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Review

Visualization of the Macrophage's Dynamic in TB-HIV Co-Infection Using the Molecular Imaging Techniques: A Narrative Review

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ABSTRACT

Introduction: Mycobacterium tuberculosis (Mtb) and human immunodeficiency virus (HIV) collaborate in order to weaken the immune system and increase the burden of both illnesses. Macrophages as the first intracellular niche against Mtb infection, are also involved in the persistence of the HIV infection, and may have an important role in the of tuberculosis (TB)-HIV co-infection. Improved knowledge of the macrophage function and pathogenesis dynamics may contribute to the development of newer and better diagnosis technique, prognosis assessment, and therapeutic intervention. By monitoring changes in the expression of molecular targets, macrophage identification methods that use molecular imaging techniques for cell image analysis can efficiently provide important information about macrophage biology and evaluate early response to therapy, which can facilitate medical personnel in the identification and treatment of TB-HIV disease. **Methods:** This study is a narrative review highlighting the utilization of molecular imaging techniques to capture macrophage dynamics in TB-HIV co-infection. **Result and conclusion:** Confocal laser scanning microscopy live imaging, flow cytometry, immunofluorescence microscopy, histochemical staining, scanning electron microscopy (SEM), and deconvolution microscopy images are among several molecular imaging techniques that can be used to visualize macrophage dynamics in TB-HIV co-infection.

Keywords: Tuberculosis; human immunodeficiency virus; macrophages; molecular imaging techniques

1. INTRODUCTION

Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) are still health problems for people in the world and in Indonesia, where both diseases are prioritized to be free from both diseases by 2030.[1] Based on data quoted from the Global Tuberculous Report 2021 by the World Health Organization (WHO), Indonesia is among eight countries that account for two-thirds of TB cases worldwide. In 2020, an estimated 9.9 million (8.9-10.9 million) people suffered from TB worldwide, as much as 8% of people with HIV. In the same year, 1.5 million people died from TB, including 214,000 people with HIV.[2]

According to the Ministry of Health in 2019 there were 845,000 TB cases in Indonesia and 19,000 TB-HIV patients. It is estimated that out of a population of 247 million, there were 543,100 people living with HIV and 4,700 people with TB-HIV died out of an estimated 96,000 deaths from TB. When HIV is co-infected, the likelihood of active tuberculosis disease is 15-21 times higher than when tuberculosis is the only infection and mycobacterium tuberculosis co-infection

is a major factor in mortality in HIV-infected people.[3,4] The epidemiology of these two illnesses may interact and be influenced by each other's causes.[5]

According to Bell & Noursadeghi, (2017) HIV co-infection substantially increases the risk of developing active TB and conversely, TB co-infection will increase the rate of replication, spread, and genetic diversity of HIV-1.[4] When an individual has M. tuberculosis infection, their HIV replication rises and their development to AIDS is accelerated. On the other hand, HIV-1 infection is the biggest risk factor for Mycobacterium TB infection to develop to active disease, and the global HIV epidemic has played a major role in the tuberculosis outbreak. For this reason, co-infection benefits both organisms. [6]

Macrophages, the first intracellular niche to fight tuberculosis, are also infected with HIV-1 and may play an important role in the pathogenesis of HIV-1. Cluster of differentiation 4 (CD4)+ T cells are considered the main target cells for HIV-1. In addition, also considered important for host defense against M. tuberculosis are CD4+ T cells and macrophages.[4]

Macrophages are involved in both HIV infection and M. tuberculosis progression. They are the main effector cells against M. tuberculosis and act as a site for intracellular progression of both infections.[6] Given the important function of macrophages in protecting against M. tuberculosis, a higher conversion rate of circulating monocytes to lung macrophages may indicate impairment in tuberculosis and HIV-positive patients. These results raise the question of how Simian Immunodeficiency Virus (SIV) and M. tuberculosis infect lung macrophages simultaneously. Are these macrophages infected with SIV after first contracting M. tuberculosis, or vice versa? The higher frequency of active TB among HIV-positive patients may also be related to inadequate early TB control in these individuals if HIV infection of alveolar macrophages may inhibit M. tuberculosis control.[7]

In a study Maddocks et al., (2009), it was found that M. tuberculosis infection increased the HIV replication rate in macrophages over a co-infection period of more than 12 hours, which affected the transcriptional response to M. tuberculosis. Macrophages are an important parameter for identification in the progression of TB-HIV co-infection. Improved knowledge of macrophage function and pathogenesis dynamics will open up new opportunities for better diagnosis, prognosis assessment and therapeutic intervention.[8]

In the field of medicine, the advancement of molecular imaging technologies has been crucial to numerous biological investigations and clinical diagnostics. Because images may clearly communicate information about a cell's size, shape, morphology, and the distribution or position of tagged biomolecules within the cell, imaging technology is essential for cell study.[9] The benefits of molecular imaging technologies above conventional imaging methods can be summed up as follows: (1) turning intricate biological processes (such as gene expression and biological signal transduction) into understandable visual representations; (2) identifying pathological alterations and early molecular variations in cells prior to anatomical changes in the disease; (3) evaluating therapeutic responses early through the measurement of changes in molecular target expression; and (4) quantifying the biological distribution of drugs in vivo.[10,11] Thus, either alone or in combination, these imaging techniques can aid in patient stratification prior to or during the initial phases of immunotherapy.[11] This review mainly discusses the application of immunotherapy to macrophage-based TB-HIV co-infection and highlights recent advances in molecular imaging technologies for macrophage tracking. The development of molecular imaging technology can facilitate the edintification and treatment of TB-HIV disease by looking at innate immune responses such as macrophages.

2. GLOBAL AND REGIONAL EPIDEMIOLOGY OF TB-HIV CASES IN INDONESIA

The epidemiology of tuberculosis differs by WHO region. The region with the highest rate of HIV infection is Africa. HIV co-infection plays a significant role in the TB epidemic and contributes to the high death rate among TB patients in this area. The prevalence of tuberculosis in Southeast Asia is comparable to that in Africa. The low frequency of HIV infection, however, points to other causes, such as poverty or hunger, as the main culprits behind the epidemic in this area. Multidrug-resistant (MDR) strains of tuberculosis (TB) present a treatment difficulty. In Europe, where the proportion of cases of MDR TB is five to ten times higher than in any other region, MDR TB is a serious issue. Better elimination strategies based on region-specific risk

factors are required. These might include screening for tuberculosis among individuals with HIV infection and high-risk groups, addressing poverty and malnutrition, and testing for and treating drug-resistant tuberculosis.[12]

Indonesia is among the top twenty countries in the world in terms of global TB burden, TB-HIV co-infection, and MDR-TB. In addition to the significant impact of TB-HIV on health and human resources, the economic burden of TB-HIV is also considerable.[2] TB as one of the infectious diseases that causes the top 10 deaths worldwide is known to be strongly influenced by the body's immune status. The presence of Acquired Immunodeficiency Syndrome (AIDS) caused by the HIV makes it easier for patients who have latent TB to become active TB.[13] In Indonesia, sexual activity carries the largest risk of HIV/AIDS transmission (62.5%), followed by drug injection (16.1%), pregnancy (2.7%), and homosexuality (2.4%).[14]

In Indonesia, the prevalence of HIV in TB patients is around 2.4%. TB is the most common opportunistic infection (49%) in people with HIV/AIDS. TB patients with HIV have a higher risk of death than TB patients without HIV.[15] Since 2013 in Indonesia, every TB patient has been offered HIV testing as a measure to reduce the social burden of both diseases.[13] Due to their rising incidence, two infectious diseases that medical professionals have paid particular attention to are tuberculosis and HIV. Regarding Tb-HIV co-infection, the same holds true. These two illnesses are connected by the immune system, which is in charge of fending against infections.[16]

3. ROLE OF INNATE AND ADAPTIVE IMMUNE RESPONSES TO TB-HIV COINFECTION

HIV infection increases a person's susceptibility to M. tuberculosis infection. TB disease that occurs in HIV-infected patients is caused by the reactivation of pre-existing (latent) TB infection or new infection with Mycobacterium tuberculosis. This risk increases with increasing immunosuppression.[17] HIV not only increases the risk but also the progression from new infection or latent TB infection to TB disease.

HIV that infects humans will attack CD4 cells on T cells or T-helper lymphocytes. The HIV cover called cover gp120 has a toxic effect that will inhibit T cell function, besides that the outer layer of the HIV protein, namely cover gp120 and anti p24, interacts with CD4 which then inhibits the activation of cells that represent antigens.[18] Normally, the number of CD4 cells in the human body ranges from 500-1000 cells/mm3. In people with HIV/AIDS, the number of CD4 cells can drastically decrease to below 200 cells/mm3. The condition of decreasing CD4 counts in people with HIV/AIDS indicates that the immune system is decreasing so that opportunistic infections can attack the body.[19]

HIV replicates itself including lymphocytes, CD4 cells, cluster of differentiation 8 (CD8), and macrophages so that there is a drastic decrease in the number of immune cells in patients. The decrease in CD4 and CD8 cells in HIV contributes to an increased risk of reactivation of latent TB. Other mechanisms affecting TB reactivation by HIV are manipulating receptors of the macrophage bactericidal pathway responsible for TB management, degrading chemotaxis, and interfering with tumor necrosis factor (TNF) which mediates the apoptotic response in cells infected with M. tuberculosis. Based on these facts, epidemiologic evidence suggests that innate and adaptive immune deficiencies probably increase the incidence of tuberculosis (TB) in individuals living with HIV.[20,21]

4. MACROPHAGES AS AN INNATE IMMUNE RESPONSE IN TB-HIV COINFECTION

An essential part of the first innate immune response to M. tuberculosis are alveolar macrophages. In cases of HIV co-infection, impaired alveolar macrophage function leads to poor initial immune control against M. tuberculosis. HIV makes macrophages more permissive to M. tuberculosis micro-bacterial growth and will place a greater burden on the activated adaptive immune response.[22] Both tuberculosis (TB) and HIV induce a cytokine milieu in the alveolar space that primes macrophages for absorption of foreign microbes by inducing an inflammatory phenotype. Even though macrophages are generally quite good at eliminating pathogens, the intracellular impacts of HIV and TB make them less effective, which allows the pathogen to continue growing. [22]

The expression of macrophage cytokines can also differ based on the stage of M. tuberculosis infection. In this case, the secreted Early Secreted Antigenic Target 6 kDa (ESAT-6) protein first guides macrophages towards the type 1 (M1) phenotype, which may aid in the

formation of granulomas, and subsequently to the more permissive type 2 (M2) phenotype.[23] It has been discovered that ESAT-6 binds to toll like receptor 2 (TLR2) and prevents mouse macrophages from undergoing LPS-induced inflammatory reactions. This implies that TLR2 is among the possible receptors via which ESAT-6 could have acted to reduce inflammation in M1.[24]

Early Mtb with enhanced pro-inflammatory activity is killed and controlled, resulting in a lower mycobacterial set point. On the other hand, early M. tuberculosis growth and dissemination with heightened anti-inflammatory action is responsible for the higher mycobacterial set point. Increased mycobacterial set points and earlier Mtb growth and spread were facilitated by HIV infection (Figure 1).

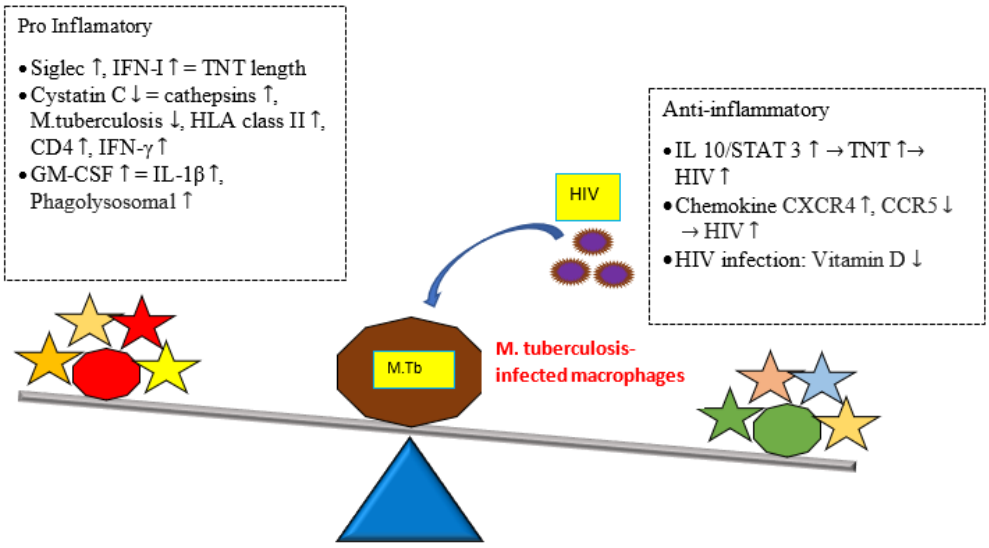

Figure 1. Macrophage activity balance between M. tuberculosis and HIV co-infection

5. EFFECT OF PRO-INFLAMMATORY AND ANTI-INFLAMMATORY CYTOKINES ON TB-HIV CO-INFECTION

HIV modifies the cytokine responses of macrophages to M. tuberculosis infection. Only GM-CSF, IL-1β, and IL-10 were differently released in TB/HIV coinfection cells out of all the assessed macrophage cytokines (IL-6, IL-10, TNFα, IFN-γ, and GM-CSF). It's interesting to note that variations in IL-10 secretion were only seen at early time points and IL-1β secretion at later times. At baseline, coinfected macrophage cells also produced considerably less GM-CSF.[25]

GM-CSF plays a dual role in modulating the inflammatory response by amplifying the inflammatory milieu through IL-1β production and by activating antimicrobial pathways. In murine macrophages, GM-CSF also aids in the promotion of phagolysosomal fusion. An essential mechanism of macrophage inflammation and improved mycobacterial control is GM-CSF signaling. Pathogens can control this signaling to encourage a more permissive bacterial condition.[25]

When GM-CSF was administered instead of other classical macrophage activators (Vitamin D, TNFα, IFN-γ), Mtb killing in HIV-infected macrophage cells was noticeably improved. Vitamin D-treated cells similarly showed a decrease in p24 staining, but they were unable to enhance M. tuberculosis control in co-infected macrophages.[25] Through the upregulation of CCR5 usage by HIV-1 and the upregulation of CC chemokine production in macrophages, tuberculosis (TB) creates an environment that is favorable for viral replication. These modifications help to explain why TB quickens the development of AIDS. CXCR4 inhibitors are a sensible treatment strategy for co-infection with HIV and TB.[26]

6. EFFECT OF TB-HIV COINFECTION ON MACROPHAGE MEMBRANE ENDOCYTOSIS PATHWAY

HIV and TB work in concert to alter the host immune system, which promotes both viruses' growth and reproduction. Through the creation of favorable intracellular conditions, both pathogens infect macrophages in pulmonary immunity. To prevent harm,

both alter the endocytic pathway. Important participants in the endocytic system that regulates pathogens are the natural inhibitor of endolysosomal proteases, known as cystatin, and cathepsins. When macrophages lose their Cystatin C (CstC), the amount of Mtb that is killed intracellularly increases dramatically. This is accompanied by an increase in cathepsins' overall proteolytic activity. Furthermore, reduced CstC modulation resulted in elevated HLA class II expression on macrophages and increased CD4+ T cell proliferation along with elevated IFN-γ release. A promising strategy to enhance the management of mycobacterial infections, including multiple drug-resistant (MDR) tuberculosis (TB), is to target CstC on human macrophages.[27]

The regulation and inhibition of cathepsin S by CstC is crucial for the regulation of the cleavage and transfer of Major Histocompability System (MHC) class II invariant chains.[28,29] Additionally, it suppresses MHC-II chaperone (H2-DM), which lowers the presentation of MHC-II peptides and T cell proliferation.[30] It has been demonstrated that MHC class II antigen processing and presentation are aided by CstC and cathepsin S.[30,31] It is inevitable that the observed increase in IFN-γ release will activate proinflammatory macrophages, which will then increase their microbicidal action against tuberculosis.[32] IFN-γ has the potential to mitigate inflammation in cases of active tuberculosis by preventing the generation of IL-1β and potentially lowering pulmonary immunopathology.[33]

7. EFFECT OF TB-HIV COINFECTION ON TUNNELING NANOTUBES (TNT)

Tunneling nanotube (TNT) production in the TB-associated milieu exacerbates HIV-1 infection in macrophages The molecular factor of TNT function on macrophages is an increase in the Sialic acid-binding immunoglobulin-type lectins (Siglec-1) receptor. Siglec-1 expression is reliant on TB-induced IFN-I production. Siglec-1 co-infection in non-human primates is correlated with disease and activation of the IFN-I/STAT1 pathway, and alveolar macrophages express Siglec-1 at high levelsIFN-I in the TB-associated milieu and the role of the IFN-I/STAT1/Siglec-1 axis in TB pathogenesis and retrovirus co-infection regulate Siglec-1 expression in human macrophages.[34]

Siglec-1 on TNT is thick and microtubule (MT)-positive, which positively correlates with length and high HIV-1 or mitochondrial load. This suggests that Siglec-1 + TNT has the functional ability to communicate material to distant recipient cells. Viral uptake experiments show that Siglec-1 can connect with virus-like particles that contain sialylated lipids, even on thick TNT. Additionally, loss-of-function methods imply that Siglec-1 plays a crucial role in engulfing these viral particles. The length of thick TNT decreased in correlation with Siglec-1 depletion, but the overall amount of thick TNT remained unchanged. The TB-associated microenvironment induces TNT production, which is reliant on the IL-10/STAT3 axis. Siglec-1 expression brought on by TB is essential for HIV-1 absorption and effective cell-to-cell transmission, which exacerbates HIV-1 infection and increases the synthesis of M(IL-10) by macrophages.[34]

Direct cell-to-cell bridges are formed by these M(IL-10) macrophages, and we have identified them as TNT engaged in viral transmission. The IL-10/STAT3 signaling pathway is necessary for TNT synthesis, and targeted TNT suppression significantly decreased the rise in HIV-1 cell-to-cell transmission and overproduction in M(IL-10) macrophages. Our findings suggest that TNT production should be investigated as a mechanism in future TB/HIV treatments since it promotes viral transmission and multiplication.[35] In the case of Tb, TNT production is probably the main cellular mechanism via which the IL-10/STAT3 signaling axis promotes viral dissemination in human macrophages. M(IL-10) macrophages can disseminate HIV-1 to uninfected macrophages via a process that depends on intercellular contact.[35] If TNTs can also develop between M(IL-10) macrophages and other cell types, like T or B cells, to transfer HIV-1 and/or viral material, that would be fascinating to know.[35]

8. EFFECT OF TB-HIV COINFECTION ON MACROPHAGE CELL APOPTOSIS

The processes leading to the demise of alveolar macrophage cells include necrosis, autophagy, and apoptosis. It has been demonstrated that M. tuberculosis produces the antigen Rv3416, which causes macrophages to become more latency-prone and mediates immunosuppression[36,37] In a similar vein, HIV-Nef is an antigen that is produced early in infection and functions to promote viral replication via a number of means, including apoptosis regulation. When the two antigens are combined, they work in concert to decrease macrophage apoptosis by suppressing the production of

pro-apoptotic molecules while concurrently raising that of anti-apoptotic molecules. The unique function of TLR2 in mediating both antigens' anti-apoptotic actions. This was true for both the expression levels of pro- and anti-apoptotic molecules as well as the level of Annexin V staining. It's interesting to note that TLR2 participation was only seen following co-stimulation of macrophages with both antigens, not during solo stimulation.[38]

9. EXAMINATION USING MOLECULAR IMAGING TECHNIQUES TO DETERMINE MACROPHAGE IMMUNE RESPONSE IN TB-HIV CO-INFECTION

Due to the high incidence of extrapulmonary TB and BTA-negative illness, diagnosing TB in individuals with HIV co-infection can be extremely difficult. Conventional laboratory methods do not yield fast enough data to manage HIV co-infected individuals accurately. Molecular techniques have advanced significantly in the last decade in the battle against tuberculosis.[39]

One promising approach to bringing the TB epidemic to an end is the development of more practical, quick, and sensitive molecular diagnostic assays to detect subclinical HIV co-infection.[39] At present, Xpert MTB/RIF stands as the most popular cartridge-based nucleic acid amplification test (NAAT) in use across the globe. Since 2013, the World Health Organization has advised using this test as a first diagnostic procedure for people or children who may have multidrug-resistant TB or HIV-associated tuberculosis.[40] Currently undergoing clinical review is the Xpert MTB/RIF Ultra molecular technology, which is a more sensitive test since it uses greater amounts of extracted DNA and includes multicellular DNA targets.[41]

In addition to Tb-HIV co-infection detection, there are several examination techniques to view molecular immune responses such as specific cells in the form of images and/or videos. This literature review provides information on various molecular imaging techniques of macrophage immune response to Tb-HIV co-infection, as follows (Table 1).

Table 1. This is a table. Tables should be placed in the main text near to the first time they are cited

No.	Research source	Molecular imaging techniques	Function on research sources
1	[42]	Confocal Laser Scanning Microscopy Live Imaging	Recognizing intracelluar infection of THP-1 machrophages by HIV-1 and Mtb
		Flow cytometry	Identifying THP-1 machropages infected with HIV-1 and Mtb
2	[34]	Imunofluorosense microscope	Assist in identifying siglec-1 expression that plays a role in M. tuberculosis-induced machrophage TNT for HIV capture
3	[35]	Scanning electron microscopy (SEM)	Assist in observing TNT day 6 of HIV-1 infected macrophage, treated with CmMTB.
		Deconvolution microscopy image	Assist in observing the picture of TNT formation triggered by TB in spreading HIV between M (IL-10) macrophage.

Detailed description of molecular imaging techniques of macrophage-mediated immune responses to Tb-HIV co-infection:

a. Confocal Laser Scanning Microscopy Live Imaging

The Confocal Laser Scanning Microscopy Live Imaging examination in Figure 2 proved that intracellular co-infection in THP-1 macrophages between cultures infected with HIV-VSV-G-PVP and M. tuberculosis, and cultures infected with HIV-BAL-PVP and M. tuberculosis. Readings were taken 72 hours after infection at 63X magnification. Green signal (green fluorescent protein) indicates HIV infection of host cells. Red signal (mCherry) indicates host cell infection by M. tuberculosis.[42]

b. Flow Cytometry

The flow cytometry examination identified THP-1 cells infected with HIV and M. tuberculosis based on their size and granularity, while single cells were identified based on area and height proportionality. Readings can also be viewed by color, with mCherry used to identify M. tuberculosis-infected cells and green fluorescent protein (GFP) used to identify HIV-infected cells (Figure 3).[42]

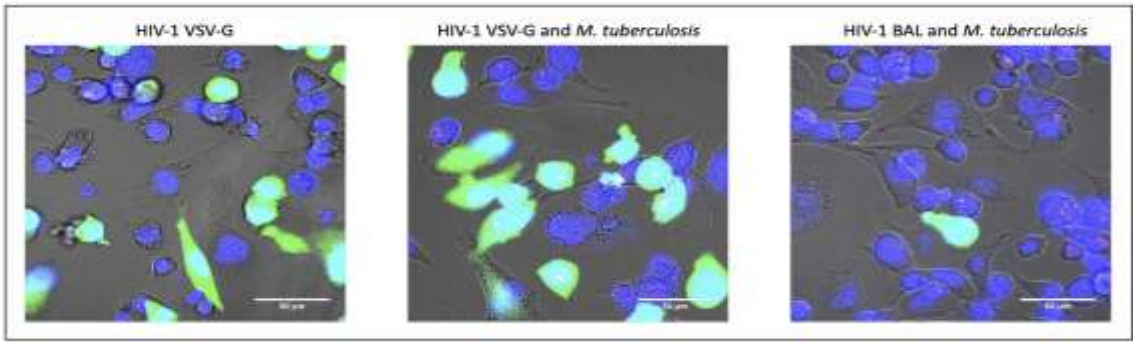

Figure 2. Examination of HIV-Mtb by confocal laser scanning microscopy live imaging[42]

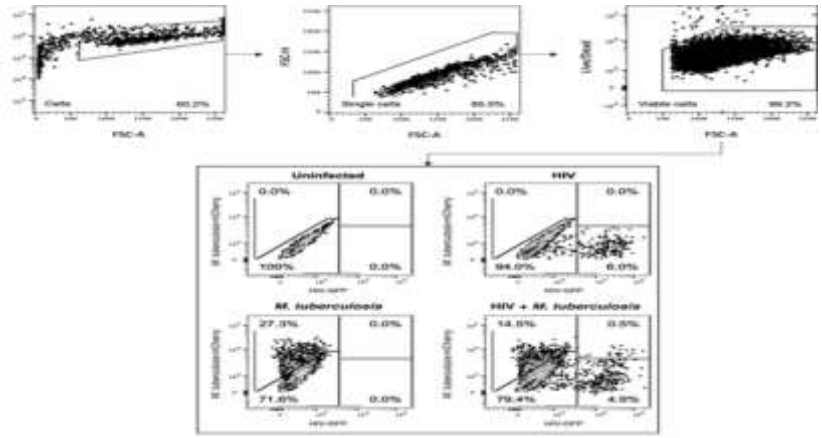

Figure 3. Flow cytometry was performed to determine the impact of co-infection on the relative frequency of HIV-1 (HIV) and/or Mycobacterium tuberculosis infection in THP-1 cells[42]

c. Imunofluorosense Microscope

Identification of siglec-1 expression, which is involved in M. tuberculosis-induced macrophage TNT to trap HIV, was made possible by this immunofluorescence analysis. During the HIV virus's propagation, intercellular TNT was reduced in macrophage cells treated with siRNA due to the depletion of siglec-1 (Figure 4). The experiment was conducted utilizing intracellular cell labeling with DAPI (blue), F-actin (red), and HIV-1Gag (green).[34]

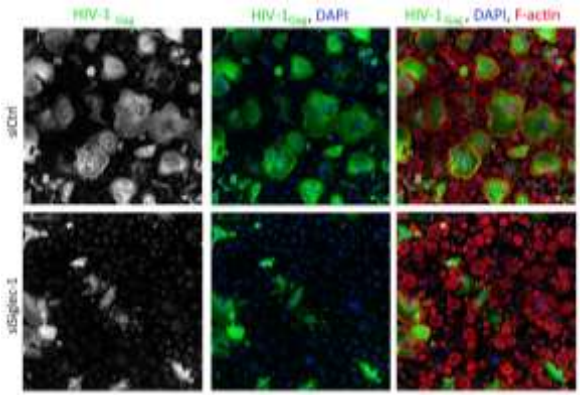

Figure 4. Representative immunofluorescence of siRNA-transfected cells treated with cmMTB, 14 days after HIV infection[34]

d. Scanning Electron Microscopy (SEM)

SEM was used to observe increased TNT formation on macrophages in an HIV-1-induced TB environment (Figure 5). TNTs are shaped like long tubes that contain F-actin in their membrane and function to connect cells, TNTs can be divided into thick (right) and thin (left) (35).

e. Deconvolution Microscopy Image

Observed image of TB-triggered TNT formation in propagating HIV among M (IL-10) macrophages. HIV-infected macrophages will accelerate self-propagation via TNT from HIV-infected macrophages (donor, Gag+, red) to recipient macrophages (recipient, CellTracker+, green).[35]

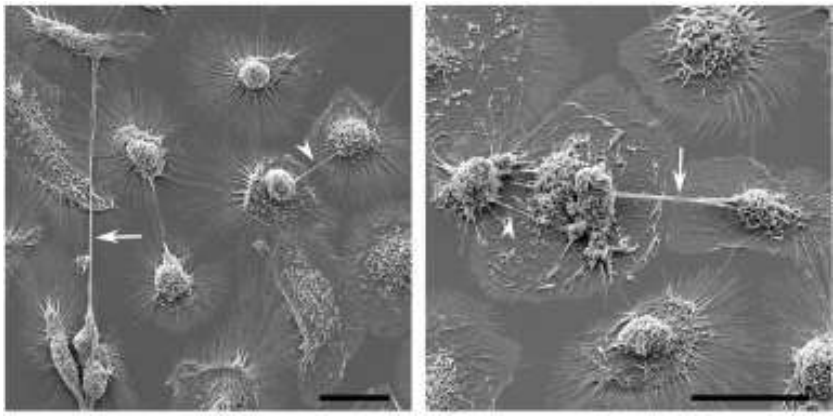

Figure 5. Scanning electron microscopy (SEM) images of TNT on HIV-infected macrophages with cmMTB drug administration[35]

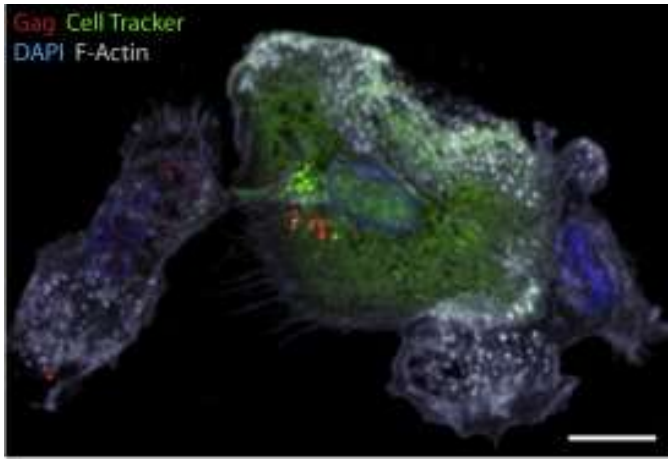

Figure 6. Deconvolution microscopy image demonstrating HIV-1 Gag transmission to acceptor cells identified by CellTracker+. Observation after co-culture of HIV macrophages and CellTracker+ macrophages for 24 hours[35]

10. CONCLUSION

HIV and MTB harm the immune system in concert, increasing the burden of both illnesses. HIV co-infection substantially increases the risk of progression to active TB and conversely, TB co-infection will increase the replication rate, spread, and genetic diversity of HIV-1. When an individual has M. tuberculosis infection, their HIV replication rises and their development to AIDS is accelerated. Macrophages, the first intracellular niche against tuberculosis, are also infected with HIV-1 and may play a significant role in the pathogenesis of HIV-1. CD4+ T cells are thought to be the primary target cells for HIV-1. There are various detection techniques by molecular imaging of macrophage immune response to Tb-HIV co-infection, such as Confocal Laser Scanning Microscopy, Live Imaging, fluorometry, Immunofluorescence Microscopy, Scanning electron microscopy (SEM), and Deconvolution microscopy image.

Conflict of Interest

The authors declare no conflict of interest

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