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HIV: will no more be a dreadful disease

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Abstract:

HIV is the most dreadful disease that has become the cause of death to thousands of people from the day it got introduced to the human body. It is a disease of human immune system that turns fatal with the weakening of this system and causes AIDS. HIV weakens the immune system by depleting CD4+ T cells making the body prone to other opportunistic infections. Of the two HIV forms found, HIV-1 has been reported to be more virulent than the HIV-2. In the today's world scientists and doctors are using therapeutic vaccines, gene therapy, immune based therapies or combination of such few techniques to treat HIV patients. This paper reviews how few patient were reported to cure of HIV by advanced developing techniques and focuses on how these cures made scientists to think of other alternate treatment methods and recently are found to report special antibodies that works against the HIV virus. A team of researchers reported that cell's DNA repairing machinery can be used to destroy HIV virus. Development of HIV resistant cells and other developing methods are seems promising to provide this world a feasible cure to HIV.

Keywords: HIV, CCR5, STDs, Lentivirus, Retrovirus.

Introduction:

Human immunodeficiency virus infection is a disease of the human immune system which is caused by the human immunodeficiency virus (HIV) (Sepkowitz KA, 2001). During the initial phase of the infection a person may experience a short term influenza-like illness. Later on this is followed by a prolonged period without symptoms. But as the illness progresses it interferes a lot more with the immune system, causing a significant weakening of the immune system, and thus leading the patient more prone to get other infections, including tumors and opportunistic infections that do not usually affect people with active immune systems.

HIV may be transmitted when infected blood, semen, or vaginal secretions of the affected person come in contact with an uninfected person's broken skin or mucous membranes. Even there are more chances of that an infected pregnant women can transmit HIV to her baby during pregnancy, delivery and breast-feeding to its young one. In the later stages of the infection HIV affected people will develop AIDS as a result of their HIV infection.

AIDS can be best defined as a medical diagnosis for the combination of systems which results from a breakdown of the immune system. The immune system acts like a defense system of the body against infections and diseases. The immune deficiency is caused by a viral infection. In AIDS, 'A' stands for "Acquired" which means something which does not ordinarily exist within one's body but has been obtained or received by a person. 'ID' stands for "Immune Deficiency" i.e. deficiency of immune system. 'S' stands for "Syndrome" which means a variety of symptoms

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leading to various infections and a set of diseases. AIDS is the most dreadful disease in the history of mankind which has killed many people till today (Rabindra Kumar Behuria, 2005).

History:

In 1981, a disease syndrome was seen in human population in the US which was characterized by a deficiency in the immune system (Gottlieb MD et al., 1981). Patients suffered with unusual infections such as cancers pneumonia and Kaposi's sarcoma, and other illnesses were being reported by doctors in Los Angeles and New York among a number of male patients who were keen on man to man sex. These were conditions not usually found in people with healthy immune systems. After the recognition of AIDS, in 1983 scientists discovered the causative virus for the AIDS. The causative agent for this disease was found out to be a human retrovirus from the lentivirus family, (Barre-Sinoussi F et al., 1983; Levy JA et al., 1984). Early observations indicated that intimate sexual contact (e.g., genital fluids), blood and blood products, and through mother-to-child transmission were the cause for the spread of this virus (Jay A. Levy, 2009; Jaffe HW et al., 1983). Although those three means of transmission have not changed, till today great progress has been achieved in preventing HIV infection from contaminated transfused blood and blood products and mother-to-child transmission with antiviral drugs. The discovery of HIV has rapidly led to its cloning and the identification of its genes, and a necessity to find its treatment and prevention, particularly via vaccine. Within the past 15 years, effective antiretroviral therapies have become available which are directed to act at the major enzymatic action sites of the virus (reverse transcriptase, protease, and integrase) as well as its attachment and fusion sites (Jay A. Levy, 2009). This kind of therapies and drugs offer great hope to those who are at risk of their advancing HIV infection to AIDS. Because of toxic drug side effects and drug resistance long term therapies may not have been possible (Jay A. Levy, 2009).

Transmission, Signs and Symptoms

Transmission

HIV is transmitted by three main routes: intimate sexual contact (e.g., genital fluids), blood and blood products, and through mother-to-child transmission during pregnancy, delivery, or breastfeeding (Steven B., 2007). There is no case of acquiring HIV reported if exposed to feces, saliva, sputum, nasal secretions, sweat, tears, urine, or vomit but if these are contaminated with blood such exposures could also cause an HIV infection (Kripke C, 2007). One can be simultaneously infected by more than one strain of HIV known as HIV super infection (van der Kuyl AC, Cornelissen M, 2007).

Sexual transmission

Intimate sexual contact with an infected person is the most frequent mode of HIV transmission. The majority of cases of transmission all over the world are reported to occur through heterosexual contacts (Steven B., 2007). However, the pattern of transmission varies significantly country to country like in the US, as of 2009, most sexual transmission occurred

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through homosexual contacts among men(Steven B., 2007) accounting for 64% of all new cases (Center for Disease Control and Prevention, 2012).

Regarding unprotected heterosexual contacts, it is reported that the possible risk of HIV in low-income countries is 4 to 10 times higher as compared to the high-income countries (Boily MC et al., 2009). The risk of getting infected by AIDS from anal intercourse is equally high in both the homo and heterosexual relations (Beyrer C et al., 2012). Risk of transmission from oral sex is very low and is having its frequency as "nil" but is still present and some cases are also reported (Yu M; Vajdy M, 2010; Sturchler, Dieter A., 2006).

Risk of transmission increases to a extent when many sexually transmitted infections like gonorrhea, chlamydia, trichomoniasis, and bacterial vaginosis are already present in the body (Dosekun O; Fox J, 2010). While in case of Genital ulcers the risk of transmission appears to increase approximately five fold (Boily MC et al., 2009). Rough sex and sexual assault are believed to cause an enhanced risk of HIV transmission as no precautionary measurements are supposed to be followed and also some physical damage to the vagina and rectum can occur with possibility of concurrent sexually transmitted diseases (Draughon JE; Sheridan DJ, 2012).

From blood and blood products

This is the next frequent mode of HIV transmission after sexual mode of transmission (Steven B., 2007). This form of transmission can be via transfusion of contaminated blood or blood products, medical injections with unsterilized equipment, or by needle-sharing during intravenous drug use. The risk of transmission during sharing a needle for drug injection is 0.63-2.4% per act with an estimated average of 0.8% (Baggaley RF et al., 2004).

In case of developed countries the risk of getting HIV from a blood transfusion is very low because in these countries proper HIV screening and donor selection is done prior to the blood transfusion (Steven B., 2007). Where as in low income countries this risk is more as compared to the developed countries as only fifty percent of the blood used for transfusions may be properly screened (UNAIDS, 2011). Up to 15% of HIV infections are estimated to cause by transfusion of infected blood and blood products in these areas (WHO, 2001).Unsafe medical injections are a major cause to the HIV transmission in sub-Saharan Africa. It was reported in 2007 that between 12-17% of infections in the area were caused by the use of infected medical syringe (Reid SR, 2009).

Mother-to-child

HIV transmission through this mode is the third most frequent mode of transmission in which infection can be transmitted to child during pregnancy, delivery, or through breast feeding (Steven B., 2007). In the absence of prior treatment to HIV, the possible risk of transmission before or during birth is around 20% (Coutsoudis A et al., 2010). With proper treatment the risk of mother-to-child transmission can be limited to about 1% (Coutsoudis A et al., 2010). Preventive measure includes antiretroviral therapy to the mother during pregnancy and delivery, avoiding breastfeeding to the newborn, and antiretroviral drug administration to the newborn baby (Thorne C; Newell ML, 2007). Most of such effective measures are however not accessible to the developing countries (Thorne C; Newell ML, 2007).

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Signs and symptoms

Three main stages of HIV infection are:

Acute Infection

The initial period of HIV is called acute HIV or acute retroviral syndrome (Mandell, Bennett, and Dolan, 2010). Influenza-like illness or a mononucleosis-like illness 2–4 weeks post exposure has been reported in case of many individuals while others have no significant symptoms (Tarrytown NY; Marshall Cavendish, 2008). Symptoms most commonly include fever, throat inflammation, large tender lymph nodes, a rash, headache, and sores of the mouth and genitals (Mandell, Bennett, and Dolan 2010). The rashes, which usually have been reported to occur in 20–50% of cases, present itself on the trunk (Vogel M, 2010). Some infected patients develop opportunistic infections at this stage (WHO, 2007). Gastrointestinal symptoms such as vomiting, nausea or diarrhea may occur. The duration of the symptoms is variable; usually it is one or two weeks (Mandell, Bennett, and Dolan, 2010).These symptoms are often not considered as signs of HIV infection because of their non-specific character. In many cases these symptoms are misdiagnosed as some other common infectious diseases by the family doctors or hospital because of the similar symptoms shown by the other infections also. Thus, it is recommended to consider only those patients as HIV infected who are presenting an unexplained fever and may have risk factors for the infection (Mandell, Bennett, and Dolan, 2010).

Clinical latency

The initial phase is followed by clinical latency also called as asymptomatic HIV, or chronic HIV (U.S. Department of Health & Human Services, 2010). This second stage of the HIV infection can last for about an average of eight years (Elliott Tom, 2012). Basically there are no or very few symptoms of the infection in the initial stage but lately near the end of this phase many patients suffers from gastrointestinal problems, fever, weight loss, and muscle pains (U.S. DHHS, 2010). Nearly 50-70% of people develop persistent generalized lymphadenopathy, which is symbolized by unexplained, non-painful enlargement of more than one group of lymph nodes (other than in the groin) for over 3 to 6 months (Mandell, Bennett, and Dolan, 2010).Mostly HIV-1 infected persons have significantly detectable viral loads which can later advances to AIDS in the absence of treatment, but as a matter of fact nearly 5% of the infected individuals retain high levels of CD4+ T cells without antiretroviral therapy for more than 5 years (Blankson JN, 2010).

Acquired immunodeficiency syndrome

Count of CD4+ T cell below 200 cells per µL in an individual or the occurrence of particular diseases in association with an HIV infection marks an individual as positive for AIDS. Without any specific treatment nearly 50% of the people infected with HIV develop AIDS within a time period of 10 years (Mandell, Bennett, and Dolan 2010). The most common initial symptoms of all that marks the presence of AIDS are pneumocystis pneumonia (40%), esophageal candidiasis and cachexia in the form of HIV wasting syndrome (20%) (Mandell, Bennett, and Dolan, 2010). Other common signs involves recurring respiratory tract infections (Mandell, Bennett, and Dolan 2010).There is unusual enhanced risk of opportunistic infections when one is infected by the

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HIV. These opportunistic infections can be caused by bacteria, fungi, viruses and parasites that are normally controlled by the immune system (Holmes CB et al., 2003). Individual suffering with AIDS are at enhanced threat of developing various viral induced cancers like Kaposi's sarcoma, primary central nervous system lymphoma, Burkitt's lymphoma, and cervical cancer (Vogel M, 2010). Kaposi's sarcoma and the lymphoma are the most common cancers and together cause the death of nearly 30% of people with AIDS. Both these cancers are linked with human herpes virus (Mandell, Bennett, and Dolan 2010).Prolonged fevers, swollen lymph nodes, sweats (particularly during night), chills, weakness, and weight loss are some of the additional symptoms of the AIDS ("AIDS", MedlinePlus). Diarrhea is the most common symptom present in about nearly 90% of people infected with AIDS (Sestak K, 2005).

Virology

HIV belongs to the genus Lentivirus (ICTV, 2002) a part of the Retroviridae family (ICTV, 2002) which affects essential cells of the human immune system such as CD4+ T cells, macrophages and dendritic cells. Lentiviruses share many biological as well as morphological characteristics. Mammalian species are affected and infected by lentiviruses, which are characteristically responsible for long-term illnesses and incubation period (Levy J. A., 1993). Lentiviruses are transmitted as single-stranded, enveloped RNA viruses. On entry into the host, the viral RNA genome gets converted into double-stranded DNA (reverse transcribed) with the help of a virally encoded reverse transcriptase enzyme which is transported along with the viral genome. Later this viral DNA is imported into the host cell nucleus and is then attached to the cellular DNA by a virally encoded integrase and host co-factors (Smith Johanna A., 2006). Once this process of integration with the host cell nucleus is finished, the virus may become latent, therefore making the virus and its host cell to get avoided from detection by the immune system (Martinez, 2010). Alternatively, the virus may be transcribed inside the host cells, making new RNA copies and viral proteins that are packaged and released from the cell as new daughter particles those can begin a new replication cycle (Washington D.C., ASM Press, 2004).

The mature HIV is typically a sphere 100 nm in diameter. The virion has an envelope consisting of a lipid bi-layer and multiple knob-like spikes projecting above the surface. The virus also has a dense cylindrical core consisting of a structural polypeptide called p24. The HIV genome includes the genes-gag, which codes for the proteins that make up the viral core; pol, which codes for the enzymes necessary to replicate (reverse transcriptase) and insert viral dna into the host genome (insertase); and env, which codes for the proteins that make up the envelope. HIV also has genes called tat, rev, and nef that regulate viral reproduction, and other genes responsible for infectivity and budding. Two types of HIV have been characterized by the scientists so far: HIV-1 and HIV-2. HIV-1 is more virulent, more infective (Gilbert PB et al., 2003), and the majority of HIV infections are caused by HIV-1, and HIV-2 , a biologically distinct second type of aids virus, identified in 1986 and generally restricted to west Africa(Reeves J. D. and Doms R. W, 2002; Wormser GP, 1992). The structure of HIV-2 is similar to that of HIV-1. However, HIV-2 has a distinct genes and different configurations of the envelop proteins, particularly gp 120(Wormser GP, 1992)

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Pathophisiology

HIV causes AIDS by depleting CD4+ T cells and this leads to the weakness in the immune system and there by allows opportunistic infections. We find that T cells are very essential to the immune response and so there by without them the body is not able to fight infections and kill cancerous cells. The process of CD4+ T cell depletion varies in the chronic and acute phases (Hel Z et al., 2006). During the acute phase, CD4+ T cell count depletes firstly because of cytotoxic T cells starts killing of infected cells and secondly because of HIV induced cell lysis. During the chronic phase, there is a slow decline in CD4+ T cell numbers which is because of the gradual loss in the capacity of the immune system to produce new T cells (Arie J. Zuckerman et al., 2007).

It has been found out that the symptoms for immune of AIDS do not appear for a long time after a person has been infected, bulk of CD4+ T cell loss has seen during the first week of infection, mostly in the intestinal mucosa (Mehandru S et al., 2004). The CCR5 protein which is used by HIV as a co-receptor to get entry into the cells is expressed by the majority of the mucosal CD4+ T cells and this is the reason why there is preferential loss of mucosal CD4+ T cells as compared to those of bloodstream CD4+ T cells among which only a small fraction of cells do so (Brenchley JM et al., 2004).

During acute infection HIV finds and kills CCR5 expressing CD4+ T cells (Julio Aliberti, 2011). A panache immune response usually controls the infection and initiates the clinical latent phase. Generalized immune activation persists throughout the chronic phase because of the continuous HIV replication (Appay V, Sauce D, 2008). Ongoing HIV replication and several HIV gene products cause the enhanced activation of immune cells and discharge of pro-inflammatory cytokines. (Brenchley JM et al., 2006).

Tests for HIV

A positive HIV test can be validated within one month of infection. Infection can be diagnosed by two ways, either by a biological test that confirms HIV antibodies in the blood or by identification of an opportunistic infection that marks the presence of HIV. ELISA (enzyme-linked immunosorbent assay) is the largely used biological test in developed countries to test for HIV positive or negative using a blood sample. It could take several days to get a result. Result can also be provided within 20 minutes with the help of Rapid tests and that are being used more largely as and how their costs fall. In case of developed countries where the previous probability of infection is less and resources are sufficient, western blot test is recommended even after the result of first and second ELISA test comes out to be positive. Whereas in a environment where there is a high prevalence of the disease with the large previous probability and scarcity in resources, such an approach is almost not recommended and performed. Because each additional confirmatory test decreases the chances of false positive outcome, hence exceeding the costs associated with such a result (Stefano Bertozzi et. al, 2006)

HIV Prevention

Various HIV prevention interventions like Information, education, and communication include education on HIV/AIDS and use of condom through brochures, pamphlets or through the

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television, radio, or press. School-based sex education program is a part of IEC itself and provides information to young generation and ensures healthy conditions in a school setting (Peersman and Levy, 1998).Voluntary counseling and testing helps people to know about their HIV status and provides them counseling support to help cope with the results. Information of serostatus may enable individuals to keep away from getting in risky behaviors (Sweat et al., 2000). Peer-based programs use impactful members of a targeted community to teach specific skills or spread information. Peer based program for sex workers is likely to be more cost-effective and is about one-fifth the cost of blood safety intervention (Hutton et al., 2003) Interventions for sexual transmission is for Condom promotion, distribution, and social marketing, with awareness for STI(sexually transmitted infections)screening and treatment (Orroth et al., 2003). Intervention for Mother-to-Child Transmission includes avoidance of unwanted pregnancies among infected mothers and use of antiretroviral therapy with combination of other useful available strategies to the mother before the pregnancy and to the new born after the delivery, and allowing a Feeding substitution to the new born in spite of the breast feeding to avoid the chances of postnatal HIV transmission (Nduati et al., 2000). Prevention of Blood borne Transmission causes Harm reduction for injecting drug users by avoidance of sharing drug injections or needles (Mesquita et al., 2003), and implementation of blood safety practices like selection and screening of the blood donors for the necessary and appropriate blood transfusions (UNAIDS, 1997).

Possible Methods of HIV cure

Currently it has been proved in many cases that a combination of various medicines has helped to cure & in many cases stop the advancement of the virus. The following strategies are found more efficient in combination with each other (Aids media release, 2012)

1. Gene therapy
2. Treatment Optimization and Intensification (eliminate all replication)
3. Reversal of HIV latency (increase virus production)
4. Immune-based Therapies (reverse pro-latency signaling)
5. Therapeutic Vaccination (to enhance host-control)

These all above techniques are currently in the use as an attempt to cure HIV.

HIV CURE Feasible or it's a dream!!

Many recent observations make scientists under the notion of finding cure research. The case of Timothy Brown a "Berlin Patient" has given a hope to the scientist to have a cure; Brown received a stem-cell bone-marrow transplant in 2007 and is now inquired as cured of HIV. This transplant worked because Brown was among the 1 % of Northern Europeans who lack CCR5, the protein which is used by HIV as a co-receptor to get entry into the cells. While it is supposed unrealistic to use this costly and risky therapeutic approach for most people, in spite of that it has got scientists vote to make use of gene therapy to alter a patient's immune cells to turn them resistant to HIV infection (Nature Reviews Immunology, 2012). The molecular biology aspect of how HIV DNA becomes attached to the chromosomes of affected people is the centre of intense research. Recently a test is performed on HIV+ patients from which David Margolis and

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colleagues found out that dose of a drug that hinders an enzyme linked to silencing of HIV leads to fast production of HIV RNA in the patient's infected cells (Archin NM et al., 2012). Scientists have also become aware of rare HIV infected peoples those seems to have natural cure of their infection. These people are called elite controllers,. Yet they are HIV positive, they do not have readily apparent virus in their blood. Scientists are trying to get a better understanding of this group and are researching to understand them. There is an another interesting story of unique group of patients in France those were HIV infected, but got their therapy started early, and hence forth were able to successfully stop further infection. The study clearly confirms the advantages of having HIV treatment at the very early stages of infection and shows that early detection and immediate therapy helps in a long running. There is vast information to be learned by understanding the immunological characteristics that made therapy superfluous for these patients (Hocqueloux, L. et al., 2010). All these incidents and findings are supposed as these may leads to a better study, cure & prevention in the near future.

Advancement to Possible HIV CURE

Following are the some of the recent observations that has been found out and promises for the cure of this dreadful disease in the near future or tomorrow.

Unique antibodies are found inside a Gay man

HIV research is undergoing a revolution that could turn to ways to develop new vaccines against the AIDS virus. In the latest development research program, U.S. government scientists have said that they have discovered an antibody from the body of a 60-year-old African-American gay man (known as Donor 45 in scientific literature), that neutralizes 91% of HIV strains, more than any AIDS antibody discovered so far. They are now deploying the technique used to find those antibodies to identify antibodies to influenza viruses. Now the scientists are trying their very best to develop a vaccine or any possible method to enable anybody else to produce them as well (Advance in Quest for HIV Vaccine, 2010).

Cells' DNA Repair Machinery Can Destroy Viruses

A group of researchers at Johns Hopkins has analyzed and interpreted a system that makes certain types of immune cells unable to be affected by HIV infection. The system's 2 essential parts are high levels of a molecule that remains implanted in viral DNA like a code written in invisible ink, and second is an enzyme that, which when reads the code, starts chopping down the DNA into unusable pieces in spite of repairing it. The researchers suppose this discovery to point towards a new approach to eradicate HIV from the body (Johns Hopkins Medicine, 2013)

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Natural Antiviral Protein Stops HIV Virus Entering into the Cells

Once again the Researchers in the US have identified a natural antiviral protein that stops HIV and few other dreadful viruses such as Ebola, Nipah and rift valley fever from entering host cells. Researchers hope that this discovery will help to develop broad-spectrum antiviral vaccines against many of the dreadful viruses that have been listed as "priority pathogens" by National Institute of Allergy and Infectious Disease lists for national biosecurity purposes. The protein found is cholesterol-25-hydroxylase (CH25H), that convert cholesterol in the cell to an oxysterol called 25-hydroxycholesterol (25HC), which permeates the cell wall and blocks the virus from getting in (HIV/AIDS, medical news today, 2013).

Scientists have successfully Developed HIV-Resistant T-cells

Scientists have discovered a technique to genetically engineer HIV-resistant T-cells, this method which if proven effective in humans, could bring about a revolution against HIV and HIV positive patients will be able to have a alternate to a lifelong medication schedule. HIV is dreadful because of the virus' ability to break into and eliminate T-cells, slowly advancing to AIDS causing the breakdown of the immune system. The virus is able to do so with the help of two genes - CXR4 and CCR5. The medications prescribed now a days to counter attack HIV are aimed at both of these receptor genes. But, if it could be possible to modify the genes in a way that makes them naturally immune to HIV, the daily medication schedule would no longer be required(HIV/AIDS, medical news today, 2013).

Conclusion

HIV/AIDS is no less than havoc in today's world. It has therefore become essential for human race to find an exact cure to this deadly disease or else we will have to continue loosing thousands and lakhs of our people as we are doing it from the decades. Advancement in science and technology has made it possible to limit its further infection and sometimes giving a cure as seen in few cases. Reports from the recent findings of the researchers and the scientists are seems to give us a hope for the possible known treatment to HIV. This will not just be a victory of human brains over these kinds of diseases but also like a second chance to live for the lakhs of HIV patients who are living with a fear to finite death.

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