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Review Article

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Assessing the Causal Relationship Between HIV Infection and AIDS Development: A scoping Review

Mekuriaw Dereje[1*] and Abeba Gebreslassie[2]

[1]*Department of Pharmacy, College of Medicine and Health Science, Mizan-Tepi University, Mizan-Aman, Ethiopia*

[2]*Department of Pharmacy, Mizan-Tepi University Teaching Hospital, Mizan-Tepi University, Mizan-Aman, Ethiopia*

[*]Corresponding Author
Mekuriaw Dereje, Department of Pharmacy, College of Medicine and Health Science, Mizan-Tepi University, Mizan-Aman, Ethiopia.

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Abstract

In scoping review, the causal relationship between HIV infection and AIDS development using the Gordis criteria of Epidemiology was explored. The review aimed to provide a concise overview of existing literature and highlight key findings in this area.

Keywords: Gordis Criteria, Causal Relationship, HIV, AIDS.

1. Introduction

HIV (Human Immunodeficiency Virus) has been a significant global health concern since its discovery in the early 1980s [1]. The virus attacks the immune system, specifically CD4 cells, leading to a progressive weakening of the body's ability to fight off infections and diseases. Left untreated, HIV can progress to Acquired Immunodeficiency Syndrome (AIDS), a condition characterized by severe immune system damage and increased vulnerability to opportunistic infections [1-20].

While the link between HIV infection and AIDS development is well-established, the exact causal relationship between the two remains a topic of ongoing research. Understanding the mechanisms by which HIV leads to AIDS is crucial for developing effective prevention strategies and treatment interventions.The exploration of the relationship between HIV infection and the development of AIDS is guided by the esteemed Gordis criteria, a set of principles developed by Dr. Leon Gordis to assess causality in epidemiological studies. By applying these criteria to the body of evidence linking HIV to AIDS progression, this scoping review aim to rigorously evaluate the following:

1. Strength of Association: the magnitude of the association between HIV infection and the development of AIDS was examined through reviewing epidemiological studies, cohort studies, and meta-analyses that quantify the risk and relative risk of progression to AIDS in individuals infected with HIV.

2. Consistency: Through a systematic review of the literature, this scoping review assessed the consistency of findings across different populations, settings, and study designs to determine the reproducibility of the link between HIV infection and AIDS development.

3. Temporality: By analyzing longitudinal studies and temporal relationships between HIV infection and the onset of AIDS-defining illnesses, this scoping review elucidated the temporal sequence of events that underlie the progression from HIV to AIDS.

4. Biological Plausibility: this scoping review tried to delved into the biological mechanisms by which HIV induces immunosuppression and compromises the immune system's ability to mount an effective response against opportunistic infections, ultimately leading to the clinical manifestations of AIDS.

5. Biological Gradient (Dose-Response): Explore the presence of a dose-response relationship between HIV viral load or CD4 cell count and the progression to AIDS. Evaluated whether higher levels of viral replication or lower CD4 counts are associated with an increased risk of developing AIDS.

6. Extent to which alternate explanations have been considered: research also addresses alternative explanations for AIDS.

7. Cessation of Exposure: The principle of cessation of exposure suggests that reducing contact with a causative agent will decrease the risk of disease and this scoping review tried to address this criteria from available literature.

8. Replication of Findings: It is supportive of causal association if the same finding can be replicated in different populations and/or by using various study designs.
9. Specificity: whether the AIDS ever occurs without the HIV ?

2. Methods

2.1 Study Design

A scoping review methodology was employed to systematically map the existing literature on the causal relationship between HIV infection and AIDS development.

2.2 Search Strategy

A systematic search strategy were developed to identify relevant studies from electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. Using the following search terms “HIV infection and AIDS development”, "HIV pathogenesis and progression to AIDS", "HIV causation of AIDS", "HIV/AIDS relationship", "Epidemiology of HIV and AIDS", "HIV/AIDS causation"and "HIV/AIDS progression factors"

2.3 Inclusion Criteria

Studies were included if they examine the relationship between HIV infection and the progression to AIDS, regardless of study design or publication date. Both quantitative and qualitative studies were considered for inclusion in this scoping review.

2.4 Study Selection

Two independent reviewers were involved in the selection of search results based on predefined inclusion criteria. Any discrepancies in study selection was resolved through discussion and consensus between the reviewers.

2.5 Data Extraction

Data extraction were conducted by extracting key information from the selected studies, including study characteristics, methodologies, key findings, and conclusions. A standardized data extraction form was used to ensure consistency across the extracted data.

2.6 Data Analysis

A thematic analysis approach was employed to identify common themes, patterns, and gaps in the literature related to the causal relationship between HIV infection and AIDS development. The findings from the included studies were synthesized to provide a comprehensive overview of the current state of knowledge in this area.

3. Result and Discussion

3.1 Temporal Relationships

The temporal relationship between HIV and AIDS is indeed significant.The appearance of AIDS in the human population closely followed the emergence of HIV. The first cases of AIDS were reported in 1981 among homosexual men in New York and California [1].

A retrospective study of frozen blood samples from a US cohort of gay men revealed the existence of HIV antibodies as early as 1978. This suggests that HIV was present before the clinical manifestation of AIDS [2].

Similar patterns have been observed in other regions of the world, where evidence of HIV infection has preceded the development of AIDS [3]. For example, in Thailand, as HIV prevalence increased in the 1990s, there was a significant increase in AIDS cases [4].

3.2 Dose-Response Relationship and Strength of Association

A dose-response relationship exists when graded increase in the risk or severity of AIDS with higher levels or longer duration of HIV infection, this relationship has been demonstrated in several studies [5]. For instance, a prospective multi-center cohort study of 1604 HIV-1 infected men showed that a higher viral load was associated with a greater proportion of patients developing AIDS. Specifically, the study found that 80% of participants who progressed to AIDS and 69.5% who died of AIDS were in the risk group with more than 30,000 copies of viral RNA/ml, compared to those with 500 or less copies/ml [6].

Similarly, a prospective study of 1769 HIV-infected women found that higher quantitative plasma HIV-1 RNA levels and lower CD4 Cell counts were associated with shorter survival. The relative hazard of dying increased for women with higher HIV-1 RNA levels in blood. For example, 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 [7].

3.3 Replication of Findings

In a prospective study (Multi-center AIDS Cohort Study) involving 1604 HIV-1 infected men, a higher viral load was associated with a greater proportion of patients developing AIDS and Prospective Study(Multi-center AIDS Cohort Study) of 1769 HIV-infected women, higher quantitative plasma HIV-1 RNA levels and lower CD4 Cell counts were associated with shorter survival clearly reflect replication of the association or findings [6-7].

3.4 Biological Plausibility

The biological mechanisms by which HIV leads to AIDS are well-documented. HIV targets immune cells, particularly CD4+ T cells, leading to their destruction. This process undermines both innate and adaptive immunity, allowing the virus to evade the host's immune response. During the acute phase of HIV-1 infection, virus-specific cytotoxic T-lymphocyte (CTL) responses are generated, which initially reduce viremia. However, the infection is characterized by the gradual depletion of naïve and memory CD4+ T lymphocytes, culminating in AIDS, the end stage of the disease. Various mechanisms, including immune activation, have been proposed to explain the continuous loss of CD4+ cell reservoirs. Long-term non-progressors (LTNPs) do not develop AIDS, highlighting the role of individual factors such as genetic makeup, lifestyle, nutritional status, and access to antiretroviral therapy in the progression of the disease [8-11].

3. 5 Cessation of Exposure

The principle of cessation of exposure suggests that reducing contact with a causative agent will decrease the risk of disease [5]. This is evident in the context of HIV/AIDS, where interventions such as HAART have significantly lowered morbidity and mortality rates [4]. By suppressing HIV viral replication, HAART increases CD4+ T cell counts, leading to immune reconstitution and delayed progression to AIDS [12-14].

Epidemiological evidence supports the causal relationship between HIV and AIDS. For instance, in Uganda, educational campaigns have halved HIV prevalence from 1990 to 2005, resulting in a substantial decrease in AIDS-related deaths [15]. Similarly, Thailand's comprehensive HIV prevention and treatment programs have led to an 80% reduction in new HIV infections and a corresponding decrease in AIDS mortality [16].

Preventive measures, such as consistent condom use, have been associated with reduced HIV prevalence. In Cambodia, the prevalence of HIV declined as condom use during commercial sex increased from 53% to 96% between 1997 and 2003 [17].

3.6 Consistency of Association

The epidemiological criterion of consistency of association is met when the relationship between a potential cause and an effect is observed repeatedly in different settings, populations, and times. In the case of HIV and AIDS, this consistency is evident across various demographics and geographic regions [5].

Globally, the rise in AIDS cases has been closely linked with the prevalence of HIV. For example, in Thailand, the number of reported AIDS cases surged from 14 in 1988 to over 13,000 by 1994, paralleling an increase in HIV among injecting drug users and sex workers [18].

Intervention studies provide further evidence of the causal link. The introduction of highly active antiretroviral therapy (HAART) and other treatment programs in countries like Thailand has led to significant reductions in both HIV infections and AIDS-related deaths and the prevalence is increasing, particularly in sub-Saharan Africa [7,15].

3.7 Consideration of Alternate Explanation

Research also addresses alternative explanations for AIDS, such as drug use. Studies comparing HIV-positive and HIV-negative injecting drug users have shown that while drug use may lead to some immune suppression, the specific immune deficiency leading to AIDS—characterized by progressive CD4 T cell loss—is predominantly observed in HIV-positive individuals [6,7].

3.8 Specificity

HIV exhibits a high degree of specificity for causing AIDS. The virus induces persistent immune suppression and the emergence of opportunistic infections, which are hallmarks of AIDS. This specificity supports the assertion that HIV is the causative agent of AIDS [19,20].

4. Conclusion

Remember that while HIV is a necessary cause for AIDS (meaning it must be present for AIDS to occur), it is not a sufficient cause on its own. Other factors, such as immune system status and opportunistic infections, also contribute to the progression from HIV infection to AIDS.

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