical implications. Therefore, the test should be repeated if there is uncertainty regarding its clinical implications.

Following therapy, the aim is to reduce viral load to <50 copies/mL. This indicates that viral turnover is significantly limited and the ability of the virus to develop drug-resistant mutants is greatly curtailed.

CD4+ T CELL COUNTS

CD4+ T cell counts are reported as percentage of total lymphocytes and as absolute number of cells/µL of whole blood. Usually, the absolute count rather than the percentage is used to make clinical decisions. The normal level of CD4+ T cells is >500 cells/µL. Current recommendations state that antiretroviral therapy commences at 350 to 500 cellsµ/L. CD4+ T-cell counts <200 cells/µL indicate severe immunocompromise and susceptibility to opportunistic infections. Chemo-prophylaxis for opportunistic infections should commence when CD4+ T cell counts approach this level. CD4+ T cell counts less than 100cells/µL are associated with increasing susceptibility to a range of opportunistic infections particularly recurrence of previously quiescent CMV and Toxoplasmosis infections.

Like lymphocyte counts, CD4+ T-cell counts will vary with time. In general, changes in CD4+ T-cell counts >30 cells/µL are clinically significant. Usually the % CD4 varies less than the total count. In individuals who are hypo or asplenic then the % CD4 value should be monitored as the peripheral lymphocyte count will be spuriously raised.

Post initiation of therapy, CD4+ T-cell counts usually rise. Effective therapy usually results in an initial rapid rise in the CD4+ T-cell count followed by a stabilisation or more gradual rise in CD4+ T-cell count that persists over several months or even years.

INDICATIONS

CD4+ T cell counts and viral loads should be used to monitor established HIV infection and the response to anti-retroviral therapy. Normally these tests are performed together 3-4 times per year depending on clinical indications. CD4+ T cell counts and viral load should be performed immediately prior to commencing therapy in order to establish an “off treatment” baseline. A significant fall in viral load should be seen within 4 weeks of commencing therapy and a viral load less than 50 copies/ml should be attained within 16-20 weeks of therapy. Once stable on a therapeutic regimen then CD4 counts and viral loads can be performed 3-4 time/year unless there is a change in clinical status.

SUPPLEMENTAL TESTS

A full blood count must be ordered in conjunction with a request for CD4+ T-cells. Once the diagnosis is established it is not necessary to repeat the serological tests performed for the

diagnosis of HIV (western blot and ELISAs). In established infection the p24 antigen test provides less information than the viral load and should not be ordered. When a CD4 count is ordered the results will include a CD8 and total T-cell count. The CD8 T-cell count does not usually provide any prognostic information. Measures of immune activation such as ?2-microglobulin and neopterin or CD8+ CD38+ cell counts do not provide extra clinical information except in particular circumstances. A failure of response to initiation of therapy or a failure of an established therapeutic regimen requires further investigation, including HIV genotypic resistance testing.

HIV tropism testing is used to determine whether a patient's HIV is sensitive to CCR5 antagonist therapy. About 70% of HIV strains use the CCR5 chemokine receptor as a means to infect T-cells. CCR5-using strains can be blocked using a CCR5 antagonist (currently, maraviroc is the only licensed CCR5 antagonist). HIV tropism is determined by sequencing the envelope region of HIV that binds to CCR5 and CXCR4 (the other chemokine receptor for HIV). The assay should be performed in the 3 months prior to commencing CCR5 antagonist therapy.