Standard of care for HIV infected individuals/aids patients in Slovenia. Short review

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SUMMARY

The routine screening protocol for Slovenian patients with established HIV infection is presented. Complete blood count is especially important in patients with HIV infection since anemia, leucopenia, lymphopenia and thrombocytopenia are found in 30% to 40% of patients. Serum chemistry panel is commonly advocated in the initial evaluation of HIV infection due to high rates of hepatitis, multisystem diseases and multiple drugs that are potentially toxic. CD4 cell count is a standard test to stage the disease, to predict clinical progression and to make therapeutic decisions regarding antiviral treatment and prophylaxis for opportunistic pathogens. Quantitative plasma HIV RNA is useful for diagnosing acute HIV infection, for predicting progression in chronically infected patients and for therapeutic decisions and monitoring. Genotypic resistance testing is indicated for chronically infected patients receiving antiretroviral drugs with treatment failure. Serological tests for hepatitis viruses, toxoplasmosis and cytomegalovirus infection, purified protein derivative (PPD) skin test, the venereal disease research laboratory (VDRL) test, *Treponema pallidum* hemagglutination (TPHA) test, Papanicolaou (PAP) smear test, fasting glucose and lipid profile are also performed. Chest x-ray is indicated for symptoms and signs suggesting pulmonary disease or newly detected positive PPD. When to start antiretroviral therapy remains controversial. Though treatment is individualized, there are a lot of problems with compliance, adherence, tolerance, side effects, patient's quality of life and resistance of the virus.

KEY WORDS

HIV, AIDS, patients, standard care, Slovenia

Screening for patients with HIV infection (routine laboratory tests in asymptomatic patients)

Complete blood count (CBC)

The CBC is especially important in patients with HIV infection since anemia, leucopenia and thrombocytopenia are found in 30% to 40% of AIDS patients. The CBC should be repeated at 3 to 6 months intervals, in part because this is a necessary of monitoring the CD4 cell count. More frequent testing is recommended in patients with symptoms suggesting bone marrow suppression, those receiving bone marrow-suppressing drugs such as zidovudine, and those with marginal or low CD4 cell counts (1).

Serum chemistry panel

This panel is of limited value in a general health screen but is commonly advocated in the initial evaluation of HIV infection due to high rates of hepatitis in patients at risk for HIV. It can be used to obtain baseline values in patients who are also likely to have multisystem disease, and as a baseline test in patients who receive multiple drugs that are potentially hepatotoxic. These tests are repeated annually or more frequently in patients with abnormal results and with administration of hepatotoxic or nephrotoxic drugs (1).

CD4 cell count

This is a standard test to stage the disease, to formulate the differential diagnosis from patients' complaints. It represents a milestone for therapeutic decisions regarding highly active antiretroviral treatment (HAART) and prophylaxis for opportunistic pathogens. It is also a relatively reliable indicator of prognosis that complements the viral load assay. These two assays independently predict clinical progression and survival. CD8 cell counts have not been found to predict the outcome. The standard method for determining CD4 count uses flow cytometers and hematology analyzers that are expensive and require fresh blood. This test should be repeated every 3 to 6 months (2).

Quantitative plasma HIV RNA (viral load)

Viral load is useful for diagnosing acute HIV infection, for predicting progression after primary infection (set point) and progression in chronically infected patients, and for therapeutic decisions and monitoring.

Acute HIV infection: plasma HIV RNA levels are commonly used to detect the acute HIV infection prior to seroconversion. However, the use of HIV DNA qualitative assay performed on whole blood is more appropriate for diagnosing acute HIV infection.

Prognosis: there is a strong association between initial HIV RNA load and rate of progression that was independent of the baseline CD4 count.

Probability of transmission: The probability of HIV transmission with nearly any type of exposure is directly correlated with viral load.

Therapeutic monitoring: following initiation of therapy, there is a rapid initial decline in HIV RNA level (alpha slope), reflecting activity against free plasma HIV virions and virions present in acutely infected CD4 cells. This is followed by second decline (beta slope) that is longer in duration (months) and more modest in degree. The maximum antiviral effect is expected in 4-6 months after starting of therapy.

Method: HIV RNA PCR (Amplicor HIV-1 Monitor version 1.5, standard and ultrasensitive assay, Roche Molecular Systems, Mannheim, Germany).

Frequency of testing: at baseline (twice), followed by testing at 3 to 4 months intervals. With introduction of new therapy and changes in therapy, HIV RNA should be measured at 2 to 4 weeks (alpha slope), 12 to 16 weeks, and at 16 to 24 weeks. An optimal response to therapy should be associated with at least 1.5 to 2 $\log_{10}$ decrease of viral load at 4 weeks, <500 copies HIV RNA/mL plasma at 12 to 16 weeks, and <50 copies/mL at 16 to 24 weeks (3,4).

Genotypic resistance testing

Resistance testing is an *in vitro* method to measure resistance of HIV to antiretroviral agents. Resistance testing most reliably identifies drugs that should be avoided, but not necessarily the drugs that are most likely to be active. Testing should be performed in the presence of the antiretroviral agents in question, since discontinuation of therapy often results in the proliferation of wild type virus that may deceptively suggest susceptibility. The time between discontinuation of HAART and the shift from resistant strains to wild type virus is usually 2 to 8 weeks.

Indications for resistance testing: chronically infected patient receiving HAART with failure to decrease viral load >0.5 to 0.7 $\log_{10}$ copies/mL by 4 weeks, failure to decrease viral load >1 $\log_{10}$ copies/mL by 8 weeks or viral load >1000 copies/mL after 16 to 24 weeks (5).

Consider resistance testing: acute HIV syndrome

Not recommended: before starting therapy in naïve patients with chronic HIV infection

in patients without HAART for more than 2 weeks if viral load is less than 1000 copies/mL

Method: DNA sequencing (ViroSeq HIV-1 Genotyping System, Abbott Laboratories, Chicago, USA)

PPD skin test

Mantoux-method tuberculin skin test, using 5 units of purified protein derivative (PPD), is recommended for HIV-infected patients who have not had a prior positive test. Test should be repeated annually if initial test was negative and if patient belongs to population with a high risk of tuberculosis (homeless individuals, injecting drug users, prisoners). Induration of ≥5mm represents a positive result (6).

Serology for hepatitis viruses

Guidelines recommend screening for hepatitis core antibody (anti-HBc) with HBV vaccination of those who are susceptible. Antibody screening is advocated for high-risk populations to avoid the expense of unnecessary vaccination. Postvaccination serology with anti-HBs is recommended 1 to 6 months after the third dose of vaccine to confirm an antibody response (7).

All HIV-infected persons should be tested for HCV infection using the EIA screening assay for anti-HCV antibodies. Supplemental antibody testing with recombinant immunoblot assay (RIBA) and qualitative RT-PCR for HCV RNA are also advocated (8,9).

The usual purpose of hepatitis A serology is to identify candidates for HAV vaccine. Some authorities believe that all HIV-infected persons should be vaccinated for HAV (10).

Toxoplasmosis serology

Toxoplasma serology (IgG) is recommended to assist in the differential diagnosis in the case of complications involving the CNS, to identify candidates for toxoplasmosis prophylaxis if trimethoprim/sulfamethoxazole (TMP/SMX) cannot be taken, and to counsel patients on preventive measures if seronegative. Screen all patients and repeat test in seronegative patients if symptoms suggest toxoplasmosis or encephalitis (1).

Cytomegalovirus (CMV) serology

CMV serology (IgG) is advocated to identify seronegative patients for counseling on CMV prevention (although the message is not different from the »safe sex message« for preventing HIV transmission), to assess the likelihood of CMV disease in late-stage HIV infection, and to identify seronegative individuals who should receive CMV-antibody-negative blood or leukocyte-reduced blood products for non urgent transfusions (1).

Syphilis serology

The usual screening test (VDRL) should be performed at baseline and repeated annually. A lumbar punction is recommended for patients with early syphilis (<1 year) when it is accompanied by neurologic signs or symptoms, when it is not treated with standard regimen (2.4 million units of benzathine penicillin), and in all patients with latent syphilis regardless of the clinical findings. A relapse is common even with recommended therapy, so follow-up VDRL tests with titers are advised at 3, 6, 9, 12, and 24 months for primary and secondary syphilis, and every 6 months thereafter until becoming negative (1).

PAP smears

A gynecological evaluation with pelvic examination and a Papanicolau (PAP smear) should be performed at baseline and repeated at 6 months and then annually if results are normal. There is strong association between HIV infection and detectable and persistent human papillomavirus (HPV) infection (1).

Monitoring adverse drug reactions

Adverse drug reactions attributed to antiretroviral agents include diabetes mellitus, blood lipid changes associated with risk of coronary artery disease and stroke, and lactic acidosis/steatosis attributed to nucleoside analogs. Fasting blood glucose, total cholesterol, HDL, LDL, triglycerides measurements should be performed at baseline and every 3 to 4 month intervals. Other tests commonly recommended in patients receiving PIs are fasting insulin level and 2-hour glucose tolerance test. Routine therapeutic monitoring is not recommended for lactic acidosis, but lactic acidosis should be considered in patients who are receiving nucleoside analogs and who have unexplained nonspecific symptoms (fatigue, abdominal pain, vomiting, hepatitis, and weight loss) (11).

Chest x-ray examination

A routine chest x-ray examination is recommended for detection of asymptomatic tuberculosis in patients with newly detected positive PPD test and in patients in whom various pulmonary disorders are suspected (1).

Treatment

Treatment of the HIV infection is likely to be lifelong. Since we are only 6 years into the era of HAART, many questions concerning its best application remain to be answered. Despite a huge reduction in morbidity and mortality seen over last years, we are still facing problems regarding when to initiate HAART and what drugs to use. The current strategy leads to frequent switching of HAART regimens which may exhaust effective treatment options. So it still remains controversial when to start HAART. Through treatment is individualized, there are problems with compliance, adherence, tolerance, side effects, patient's quality of life and resistance of the virus. Our national guidelines recommend starting HAART in symptomatic patient (aids or severe symptoms), in recently infected patients (primary infection) or asymptomatic patients with CD_4 count below 300 cells/mm^3 and/or HIV–RNA PCR more than 30 000 – 100 000 copies/mL (12-14).

Conclusions

It is important for HIV infected individuals to be under continuous medical supervision. The physician and his patient usual establish a long-term partnership, in which each understands and respects the other's views, and treatment decisions are made together. Regular appointments are usually planned at least at 3-

monthly periods, including assessments of recent blood tests and a discussion of any new problems that have arisen since previous visits. If treatment was started recently, if there appeared some changes in laboratory results or the patient noticed any alarming symptom, an appointment should be arranged immediately or at shorter intervals.

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