

Review Article: The role of mucosal immunity in HIV-1 infection and combination of antiretroviral treatment therapies for HIV-1 infected pregnant women and prevention in infants.

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Abstract-Hiv-1 is naturally transmitted through mucosal surfaces of gastrointestinal tract and vagina. These two sites are most vulnerable and primary source of initial HIV replication, its amplification and rapid CD4⁺ T cell depletion also.. The combination of Anti-retroviral therapy is recommended as a possible treatment of HIV-1 infection. In this therapy a combination of two or more analogues is used against HIV-1 virus. HAART is considered most operative, after that Multi-ART and ZDV immunotherapy but there is no significant difference between ARV treatment categories. There are several other factors that are hindrance in the way of HAART treatment efficacy as low funds, high rate of co- infections such as T.B and other bacterial diseases affect prognosis in less and middle developing countries. So rate of mortality is high in these countries as compare to high income countries but it might be lower by providing free of charge antiviral HAART therapy and other HIV-1 preventive drugs. The present review summarizes about the emerging of HIV-1 infections during pregnancy and their treatment regimen.

Index Terms-HIV-1, mucosal immunity, Antiretroviral (ARV) therapy, HAART therapy.

1 INTRODUCTION

Human immunodeficiency virus has two main types as HIV-1 and HIV-2 [1]. Each major type of virus can be divided into groups that can further subdivided into subclasses or clades [2]. HIV 1 is Major family of HIV and causes 95%of all infections worldwide. HIV-1 consists of groups M (main), O (outlier), and N (non-M or O and in developed countries, screening tests were performed for identification of group M and Clade B, subtypes of HIV [3],[30]. HIV-2 is found in some West African countries but has insignificant ratio in rest of the world.in the UNITED STATES the term HIV usually refers to HIV-1 [4]. The dispersion of HIV-1 occurs through direct contact with infected body fluids, breast feeding, and genital secretion and during birth from infected mother to child this viral transmission occurs and it gets entry to immune system by attaching to cd4 receptors found on surface of various lymphocytes [5]. This virus is highly delicate and susceptible to physical and chemical agents and becomes noninfectious outside the human body. For example HIV in blood or sexual fluid becomes noninfectious if remains outside for a few minutes [6]. In infected individuals HIV-1 actively replicates even if duration of clinical well-being

occurs so it is necessary to understand active replication sites of HIV-1 during subclinical stages of disease for accounting pathogenesis and for recommendation of better therapies [7].

1.1 Causes and effects

External viral, bacterial, fungal and parasitic pathogens usually confront several barriers to the infections of their required host. In humans mostly these barriers are provided by mucosal surfaces. These surfaces protect eyes, lacrimal glands and tear ducts, the gastrointestinal tract, the bronchial and alveolar surfaces, the mammary glands and the urogenital tracts of both males and females [8].

Most pathogens when encounter transmission barriers, survive in local microenvironment before or during migration across epithelial barriers but other use it as a permanent habitat along with the existence of their host [9]. Some pathogens have adapted unique mechanisms that allow their survival even if for short period of time. If the pathogens survive in luminal microenvironment at mucosal surfaces and breach the epithelial barriers then they must be detected and eliminated by mucosal innate and adaptive immune responses [10]. These immune responses are provided by

MALT, the most wide spread component of all human lymphoid tissue. MALT is composed of intraepithelial and sub epithelial immune cell populations and lymph nodes. The innate immune responses of MALT involve host complement system, macrophages, DCs, neutrophils, eosinophil's etc. Cell –mediated innate immune system involves TLRs, NOD like receptors and helicases [11]. Adaptive immune system involves B LYMPHOCYTES and T lymphocytes. Other MALT associated immune components that function both for innate and adaptive immunity are NK and NKT cells. The complementary and redundant epithelial barriers at mucosal surfaces keep HIV-1 transmission efficacy rate very low but some vulnerabilities in these sites increase chances for HIV-1 transmission. Among these preferential damage occurs across single cell layered mucosal barriers including endocervix and rectum, other include physical damage, local inflammation in sub epithelial sites. Mucosal co infections help in introduction or exacerbation of HIV-1 pathogenesis [12].

The GIT resides the major portion of body's lymphocytes as compare to peripheral blood which consists of only 2-5% of all lymphocytes.as it represents to a largest lymphoid organ, some characteristics of mucosal compartments makes it favorable for HIV-1 infections and its replication easily. Due to its constant exposure to external environment and microbial agents, a large number of mucosal CD4⁺ T cells are stimulated and differentiated with memory abilities. Also, GIT has proinflammatory HIV-1 stimulatory cytokines in high ratio for maintaining its physiological inflammatory state [13], [14]. As GIT is an important direction for HIV-1 entry and principal site for its replication so it is necessary to carefully analyses GI mucosal events for better understanding of early and acute HIV-1 infections. As in acute HIV-1 infections rapid depletion in CD4⁺ T cells and its memory phenotypes occur as compare to CD4⁺T cells in peripheral blood and lymph nodes [15],[16].

Hiv-1 is naturally transmitted through mucosal surfaces of gastrointestinal tract and vagina. These two sites are most vulnerable and primary source of initial HIV replication, its amplification and

rapid CD4⁺ T cell depletion also. As in HIV-1 infected humans, massive decrease in no of mucosal CD4⁺ T cells and CCR5 memory T cells as compare to peripheral CD4⁺T cells occurs in early 10-14 days of infection. Similar to some other pathogenic viruses, HIV-1 decreases the surface expression of MHC-I molecules in cells infected with HIV-1, thus it prevents lysis by cytotoxic T lymphocytes [17], [18]. This is actually due to expression of viral nef gene .Nef is an early viral gene that is important for stabilizing high viral titer and it stimulates aids and endocytosis of CD4⁺ T cells also. In various HIV-1 strains, nef decreased expression of MHC-1 at the surface of lymphoid, monocytic and epithelial cells. The MHC-1 endocytosis by nef helps in virus evasion by immune response [19], [20].

1.2 Treatments

The combination of Anti-retroviral therapy is recommended as a possible treatment of HIV-1 infection. In this therapy a combination of two or more analogues is used against HIV-1 virus [21]. As in infected pregnant women firstly in February 1994 a drug ziduvdine(ZDV) was used to reduce prenatal transmission by targeting the maternal plasma HIV-1 RNA level below the quantification that was helpful in preventing the infections of newborn infants as ZDV is a multifactorial drug that not only reduces maternal viral load but also pre exposure and post exposure prophylaxis of infants but after that ARV (Anti-retroviral drugs) therapy was used in which two or more potent drugs are used to reduce HIV-1 transmission but it is considered more effective rather than ZDV as it attacks on viral replication and reduces viral load.in some cases two nucleoside reverse transcriptase inhibitors are used in combination or in some types, nucleoside reverse transcriptase inhibitor in combination with Non-nucleoside reverse transcriptase inhibitors are used but hiv-1 prevention rate does not vary mostly by changing mode of therapy [22],[23],[24]. But a highly active ARV-HAART (Highly active antiretroviral therapy), which included a combination of three ARV (anti-retroviral) drugs or more, out of which at least one included a protease inhibitor and/or and Non-nucleoside reverse transcriptase inhibitor. Women who receive ART have threefold

decrease in rate of transmission as compare to those who are not ART treated these women also face high rate of preterm birth and low birth weight rates as compare to those who receive ARV therapy but dose response effect and duration of ART regimen have significant effect on it on the other hand the rates of preterm birth and low birth weight rates are not affected much by the types of ARV therapy. As well as cesarean delivery before labor and membrane delivery has lower chances of prenatal transmission rather than women who are delivered vaginally [25], [26] So it is concluded that hiv-1 RNA level in maternal plasma acts as a predictor for transmission of perinatal HIV-1 but potent ARV therapies are more effective in reducing risk of transmission but choice of ARV regimen may have an impact on perinatal transmission, despite of independence of its effect on maternal viral load. All these therapies are very effective in reducing risk of transmission; HAART is considered most operative, after that Multi-ART and ZDV immunotherapy but there is no significant difference between ARV treatment categories. But the risk factors associated with transmission despite the use of potent therapy are hard drugs usage during pregnancy and prolonged membrane rupture even with low viral load. the one possible way by maternal ARV treatment reduces risk of perinatal transmission is reduced through maternal ARV treatment is by providing pre exposure prophylaxis to the infant.it would result in the presence of active ARV drugs by trans placental transport in the circulatory system of infant from mother during labor and delivery because at this time the infant faces a laborious viral exposure [27],[28] .ARV drugs different ability to cross the placental barrier that could result in difference among drugs in providing pre exposure prophylaxis to the infant. Furthermore the existence of two or more potent antiviral drugs in the newborn circulatory system during delivery may provide synergistic effects to prevent the transmission [29].

2 Conclusions

The widespread use of HAART since 1960,s has an important role in improving the prognosis of HIV-1 infected patients who have access to these drugs but in low income settings in developing countries

such as Asia, Africa, and South America such therapy is limited where 90% of people live with HIV/AIDS. As WHO estimated that of June 2005 1million people were receiving HAART therapy but this number was only 15% of whole where approximately 6.5 million people are in urgent need to receive HAART treatment. There are several other factors that are hindrance in the way of HAART treatment efficacy as low funds, high rate of co- infections such as T.B and other bacterial diseases affect prognosis in less and middle developing countries. So rate of mortality is high in these countries as compare to high income countries but it might be lower by providing free of charge antiviral HAART therapy and other HIV-1 preventive drugs.

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