Pharmacology Literature Review

Recent advances of drug therapy of Acquired Immune Deficiency Syndrome (HIV treatment)

Group 20 – 2003/04 Batch

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ABSTRACT

Acquired Immune Deficiency Syndrome (AIDS) is the most serious stage of Human Immunodeficiency Virus (HIV) infection. It results from the destruction of the infected person's immune system.[2.1] HIV types, derived from retrovirus, a member of lentivirus genus, are the etiologic agents of AIDS.[1.1] There are two distinct types of human AIDS virus: HIV-1 and HIV-2.[1.2] The illness was first described in 1981, and HIV-1 was isolated by the end of 1983.[1.3] If a person is infected with HIV and his $CD4^+$ T cell count drops below 200 (cells/mm^3) or develops an AIDS-defining condition, that person has AIDS.[2.2] AIDS-defining conditions are various opportunistic infections of fungal, bacterial, viral and protozoan origin as well other diseases like neoplasm, wasting syndrome etc.[2.3]
HIV was declared as a global emergency in 2003.[3.1] There were 4.9 million people newly infected with AIDS and 40.3 million were living with HIV in 2005.[4] It is estimated that approximately 16000 new infections occur daily.[3.2] The highest prevalence was recorded in Sub-Saharan Africa, which was 25.8 million.[4] In Sri Lanka HIV infections were first detected in 1987.[5]

HIV and AIDS hinder human development in both low and high prevalence setting. It has a serious impact on household and communities.[6]

The retrovirus HIV attacks primarily the $CD4^+$ molecules of the T lymphocytes, invading them by binding to group 41 receptors.[7.1] Then subsequent chain of reactions occurs after releasing the viral materials to the host cell. DNA copies are prepared from viral RNA by reverse transcriptase enzyme of the virus. The ultimate result is forming genetic and structural materials of virus inside the host cell and budding off of a new virus, while the host cell is destructed. This process is aided by proteases in the virus. So that the efficiency of cell mediated immunity is coming down gradually.[7.2]

The whole picture of clinical manifestations lies on either the direct effect of the virus it self or the immunodeficiency caused by the virus. Neurological diseases such as sensory and autonomic neuropathies, eye diseases, mucocutaneous complications, haematological and other systemic disorders etc; are being described as the direct effects of virus.[7.3] Tuberculosis caused by typical or atypical mycobacteria has become a vast problem which increases the mortality of the HIV infected population.[7.4] It is particularly due to the resulting immunodeficiency. As well other opportunistic bacterial, viral, protozoan and fungal infections have dealt with diseases in those people to a greater extent.[7.5] Kaposi sarcoma, lymphomas, etc are well known neoplasm associated with immunodeficiency.[7.6]

The standard serologic test for screening HIV is an ELISA test, which detects antibody to HIV. Positive Screening test should be followed by a confirmatory western blot (WB) or the Immunoassay test.[8.1] After confirming HIV, screening laboratory tests should be done. It includes full blood count, serum chemistry, CMV IgM, anti-toxoplasma IgG, syphilis serology, test for other STD, Pap smear, immunological markers-$CD4^+$, $CD8^+$ counts, and HIV-viral load.[8.2]

Objectives of treatments are reduce HIV-related morbidity and mortality, improve quality of life, restore and preserve immunologic function, and maximally and durably suppress viral load.[9.1]

Non pharmacological treatment of patients with HIV or AIDS includes counseling and psychosocial management[10.4]. Counselling in HIV has two general aims: The prevention f HIV transmission and the support of those affected directly and indirectly by HIV[10.1]. A pre-test and a post-test counselling should be done. For patients at minimal risk of HIV infection, pre-test discussion provides a valuable opportunity for health education. For patients who are at risk of HIV infection it is an essential part of post-test management[10.2]. Patient's partner is also should be counselled because the adjustments to sexual behaviour and other lifestyle issues can be discussed.[10.3]

Drug therapy of HIV/AIDS patients is antiretroviral therapy.[11.1] It is indicated for all patients with history of an AIDS-defining illness or severe symptoms of HIV infection regardless of $CD4^+$ T cell count. Antiretroviral therapy is also recommended for asymptomatic patients with <200 $CD4^+$ T cells/mm^3 and asymptomatic patients with $CD4^+$ T cell counts of 201–350 (cells/mm^3).[9.2] There are four classes of antiretroviral drugs. They are non-nucleoside reverse transcriptase inhibitors (NNRTI), nucleoside reverse transcriptase inhibitors (NRTI), protease inhibitors (PI), and entry inhibitors (EI).[9.3] Since ten years a combination antiretroviral therapy is recommended for HIV/AIDS patients. This is also known as 'highly active antiretroviral therapy' (HAART).[9.4] The first-line regimen for adults and adolescents contain two NRTIs plus one NNRTI.[11.2] This combination is efficacious, generally less expensive and has generic formulations. In addition, they preserve a potent new class (PIs) for second-line treatments.[11.3] Efavirenz is the preferred NNRTI.[9.5] Efavirenz is contraindicated in first trimester of pregnancy and in women with high pregnancy potential.[9.5] Other alternative NNRTIs are nevirapine and delavirdine.[9.6] A major disadvantage of NNRTIs is that they become resistant to HIV quickly.[9.7] Main unwanted effect is skin rash.[9.8] Preferred dual NRTIs as part of initial combination therapy are tenofovir/emtricitabine (co-formulated) and zidovudine/

lamivudine (co-formulated).[9.9,11.4] Alternative dual NRTIs are abacavir/lamivudine (co-formulated) and didanosine with lamivudine or emtricitabine.[9.9] Emtricitabine may be used in place of lamivudine or vice versa.[9.9] One fixed-dose combination in first-line treatment consists of efavirenz, emtricitabine and tenofovir.[9.10] Two triple NRTI-based regimens are accepted.[11.5] They are zidovudine/ lamivudine/ abacavir (co-formulated), zidovudine/ lamivudine/ tenofovir.[11.5] Antiretroviral agents are responsible for a broad range of toxicities such as hypersensitivity reactions, renal toxicity, neuropathy.[11.6] Drug substitutions can be done due to toxicity.[11.7] First-line treatment failure is confirmed by clinically, or using $CD4^+$ cell count and virological count.[11.8] If treatment failure occurs, the entire regimen is stopped and changed into second-line regimen.[11.9] In second-line regimen PI component is included.[11.10] In PI-based regimens (1 or 2PIs + 2NRTIs) preferred PIs are atazanavir/ritonavir, fosamprenavir/ritonavir and lopinavir/ritonavir (co-formulated).[9.10] The potent inhibitory effect of ritonavir on the cytochrome P450 3A4 isoenzyme has allowed the addition of low-dose ritonavir to other PIs (with the exception of nelfinavir) as a pharmacokinetic booster to increase drug exposure and prolong plasma halflives of the active PIs.[9.11] This allows for reduced dosing frequency and pill burden.[9.11] Main side effects of PIs are metabolic disorders such as dyslipidaemia and insulin resistance.[9.12] In whom first-line triple NRTI therapy has failed, boosted PI / NNRTI can be considered.[11.11] Enfuvirtide is the first HIV fusion inhibitor to be licensed for use in clinical practice.[12] Its use is limited by the fact that it needs to be injected subcutaneously twice daily.[12] Monotherapy with NRTI or NNRTI, only dual-NRTI regimens and triple-NRTI regimens except for abacavir/zidovudine/lamivudine (co-formulated) and triple class regimens (e.g. NRTI + NNRTI + PI) are not recommended at any time.[9.13] Special considerations should be taken when giving ART with pregnancy, tuberculosis, hepatitis.[11.12]

Essential programmatic actions for HIV prevention are: Prevent the sexual transmission of HIV, Prevent mother-to-child transmission of HIV, Prevent the transmission of HIV through injecting drug use including harm reduction measures, Ensure the safety of the blood supply, promote greater access to voluntary HIV counselling and testing while promoting principles of confidentiality and consent, Integrate HIV prevention into AIDS treatment services, Focus on HIV prevention among young people, Provide HIV-related information and education to enable individuals to protect themselves from infection, Confront and mitigate HIV-related stigma and discrimination, Prepare for access and use of vaccines and microbicides.[13]

Discovery of HARRT is a huge advance in the treatment of HIV/AIDS. It has reduced the mortality rate of HIV infected people dramatically in past few years.[14] Fixed-dose combinations which came recently reduce the number of pills that should swallow daily.[9.10, 15] New and diverse classes of compounds interfering with the HIV entry process into target cells are approaching clinical application. Entry inhibitors constitute a new class of drugs to treat infection by HIV-1[16.2]. The first member of this class, enfuvirtide, previously known as T-20 and targeting gp41, has now been licensed for therapeutic use.[16.1] Recent clinical studies with a small number of HIV-infected subjects provided proof-of-principle for the antiviral effectiveness of CCR5 and CXCR4 antagonists (chemokine receptor inhibitors).[16.3] 2′,3′-Didehydro-3′-deoxy-4′-ethynylthymidine (4′-Ed4T), is a recently discovered nucleoside reverse transcriptase inhibitor (NRTI) showing a 5- to 10-fold greater anti-human immunodeficiency virus type 1 (HIV-1) activity and less cellular and mitochondrial toxicity than its parental compound, stavudine (D4T).[17] New drugs like tenofovir, emtricitabine, and enfuvirtide are being rapidly introduced into antiretroviral treatments for adult patients.[18] In addition, some well-established drugs are being modified to make them more convenient (specifically didanosine and stavudine).[18] New therapeutic options for children with HIV infection are becoming available as the pharmacokinetics and best strategies for use of newer drugs are studied.[18] Antiviral effects of mifepristone on HIV-1 was discovered recently. It targets the HIV-1 viral protein R (Vpr) and its cellular partner, the glucocorticoid receptor (GR).[19] New ideas for candidate vaccines have been developed, including several based on HIV-1 strains prevalent in Africa. HIV vaccine efficacy trials are needed in Africa to determine whether these advances can be translated into clinical and public health benefits.[20] It is recently found that virucidal agents such as platinum triazines can be used in HIV prevention. [21] In recent years, perinatal HIV-1 transmission rates in the United States have declined markedly because of widespread use of antiretroviral prophylaxis.[22] Only a tiny minority of the estimated six million people in need of antiretrovirals in resource-poor countries are receiving treatment. In 2003, UNAIDS and WHO launched a campaign—the '3 by 5' Initiative—aimed at ensuring that at least 3 million of these people have access to antiretroviral therapy by 2005.[23]

In conclusion, the past ten years has shown a lot of activity in research concerning treatment outcomes. Several studies has shown the equal importance in quality counselling. But a drug or a vaccine that can totally eradicate HIV infection is still a subject of research and discussion.

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