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Approaches for Prevention and Treatment of AIDS

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ABSTRACT

AIDS is considered one of the most dangerous and a pandemic[1,2] disease which is present over a large demographic area of the world. It has a great impact on society such as an illness, a source of discrimination and economic condition of people. AIDS is the most serious infectious disease and actively spreading worldwide among humankind. Women living in lower income countries are particularly at risk as extreme poverty and other structural factors such as gender[3] inequities, lack of education and violence reduce their ability to control health outcomes or access HIV related information and services. Generally young women become more susceptible to HIV at early stage in some areas the prevalence of infection among women between 15-24 years is more than twice that of young men. Human immunodeficiency virus infection/acquired immune deficiency syndrome (HIV/AIDS) is a disease of human immune system caused by infection with human immune deficiency virus. AIDS is called when a person infected with HIV has a CD4+ count of less than 200cells/µL or has an AIDS defining condition. HIV gradually destroys the immune system by attacking and killing CD4 cells. HIV uses the machinery of the CD4 cells to multiply (make copies of it) and spread throughout the body. Globally[4] AIDS is spreading actively among developed and developing countries. During the initial infection a person may feel a brief period of influenza like illness. As the illness progresses it interferes more and more with the immune system making the person much more likely to get infections including opportunistic infections and tumors.

Keywords: AIDS, Human immune system

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INTRODUCTION

HIV is transmitted[1-8] primarily via unprotected sexual intercourse (including anal and even oral sex), contaminated blood transfusions, hypodermic needles and from mother to child during pregnancy, delivery or breastfeeding. Prevention[9-12] of HIV infection primarily through safe sex,male circumcision, use of diaphragms, substance abuse treatment, condom use, use needle exchange programs are key strategies to control the spread of disease and may lead to a near normal life expectancy. While antiretroviral treatment reduces the risk of death and complications from the disease these medications are expensive and may be associated with side effects. Antiviral agents have made HIV/AIDS a more manageable disease in some industrialized nations and several vaccines are about to enter phase III clinical trials. HIV will doubtless continue to impose a terrible burden of morbidity and mortality. The present review gives idea about HIV transmission, stages of HIV infections and approaches for prevention and treatment of AIDS.

HIV Transmission

HIV is transmitted principally in three ways: by sexual contact, by blood (through transfusion, blood products, or contaminated needles), or by passage from mother to child. Although homosexual[13] contact remains a major source of HIV within the various countries, heterosexual[14] transmission is the most important means of HIV spread worldwide today. Treatment of blood products and donor screening has essentially eliminated the risk of HIV from contaminated blood products in developed countries, but its spread continues among intravenous drug users who share needles. In developing countries, contaminated blood and contaminated needles remain important means of infection[15]. Thirteen to thirty-five percent of pregnant women infected with HIV will pass the infection on to their babies; transmission occurs in uterus as well as during birth. Breast milk from infected mothers has been shown to contain high levels of the virus also. HIV is not spread by the fecal-oral route; aerosols; insects; or casual contact, such as sharing household items or hugging. The risk to health care workers is primarily from direct inoculation by needle sticks. Although saliva can contain small quantities of the virus, the virus cannot be spread by kissing.

Stages of HIV Infection[16]

The Centers for Disease Control and Prevention (CDC) has identified the stages of a typical HIV infection: Categories A, B and C.

In the first stage, Category A, it can be difficult to determine whether an individual is infected without performing a blood test. While at least half of infected individuals will develop a mononucleosis-like illness (headache, muscle ache, sore throat, fever, and swollen lymph nodes) within three weeks of exposure, some Category A individuals are asymptomatic.

Moreover, the symptoms themselves can be the result of many different infections. The presence of a rash may help differentiate an HIV infection from other infections, but not all HIV infected individuals get a rash. Most of these signs and symptoms subside, but swollen lymph glands and malaise can persist for years through Category A HIV. In this stage CD4 count is greater or equal to 500 cells/µl and no AIDS defining conditions

In the Category B stage indications of immune system failure begin. Persistent infections such as yeast infections, shingles, diarrhea, and certain cancerous conditions of the cervix are apparent.In this stage CD4 count is between 200 to 500 cells/µl and no AIDS defining conditions

Category C is synonymous with AIDS. Category C HIV (clinical AIDS) occurs once CD4 numbers have fallen substantially (to 200/mm*3* from the normal level of 800–1200 cells/ mm*3*).Generally in this stage CD4 count is less than or equal to 200 cells/µl and known as AIDS defining conditions. In this stage the opportunistic infections associated with AIDS appear. According to the CDC known clinical conditions affect people with AIDS; most are infections that do not usually affect healthy individuals. These include yeast infections of the esophagus, bronchi, and lungs; *Pneumocystis* pneumonia (a fungal infection); toxoplasmosis (caused by a protozoan that is spread by cats); Kaposi's sarcoma (a rare cancer of the skin caused by a virus); cytomegalovirus (CMV) infections; and tuberculosis. In addition, individuals who have been affected by HIV are more likely to become seriously ill or die than other members of the population during outbreaks of infections such as cryptosporidium (a water-borne parasite) and coccidiomycosis (a dust-borne fungus). Cytomegalovirus (CMV) causes another opportunistic infection prevalent in AIDS patients.

Approaches for prevention of AIDS

Antiretroviral therapy (HAART)

Beginning in the mid-1990s, an increasing number of HIV-infected individuals began a drug regime called highly active antiretroviral therapy (HAART) a combination of three or more anti-HIV drugs taken at the same time[17]. The simultaneous intake of multiple drugs, each targeting different aspects of the viral life cycle, circumvents the ability of the virus to mutate and become resistant to the drugs. Combined therapies, often called cocktails can knock virus back to undetectable levels and improve patient health significantly. With the advent of HAART[18,19] deaths from HIV began to decline in various countries. Unfortunately, HAART has several long-term side effects including kidney, liver, and pancreatic problems; and changes in fat metabolism which result in elevated cholesterol and triglyceride levels and an increased risk for strokes and heart attacks. In addition, some viruses have evolved resistance to HAART[20].

Table 1: FDA approved Entry inhibitors for antiretroviral therapy (HAART)

Generic Name	Adult dose(mg)/day	Brand Name	Manufacturer	FDA Approval Date
Enfuvirtide	90(2) Subcutaneously	Fuzeon	Hoffmann La Roche	March 13,2003
Maraviroc	400(2)	Selzentry	Pfizer	Aug.6,2007

Table 2: FDA approved Integrase inhibitors (IIs) for antiretroviral therapy (HAART)

Generic name	Adult dose(mg)/day	Brand name	Manufacturer	FDA approval date
Raltegravir	400(2)	Isentress	Merck	Oct.12,2007

Table 3: FDA approved Nucleoside Reverse Transcriptase Inhibitors (NRTIs) for antiretroviral therapy (HAART)

Generic name	Adult dose(mg)/day	Brand name	Manufacturer	FDA approval date
Zidovudine	200(3)	Retrovir	GlaxoSmithKline	March19,1987
Abacavir	300(2)	Ziagen	ViiV Healthcare	Dec.17,1998
Lamivudine	150(2)	Epivir	GlaxoSmithKline	Nov.17,1995
Stavudine	30-40(2)	Zerit	Bristol Meyers Squibb	June 24,1994
Zalcitabine	0.75(3)	Hivid	Hoffmann La Roche	Mar.19,1992
Didanosine	200(2)	Videx Videx EC	Bristol Meyers Squibb	Oct.9,1991
Tenofovir disoproxil fumarate	300(1)	Viread	Gilead Sciences	Oct.26,2001
Emtricitabine	200(1)	Emtriva	Gilead Sciences	July 2,2003

Table 4: **FDA approved Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) for antiretroviral therapy(HAART)**

Generic name	Adult dose(mg)/day	Brand name	Manufacturer	FDA approval date
Delavirdine	400(3)	Rescriptor	ViiV Healthcare	April4,1997
Efavirenz	600(1)	Sustiva	Bristol-Myers Squibb	Sept.17,1998
Etravirine	200(2)	Intelence	Tibotec	Jan18,2008
Nevirapine	200(1)first 14days then 2 times daily	Viramune	Boehringer Ingelheim	June21,1996
Rilpivirine	25-150(3)	Edurant	Janssen Pharmaceuticals, Inc	May 20,2011

Table 5: FDA approved Protease inhibitors (PIs) for antiretroviral therapy(HAART)

Generic name	Adult dose(mg)/day	Brand name	Manufacturer	FDA approval date
Atazanavir	300(1)	Reyataz	Bristol Meyers Squibb	June20,2003
Indinavir	800(3)	Crixivan	Merck	March13,1996
Darunavir	600(2)	Prezista	Janssen Cilag Pty Ltd.	June 23,2006
Fosamprenavir	1400(2)	Lexiva	ViiV Healthcare	Oct.20,2003
Nelfinavir	1250(2)	Viracept	ViiV Healthcare	March14,1997
Ritonavir	600(2)	Novir	Abbot Laboratories	March1,1996
Tipranavir	500(2)	Aptivus	Boehringer Ingelheim	June 20,2005
Saquinavir	1200(3)	Invirase	Hoffmann La Roche	Dec.6,1995

Table 6: Nucleotide Reverse Transcriptase Inhibitors (NRTIs) for antiretroviral therapy (HAART)

Generic Name	Brand Name	Manufacturer
Tenofovir disoproxil fumarate	Viread	Gilead Sciences

Table 7: FDA approved Fixed dose combinations for antiretroviral therapy (HAART)

Generic name	Brand name	Manufacturer	FDA approval date
Zidovudine+Lamivudine	Combivir	GlaxoSmithKline	Sept.26,1997
Abacavir+Lamivudine	Epzicom(USA), Kivexa(Europe)	GlaxoSmithKline	Aug.2,2004
Abacavir+Zidovudine +Lamivudine	Trizivir	GlaxoSmithKline	Nov.15,2000
Lopinavir+ritonavir	Kaletra	Abbot Laboratories	Sept.15,2000
Tenofovir+Emtricitabine	Truvada	Gilead Sciences	August 2,2004
Efavirenz+Tenofovir +Emtricitabine	Atripla	Gilead Sciences and Bristol Meyers Squibb	July 12, 2006
Rilpivirine+Tenofovir +Emtricitabine	Complera	Gilead Sciences and Tibotec	August 10,2011
Elvitegravir+Cobicistat +Tenofovir/emtricitabine	Stribild	Gilead Sciences	August 27.2012
Dolutegravir +Abacavir/Lamivudine	Triumeq	ViiV Healthcare	August 22,2014

Table 8: Antiviral for HIV infection

Product name	Sponsor	Development phase
Apricitabine	Avexa	Phase III
Reformulated raltegravir	Merck	Phase III
F/TAF(emtricitabine/tenofovir alafenamide fixed dose combination)	Gilead Sciences	Phase III
Cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide fixed dose combination	Gilead Sciences	Phase III
Cobicistat/darunavir/emtricitabine/tenofovir alafenamide fixed dose combination	Gilead Sciences	Phase II
Amdoxovir	RFS Pharma	Phase II
MK-1439 (doravirine)	Merck	Phase II

Vaccine Development[20,21]

HIV infects only humans and chimpanzees. HIV resides in cells that are present in the genital tract and rectal tissues of HIV-infected men and women, and secretions from these cells contain both cell-free viral particles (i.e., virions) and cell-associated HIV. Chimpanzees are scarce, expensive, and do not show signs of disease when infected. There are also ethical concerns raised because chimpanzees are our closest evolutionary relatives. An alternative is the development of a monkey model using simian immunodeficiency virus (SIV) that has been genetically engineered to express HIV components. Although the results reached statistical significance, the effect sizes were quite modest and the mechanism of action of the combination vaccine regimen was unclear. Although the level of protection was not of sufficient magnitude for promotion as a public health prevention strategy, the results of this trial may be useful in guiding future HIV vaccine research and suggest that combination vaccination strategies may be efficacious. It may be possible to enhance the immunogenicity of adenovirus vaccines by boosting them with naked DNA containing antigens similar to

those delivered by the viral vector. In addition, some of the newer vaccine trials are considering whether people who become infected after receiving the vaccine are better able to control HIV infection. These studies are based on the idea that if a vaccine cannot be fully protective against acquiring HIV, it may help a person who becomes infected to better control viral replication for many years, thus delaying the need to initiate antiretroviral therapy. This would allow the person to stay healthier for a longer period of time and may make the people who receive the vaccine less infectious to future partners.

Table 9: Cell therapy for HIV infection

Product name	Sponsor	Development phase
Cal-1(blood stem cell therapy)	Calimmune	Phase I/II
MazF gene therapy	Takara Bio	Phase I
SB-728-T(CCR5 receptor modulator)	Sangamo Bio Sciences	Phase II

Table 10: Vaccines development for HIV-1 infections

Product name	Sponsor	Development phase
AGS-004(personalized immunotherapy)	Argos Therapeutics	Phase II
GOVXB11(DNA/MVAvaccine)	Geo Vax Labs	Phase II
HIV recombinant vaccine	GlaxoSmithKline	Phase II
HIV Vaccine	Novartis	Phase I
HIV Vaccine(Ad4-mGag)	PaxVax	Phase I
HIV Vaccine(Ad4-EnvC150)	PaxVax	Phase I
HIV Vaccine(SAV001)	Sumagen Canada	Phase I
Pennvax-B(DNA vaccine)	InovioPharmaceuticals	Phase I
Pennvax-G (DNA Vaccine clades A,C,D)	InovioPharmaceuticals	Phase I
Remune (HIV Vaccine)	Immune Response BioPharma	Phase III
RemuneX(HIV combination vaccine)	Immune Response BioPharma	Phase III
Vacc-4x(Intradermal vaccine)	Bionor Pharma	Phase II
PBSVax(HIV-MAG DNA vaccine)	Profectus Bio Sciences	Phase I

Alternative medicine for AIDS

Herbal medicines provide rational means for the treatment of many diseases that are obstinate and incurable in other systems of medicine. These are gaining popularity because of several advantages such as often fewer side effects, better patient tolerance, relatively less expensive and acceptance due to long history of use. Medicinal effects of plants tend to normalize physiological function and correct the underlying cause of the disorder. Medicinal plants[22-24] are renewable in nature unlike the synthetic drugs that are obtained from non-renewable sources of basic raw materials such as fossil sources and petrochemicals. Cultivation and processing of plants often is environment friendly unlike the pollution by chemical industry. Cultivation of medicinal plants can also be a source of income for poor families. Many of the medicinal plants are locally available, especially in developing and underdeveloped countries. Also, plants are often less prone to the emergence of drug resistance. Due to all these advantages, plants continue to be a major source of new lead compounds[25,26].

Topical protection

Topical microbicides are products that may be formulated as gels, sponges, films, or rings that can be applied to vaginal or rectal mucosa with the goal of preventing or significantly reducing the risk of acquiring STIs, including HIV. A topical microbicide, the spermicidal agent[27] Nonoxynol-9 (N-9) was shown safe and effective. The current group of microbicides act through several different mechanisms of action, including vaginal defense enhancers that help maintain the acidic vaginal pH which is protective against foreign microbes. PRO2000 gel a microbicide can be used to inhibit HIV entry with an acidifying agent that those receiving PRO2000 had a 30 percent decreased risk of HIV transmission compared with a non gel comparison group and a placebo control group.The first study of a topical antiretroviral compound evaluated topical tenofovir gel.The gel was safe and well tolerated and, in a small subset of HIV-infected women, did not rapidly lead to the development of resistant strains[28].

Male circumcision[29,30]

Male circumcision can provide as an HIV-prevention strategy among heterosexual men. Male circumcision significantly reduced the risk of HIV acquisition by approximately 50 percent among uninfected men. However this approach may not be effective for other groups. For example among women one study showed that HIV-infected men who were circumcised did not become less infectious to their female partners which may be a result of increased sexual activity by the men too soon after the procedure.

Use of diaphragms[31]

The Methods for improving Reproductive Health in Africa (MIRA) trial examined the effectiveness of using a diaphragm with lubricant to prevent the acquisition of HIV among women in Zimbabwe and South Africa. The trial found that the use of diaphragms and lubrication over and above the provision of condoms did not afford woman added protection from HIV acquisition. The annual incidence among women who received diaphragms, lubricant, and condoms was 4.1 percent whereas the annual incidence among women who only received condoms was 3.9 percent. Hence addition of diaphragms and lubricant was not better than condom use alone, the study was unable to assess whether the use of diaphragms and lubricant was more effective at preventing HIV infection than not using anything.

Substance abuse treatment[32]

Substance abuse treatment is an important HIV-prevention strategy because people in treatment are less likely to engage in risky sexual behaviors and inject drugs or share needles. Substance abuse interventions that impact HIV prevention in the U.S. include pharmacotherapy (e.g. opioid substitution; although no pharmacologic interventions have

been shown to be effective for stimulant use) and behavioral interventions, including harm reduction techniques (e.g., needle exchange programs for injection drug users), as well as group and individual therapy.

The role of alcohol and other drug use in HIV prevention[33-35]

Alcohol use is associated with unprotected intercourse. These discrepancies could be a result of the ways alcohol use was measured or variations in methods of data collection and analysis regarding the timing of sexual behavior and alcohol use. Because alcohol consumption is linked to decreased inhibition and impaired judgment and in light of contradicting data on the relationship between alcohol consumption and sexual risk behavior. The effect of consuming alcohol while taking antiretroviral has been shown to be less dangerous but may promote resistance and ultimately compromise the efficacy of the medications over time.

Counselling /intervention to promote condom use[36-38]

Condom use protects from sexually transmitted infections (STIs) and unwanted pregnancies. The use of condom depends on the knowledge and attitude of users towards condom. Knowledge of condom is universal, but there are rural-urban differences observed. Approximately 85 and 69 per cent women from urban and rural areas respectively had heard of condom. Reason for choosing condoms over other spacing family planning methods includes the fear of side effects of other modern spacing methods. The most common reason for discontinuing oral pills, and intrauterine devices (IUDs) within one year of beginning their use was concerns with side effects or health concerns. Female condoms help protect against sexually transmitted infections, including HIV**.** Condoms are the only contraceptive method that can protect against both pregnancy and sexually transmitted infections. Require correct use with every act of sex for greatest effectiveness.

CONCLUSION

HIV/AIDS is one of the biggest problems in the world. It is life threatening disease but the mortality and morbidity of HIV infected individuals can be controlled through various approaches. It is better to control AIDS by taking preventive measure, awareness among people regarding AIDS.

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