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Establishing Causal Relationship between HIV and AIDS

A. Taqaddas

***Abstract*—**This mini literature review discusses casual relationships between HIV and AIDS in view of Koch's postulates.

***Keywords*—**AIDS, Causal Relationship, HIV, Koch's Postulates.

I. Introduction

SINCE the discovery of AIDS in 1981 in the coastal regions of United states such as New York, Los Angeles and San Francisco it has turned into a pandemic effecting millions of people worldwide. As AIDS affected diverse risk groups of people health experts concluded that AIDS is caused by an infectious micro-organism transmitted by sexual contact, contact with blood and blood products and from mother to child. This ensued the research for clues to the cause of AIDS. In 1983 for the first time experimental data providing association between AIDS and a retrovirus was published. Since then lot of research has been done to support that HIV-Human Immunodeficiency virus (a retrovirus) is the cause of AIDS. The aim of this essay is to establish causal relationship between HIV and AIDS using Koch's famous postulates and guidelines provided by an expert committee appointed by US Surgeon General. The views of scientists who question HIV as a cause of AIDS will also be briefly discussed.

II. Method

Literature search was performed using online databases.

III. Discussion

A. AIDS

The Acquired Immunodeficiency Syndrome (AIDS) was discovered in 1981 and since then it has become a pandemic [1], [2]. In 2007, 2.7 million new HIV infections and 2 million HIV related deaths were reported [3]. It can be caused by either of the two Human immunodeficiency viruses namely, HIV-1 and HIV-2. Both viruses are members of retrovirus family and belong to the genus Lentivirus. According to CDC [4] AIDS is defined if someone has one of 26 specific diseases but no known cause of immune deficiency other than HIV or if HIV infected individuals have a CD4+ T lymphocyte cell count less than 200 cells / uL or a CD4+ T lymphocyte percentage of less than 14% of all lymphocytes and Positive HIV test. However a more suitable definition of AIDS will take into account HIV free AIDS by removing the condition of having a positive HIV test.

A. Taqaddas is with Research Wormhole and JMIRS, Canada (e-mail: taqaddas@mail.com).

B. Casual Relationship between HIV and AIDS

A factor responsible for causing a disease can be a direct or indirect cause of a particular disease. A direct causation is one in which a factor directly causes a diseases without any intermediate step [5]. In this essay we will be focusing on direct causation between HIV viruses and AIDs. To prove that an organism causes a disease a set of criteria have been proposed including Koch's postulates (Table I) and guidelines issued by United States Department of Health, Education and Welfare [5]. See Table II for modified list of these guidelines.

TABLE I
Koch's Postulates [6], [7]

Postulate 1	The organism is always found with the disease
Postulate 2	The organism must be isolated and grown in pure culture
Postulate 3	The cultured organism must be shown to induce the disease into an healthy person or animal experimentally
Postulate 4	The germ must be re-isolated from the infected person

TABLE II
Guidelines for judging Whether an Association Is Causal [5]

Temporal Relationship
Strength of the Association
Dose Response Relationship
Replication of Findings
Biologic Plausibility
Consideration of Alternate Explanations
Cessation of Exposure
Consistency with Other Knowledge
Specificity of Association

There are 4 sub types of causal relationships namely: Necessary and sufficient, Necessary but not sufficient, Sufficient but not necessary and neither sufficient nor necessary [5]. A factor is necessary i.e. without that factor the disease never develops and is sufficient because 'in the presence of that factor the disease always develop' [5]. Keeping this strict definition in view, HIV does not seem to be a necessary factor for causing AIDS. AIDS can develop without HIV and such HIV AIDS-free condition is found in individuals who have a CD4+ T- cell count below 300 cells per cubic millimeter on at least two occasions but have no evident/measurable HIV infection or any other known cause of immune suppression or deficiency. The US Centers for Disease Control and Prevention classify this condition as Idiopathic CD4+ T-lymphocytopenia – ICL [8].

HIV is not sufficient to cause AIDS either. This is because the presence of HIV is not always sufficient to generate the disease in every infected individual. For instance there are HIV positive/ infected individuals who have not developed AIDS and such individuals are described as Long Term Non Progressors (LTNPS) [9]-[11]. This shows that HIV has a

causal relationship with AIDS but this relationship is neither sufficient nor necessary to cause AIDS. Moreover according to Gordis neither sufficient nor necessary type of causal relationship is characteristic of most chronic diseases and we know that AIDS is a chronic disease [5]. However if we are prepared to bend the rules slightly we can fit HIV into necessary and sufficient category of casual relationships and this is discussed below along with Koch's postulates.

C. HIV Causes AIDS by Fulfilling Koch's Postulates

1. Postulate 1

Recent advances in HIV/AIDS research have demonstrated that HIV satisfies these criteria as the cause of AIDS. DNA PCR and RNA PCR technologies have enabled researchers to identify the presence of HIV in AIDS patients and HIV infected individuals thereby fulfilling the first criteria stated in Table I. DNA PCR including real time techniques such as SYBR assay has detected the presence of cell–associated proviral HIV in virtually all patients with AIDS as well as in individuals in early stages of HIV disease [12]-[14]. These DNA PCR techniques enable detection of the virus in the window period prior to sero-conversion and the investigation of infants born to HIV-infected mothers [14]. Similarly RNA PCR has been used to find cell free and / or cell associated viral RNA in patients at all stages of HIV disease. A multicentre AIDS Cohort Study (MACS) observed the health of 2, 713 gay and bisexual men who showed negative HIV antibody test. Only one of the individuals showed consistent low CD4+ T cell count because he was receiving cancer therapy. This and other similar studies have demonstrated lack of severe immune deficiency among those who test HIV negative [15], [16]. Hence AIDS is extremely rare in the absence of HIV or some other known cause of immune suppression.

Almost everyone with AIDS shows positive HIV test except a few cases (47 patients out of 230,179) which show ICL or HIV free AIDS [8]. The researchers believe that ICL and unexplained opportunistic infections represent a rare disorder and most of these ICL patients (29) could not fit into conventional risk groups of AIDS such as homosexuals, injecting drug users, hemophiliacs etc. Thus it seems based on a large sample of people who have been tested positive for HIV Koch's first postulate has clearly been satisfied and also makes HIV a necessary factor to cause AIDS as without HIV AIDS is rare.

2. Postulate 2

Advances in co-cultural techniques have permitted the separation of HIV in nearly all AIDS patients as well as in almost all sero-positive individuals with both early and late stage diseases [17] thereby satisfying postulate number 2. In this study HIV-1 was isolated from peripheral mononuclear blood cells of all 409 HIV-1 antibody positive individuals.

3. Postulates 3 and 4

Fulfilling Koch's 3rd and 4th postulates are not easy as its not ethical to experimentally introduce HIV into healthy humans. However some incidents which are discussed below have fulfilled these postulates. Postulate 3 and 4 in Table I have been met in cases of 3 laboratory workers (infected in 1985, 1991) with no other risk factors who developed AIDS after accidental exposure to purified cloned HIV in the laboratory. In all three cases HIV was isolated from infected individuals and genetic sequencing showed it to be the original infecting strain of virus. All 3 infected individuals showed considerable CD4+ T cell depletion and two had CD4+ T cell count below 200/mm3 of blood – an indication of AIDS [18]-[20]. During 1981-2006 CDC was informed of 57 health care workers in USA with documented occupationally acquired HIV infection (sero-conversion), of whom 26 progressed to AIDS in the absence of other risk factors [21], [22]. Similarly 10 year follow up of 11 HIV infected children (infected by a single HIV infected donor of plasma) showed that 8 of the children died of AIDS where as remaining 3 showed progressive deterioration in cellular immunity [23].

D. Animal Models

Animal models also provide evidence of human AIDS. In one study 10 chimpanzees who were experimentally infected with HIV were studied [24]. One of them developed immunodeficiency and AIDS and 3 chronically infected chimpanzees displayed evidence of progressive HIV infection (HIV Positive Progressors) whereas 6 of them remained HIV-positive non-progressors. Progressor chimpanzees showed moderate to high plasma viral loads whereas plasma viral load was undetectable in non-progressor chimpanzees.

Similarly HIV2 caused AIDS in baboons [25]. Three of these HIV-2 infected baboons demonstrated severe loss of CD4+ cells and 2 of them developed AIDS. This clearly provided evidence for transmission of AIDS to an animal model by a Human HIV strain. Another study involving inoculation of macaques with Simian/Human immunodeficiency virus (SHIV) resulted in development of AIDS in 3 of these animals [26].

E. Casual Association between HIV and AIDS in Light of Guidelines Given in Table II

1. Temporal Relationships

Appearance of AIDS in human population across the world has closely followed the emergence of HIV. For instance first cases of AIDS were reported in 1981 among homosexual men in New York and California and retrospective study of frozen blood samples from a US cohort of gay men revealed the existence of HIV antibodies as early as 1978. Similarly in other regions of the world evidence of HIV infection has preceded AIDS [15]. For instance in Thailand as HIV prevalence increased in 1990s there was significant increase in AIDS cases [27].

2. Dose Response Relationship, Strength of Association and Replication of Findings

Dose response relationship exists when higher levels of exposure to the factor give rise to higher occurrence or risk of disease [5]. Strength of the association refers to the ratio of

disease rates with and without the factor under consideration [5]. PCR, branched DNA signal amplification assay (bDNA) and other technologies are used to measure HIV in blood (viral load). bDNA test in a prospective multicenter cohort study of 1604 HIV-1 infected men have shown that Higher the viral load, greater is the proportion of patients developing AIDS [28]. Percentage of participants who progressed to AIDS (80%) and who died of AIDS (69.5%) was highest in risk group with more than 30,000 copies of viral RNA/ml than 500 or less copies/ml.

Similarly in a prospective study HIV RNA levels and CD Cell count in 1769 HIV infected women were studied. Higher quantitative plasma HIV-1 RNA and lower CD Cell count were associated with shorter survival. The relative hazard of dying increased for women with higher HIV-1 RNA levels in blood e.g. for women with HIV-1 RNA measurements of > 500, 000 copies/ml the relative hazard of dying was found to be 7.25 compared to women with < 4000 copies/ml [29]. These two studies also show replication of the association or findings.

Dose response relationship between HIV and AIDS can also be shown with the help of mortality data. In 2007 globally there were estimated 33 000 000 (33 million) people living with HIV out of which 22 000 000 (22 million) are living in sub Saharan Africa [30]. Hence Sub Saharan Africa accounts for 67% of all people (worldwide) living with HIV and for 75% of all AIDS death in 2007 [3], [30]. Trend data from antenatal clinical from Africa from 1997/1998-2002 shows increase in HIV prevalence in Southern Africa from 21.3% to 23.8% and a drop in HIV prevalence in East Africa from 12.9% to 8.5% [31].

This study and others also indicate that not all of sub Saharan Africa has been equally affected by HIV and AIDS despite all these regions have experienced similar levels of poverty, malaria, malnutrition or food shortage and conflict. The only major factor associated with AIDS is prevalence of HIV. This satisfies the criterion of Alternate explanation as other possible explanations are taken into account and have been ruled out.

3. Consistency of Association

It can be demonstrated by the fact that association between HIV and AIDS is found in different countries, different study groups or populations and by different study designs. Similar patterns have been noted in Asia. For instance reported cases of AIDS in Thailand rose from 14 in 1988 to 13, 246 in 1994 [32]. This rise in AIDS cases corresponded with sharp rise in HIV prevalence in Thailand. From 1988-1989 HIV prevalence increased in injecting drug users and sex workers in Thailand, subsequently leading to waves of AIDS epidemic later [32]. According UNAIDS, 2008 report HIV prevalence in Thailand (estimated number of people living with HIV) continuously rose from 1991 to 1999 (470,000 – 720,000). Strength of casual association between HIV and AIDS can be showing by using a different type of population e.g. IDUs. In one Dutch study researchers compared 86 HIV sero-negative individuals who had been injecting drugs for an average of 7.6 years with 70 HIV Sero-positive IDUs who had been injecting drugs for an average of 9.1 years. Upon enrollment in the study in 1989, HIV sero-negative IDUs had higher CD+ T cell count (914/mm3) than sero-positive group (395/mm3). By 1994 there were 25 AIDS deaths in the sero-positive group out of which 10 were AIDS related where as in sero-negative group none of the deaths were due to AIDS defining diseases [33]. This study and others also negate the notion by some scientists such as Duesberg that AIDS is not caused by HIV but is caused by drugs such as Heroin, cocaine, amphetamines, nitrite inhalants and even drugs that are used to treat AIDS such as AZT. This study also negates the notion that duration of drug taking influences drug-caused immune deficiency (duration of drug use was controlled in this study). It is important to realize that there is some evidence suggesting that drug use can cause immune suppression or immune abnormalities [33] but the type of immune deficiency that leads to AIDS i.e. progressive CD4 T cell loss and persistent CD4 lymphocytopenia is rare in HIV sero-negative IDUs. This fulfills the criterion of consideration of alternate explanation.

Prevalence of HIV infection is same in both men and women. Women make up 50% of all people living with HIV worldwide and nearly 60% of HIV infections in sub Saharan Africa [3], [30]. HIV prevalence is increasing in women in many regions of the world. This is due to gender disparities, poverty, cultural and sexual norms, lack of education, violence and sexual coupling patterns of young women with older men [34], [35].

4. Cessation of Exposure

'If a factor is a cause of a disease we would expect the risk of the disease to decline when exposure to the factor is reduced' [5]. Extensive use of HAART (highly active antiretroviral therapy) in industrialized countries has resulted in a remarkable decrease in morbidity and mortality by suppressing viral replication and thus increasing CD4+ T cell count to normal values leading to a degree of immune reconstitution [27], [35]-[37]. This clearly indicates that AIDS can be delayed by reducing the viral load and there is a causal relation between HIV and AIDS. HIV prevention educational campaigns in Uganda (Eastern Africa) have resulted in reduced HIV prevalence and incidence from 14% in 1990 to 6.3% in 2005 [31], [38]. This reduced HIV prevalence and incidence in Uganda has translated into reduced estimated AIDS deaths from 120,000 (2001) compared to 77,000 (2007) [30]. Similarly implementation of HIV awareness, prevention and treatment programmes e.g. 100% condom programme in sex workers, availability of ART therapy (1999) and HAART (2000) in Thailand from 1991 and onwards has resulted in 80% decrease in new annual HIV infections [39]. Consequently AIDS deaths in adults and children in Thailand dropped from 66,000 (2001) to 30,000 (2007) [30].

In another study increased use of condoms during paid sex has resulted in reduced HIV prevalence. For instance in Cambodia decline in HIV prevalence was observed as consistent condom use during commercial sex increased from 53% in 1997 to 96% in 2003 [40]. These studies also satisfies

criterion for consistency of the association and replication of findings. Thus it can be concluded that cessation to HIV exposure by preventive measures and treatment reduces risk of AIDS development.

5. Consideration of Alternate Explanation

Alternate explanation has been discussed above in Consistency of Association and Dose response relationship sections.

6. Biological Plausibility

Studies have shown that HIV causes AIDS by destroying Immune cells such as CD4+ T cells [41]-[43]. The virus effectively counteracts innate and adapted immunity by evading recognition by host immune system. During acute HIV-1 infection virus specific cytotoxic T-lymphocyte (CTL) responses are generated which result in temporary initial decline in viremia [44], [45]. HIV infection is characteristic of gradual destruction of naïve and memory CD4+ T lymphocytes with AIDS being the end disease stage. Different mechanisms have been proposed as a cause for constant depletion of CD4+ cell reservoirs including Immune activation. LTNPs fail to develop AIDS. This is because appearance of AIDS in each individual depends on a number of factors such as genetic makeup of the individual, their life style, their nutritional or performance status, availability of antiretroviral therapy etc [46], [47].

7. Specificity

HIV causes AIDS which involve constant immune suppression and appearance of a number of opportunistic infections. HIV thus seems to show high specificity for AIDS.

IV. Conclusion

HIV not only fulfills Koch's postulates but also the guidelines provided by US department of Health, Education and Welfare to demonstrate causality. The casual relation between HIV and AIDS is seen in different regions of the world (Asia, Africa, Europe, America), in different risk groups (IDS, Homosexuals, heterosexuals, sex workers, Health workers) and in different populations subsets (Men, Women, Children).

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