JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Role of Cytokines and Vitamin D in HIV and HIV/TB Disease

Mr. Rajesh Kuma, Dr. Tun Veer Singh Arya, * Dr. Amar Prakash Garg

*Medical College and Hospital, Meerut,(UP),India;

*Shobhit Deemed University, Meerut,(UP),India;

ABSTRACT

Co-infection of TB and HIV fastens the development of latent tuberculosis into active tuberculosis by compromising the immune system. Antiretroviral therapy is an effective therapy in reducing the count of virus and increasing CD4+ T-lymphocyte count in individuals infected with HIV. Although therapeutics of HIV antiretroviral therapy (ARV) and anti TB therapy together leads to drug toxicities and initiation of immune reconstitution inflammatory syndrome (IRIS). At a higher-level of the infection, individuals on cART (combined antiretroviral therapy) undergoes to an immune reconstitution inflammatory syndrome (IRIS), due to uncontrolled inflammatory feedback to opportunistic microbes after the beginning of cART. Specific HIV inducing cytokines for example IL -1, IL-6, TNF and Vitamin D deficiency has been linked with the progression of the HIV/TB infection. Vitamin D recognized as an antimicrobial and anti-inflammatory molecule. Supplementation of Vitamin D can suppress the HIV replication, induces HIV –repressed cytokines, increases CD4+ T cell count and provides resistance to tuberculosis through mycobactericidal activity. The mechanism of action between Vitamin D and cytokines needs more attention and research. In this review, we have summarized the role of cytokines and vitamins individually and interplay of cytokines and vitamin D role in the HIV/TB co-infection.

Keywords: IL -1, IL-6, TNF, Vitamin D, HIV/TB infection, Cytokines.

Introduction:

Human immunodeficiency syndrome (HIV) infection leads to gradual failure of the immune system, which allows opportunistic diseases to expand. Tuberculosis (TB) is the most typical opportunistic infection that makes human immunodeficiency virus (HIV) infection more complex. Tuberculosis occurs in the earlier stages of HIV infection as compared to other opportunistic infections/ diseases. Co-infection of TB and HIV referred to when a person is suffering from both HIV and TB (either latent or active disease). Each condition

speeds up the progression of another condition, and also HIV infection accelerates the progress of latent tuberculosis into active tuberculosis by suppressing the immune system (Mayer and Hamilton, 2010).

The TB/HIV co-infection destructs the immune system, which leads to premature death. Globally in 2018, It is estimated that 10.0 million people (9.0–11.1 million) suffering from tuberculosis disease. There were an approximately, 1.2 million tuberculosis deaths in HIV negative people in 2018 and further, 251 000 deaths (size, 223 000–281 000) from TB/HIV positive co-infection ("WHO | Global tuberculosis report 2019,"). India contributes the highest percentage (27%) among the eight countries considered for two-thirds of the total world's population.

The beginning period of the treatment is the most crucial step in the treatment of the individual with HIV/TB co-infection, and many factors should be considered. Antiretroviral therapy is an effective therapy in reducing the count of virus and can improve the function of the immune system through increasing CD4+ T-lymphocyte count (Lakmesari et al., 2020). Conversely, the problems related to antiretroviral therapy (ARV) initiation in people infected with HIV/TB co-infection cause the initiation of immune reconstitution inflammatory syndrome (IRIS), which can magnify TB symptoms such as fever and pulmonary symptoms (Narendran et al., 2013).

Vitamin D has a crucial function in the innate immune system, calcium and phosphorous homeostasis. Inadequacy of Vitamin D has been associated with the progression of the HIV/TB infection, due to the inadequate T cell-mediated help to counter *M. Tuberculosis* (Ayelign et al., 2020). Supplementation of Vitamin D in co-infection of HIV/TB increases the antimicrobial activity in the primary immune system through the synthesis of cathelicidin (host antimicrobial peptide, CAMP) which mediates anti-mycobacterial activity (Bartley, 2010).

Cytokines affect the HIV directly or indirectly by producing soluble compounds. A reduction occurs in T-helper type 1 (Th1) cytokines production, such as interleukin (IL-2) and antiviral interferon (IFN-gamma), whereas there is an increased production in T helper type 2 (Th2) cytokines including IL-4, IL-10, proinflammatory cytokines (IL-1, IL-6, IL-8) and tumour necrosis factor (TNF)-alpha (Kedzierska and Crowe, 2001).

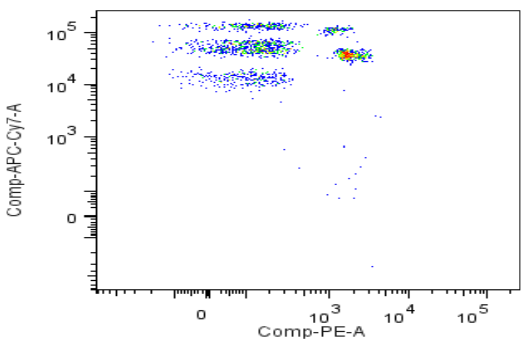
Vitamin D has dramatically shown the attributes in the innate immune system. The biochemical role of vitamin D and antimicrobial activity is still not very well elaborated. The molecular mechanism of Vitamin D and cytokines can provide a platform to understand the interplay. Cytokines help in cell communication and found to be responsible in the progression of the HIV/TB and suppression of the immune system during the infection. Specific chemokines, cytokines, macrophages and interleukins (IL) levels affects the cell metabolism with respect to the Vitamin D levels during the HIV/TB co-infection. This review broadly will discuss about the, role of cytokines involved in the HIV and HIV/TB infection, effect of vitamin D in the infection and the correlation between vitamin D and cytokines in causing HIV and HIV/TB co-infection.

A. Cytokines involved in HIV and HIV/TB infection :

Cells communicate through direct contact, indirectly by producing soluble molecules, or by both the mechanisms. Cytokines are the proteins or glycoprotein, which influence the cell to cell communication and intrinsically associated to disease continuing in HIV infection.

Several cytokines has been reported to regulate HIV-1 disease *in vitro* and replication in both macrophage derivation and CD4+ T cells lymphocytes. HIV inducing cytokines comprises: Tumour necrosis factor-alpha, Tumour necrosis factor-beta, Interleukin (IL-1) and Interleukin (IL-6) (Esser et al., 1998), which triggers replication of HIV-1 disease in T cells and monocyte-derived macrophages (MDM), up-regulation of HIV-1 in T cells by Interleukin (IL-2, IL-7, IL-15), and modulation of HIV-1 in monocyte-derived macrophage (MDM) by macrophage-colony stimulating factor (MCSF). HIV-repressed cytokines comprises: IFN-alpha, IFN-beta and IL-16. Other various types of cytokines such as IFN-gamma, Interleukin-4 and granulocyte-macrophage colony-stimulating factor have known to show both bi-functional effects (inhibitory as well as stimulatory effects) on HIV-1 (Kedzierska and Crowe, 2001).

Cytokines play an essential part in acute infection, chronic infection, inflammation and homeostasis (Freeman et al., 2016). In the naive HIV patients, multiple cytokines, for example, Th2 (IL-6, and IL-10), Th1 (IFN-γ, TNF-α & IL-2) could help in differentiating culture-positive AFB smear-negative and culture-negative AFB smear-negative (Acid Fast Bacilli microscopy). A study observed that culture-negative AFB smear-negative have lower production of cytokines against *Mycobacterium tuberculosis*-specific antigens, that are infected with some other disease/infection and does not involve pulmonary tuberculosis. A significant observation is that blood cytokine imprints could help in identifying culture-positive AFB smear-negative from those who are culture-negative AFB smear-negative and without any pulmonary tuberculosis (Kisuya et al., 2019). In acute HIV infection, there is a high rise in plasma levels of inflammatory cytokines, a reduction in CD4+ T cell numbers (of blood, mucosa and tissues) and, CD8+ T cell numbers showed an increase (Douek et al., 2003). It has also been observed that in chronic untreated HIV, the plasma inflammatory mediators such as interferon (IFNs), interleukins (IL-6) and tumour necrosis factor (TNF) is high (Funderburg et al., 2013). Still, the sources and involvement mechanism of these cytokines are not well defined. Shown in figure 1.1



Representative plot of cytometry bead array

In acute HIV infection, there is a high rise in plasma levels of inflammatory cytokines, a reduction in CD4+ T cell numbers (of blood, mucosa and tissues) and, CD8+ T cell numbers showed an increase (Douek et al.,

2003). It has also been observed that in chronic untreated HIV, the plasma inflammatory mediators such as interferon (IFNs), interleukins (IL-6) and tumour necrosis factor (TNF) is high (Funderburg et al., 2013). Still, the sources and involvement mechanism of these cytokines are not well defined.

Serum IL-10 levels: The patients with HIV-TB co-infection had reduced level of IL-10 cytokine when compared with HIV infected subjects. The level of IL-10 cytokine was 13 times higher in HIV infected patients than HIV-TB co-infected patients (Figure 1.2).

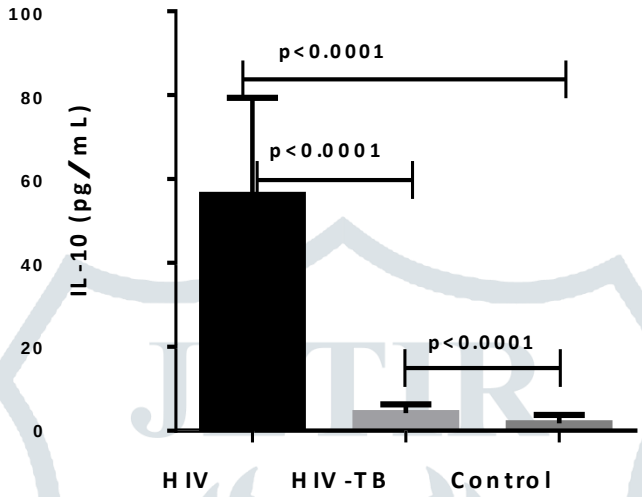


Figure 1.2: Serum IL-10 levels in HIV infected patients, HIV-TB co-infected patients and healthy controls at baseline visit.

The progression of HIV infection is dependent on CD4 T-cell stability as well as time log of symptom-free HIV infection. Patients with CD4 T-cell count that is stable as well as including other parameters ranging 7 to 10 years termed as 'slow progressors' while 'rapid progressors' shows symptoms earlier, within three years (de Medeiros et al., 2016). There are numbers of different cytokines functions that have been recognized and characterized to demonstrate HIV infection. Further, increased levels in IL-6 and IL-10 cytokines infect pre-HAART, irrespective of the decreased or increased progression of disease in the patient. This indicates a worldwide inflammatory condition and used as a biomarker of disease progression in HIV-infected patients (de Medeiros et al., 2016).

In the mid-1990s, the development of combination antiretroviral therapy (cART) used for the treatment of HIV disease remarkably reduced the count of AIDS-associated morbidity and mortality (Egger et al., 2002). Approximately, 38% of HIV affected individuals undergoing cART at a later stage of disease encountered an inflammatory immune syndrome (IRIS), indicating the uncontrolled inflammation action to opportunistic pathogens after the beginning of cART. Some countries of the world, M. tuberculosis infection is endemic, due to which tuberculosis (TB)-linked IRIS (TB-IRIS) is a typical problem within TB/HIV co-infected individuals.

Monocytes and IL-18, specific cytokines of inflammation activating complex, have been observed in tuberculosis-IRIS inflammasome activation both before and after cART in TB-IRIS individuals. A study has shown HIV/TB co-infection patients display elevated quantity of monocytes expressing activated caspase-1 (casp1) pre-cART, compared to HIV individuals who are not exposed to tuberculosis. CD64+ monocytes, a

marker of elevated casp1 expression. In HIV/TB co-infection, inflammasome activation in monocytes /macrophage rises with monocytes/ macrophages activation by T-cells. TB-IRIS patients with immediate cART indicates a greater risk of an excessive inflammatory response (Tan et al., 2016).

Around 90% of infected patients remain well after developing latent tuberculosis infection (LTBI), whereas 10% develop primary tuberculosis (TB) immediately preceding infection or its re-activation after many years (Manabe and Bishai, 2000). The epidemic of HIV increases the vulnerability to disease, and in HIV infected individuals. Tuberculosis is the primary reason of death among HIV infected individuals. A Study shows that advancement of lateral tuberculosis infection to pulmonary tuberculosis might not only be because of the reduced number of CD4 T-cell but due to functional disability of CD4 T-cell in *M. Tuberculosis* (Amelio et al., 2019). Specific pro-inflammatory cytokines such as IL-17A, IL-17F, IL-21 and IL-22 protects against tuberculosis infection (Devalraju et al., 2018).

HIV-infected individuals have been reported to have impairments in the IL-12/IFNγ receptor. Specific cytokines lower level precedes the progression of tuberculosis in the HIV infected patients such as Interleukin-12 (IL 12). Moreover, the supplementation of IL-12 adjuvant is considered as successful in the TB treatment. The mechanism is still unknown how the compromised ability of IL-12 develops the disease (Bordón et al., 2011).

To elucidate the better understanding of immune response and the HIV/TB co-infection requires the whole cytokine profiling throughout the various levels of HIV infection, which can contribute betterment of clinical assessment. Although not only cytokines itself plays an essential role in the disease, but Vitamin D levels also affect the mechanism of HIV/TB co-infection.

Table 1. List of cytokines involved diseases such as HIV, TB-IRIS and co-infection of HIV/TB

Author, Year	**Disease**	**patient population**	**Cytokine level (increased, decreased, or unchanged)**	**Outcomes with respect to disease**
(de Medeiros et al., 2016)	HIV (HAART and Pre-HAART)	>3,500 medical records	Increased level of IL-6 and IL 10	Serve as marker to detect inflammatory status in the course of HIV-infected individuals.
(Devalraju et al., 2018)	HIV/LTBI+ and HIV+ active tuberculosis patients	190 patients	Decreased IL-17 and IL-22 and increased IL-10	Functions in the protection of immune cells against *Mycobacterium tuberculosis*
(Tan et al., 2016)	TB-IRIS Patients	200 patients	Increased IL-18	A marker of inflammation responsible protein complex in TB-IRIS.
(Riou et al., 2012)	HIV/TB co-infection patients	42 patients	Reduced interferon-inducible protein-10 (IP-10) and VEGF	A surrogate marker to record sputum culture conversion in HIV un-infected persons.

(Amelio et al., 2019)	HIV/TB co-infection patients	112 patients	Decreased level of IL-1, IL-6, CRP, IL-23, and IP-10	HIV infection reduces M. tuberculosis-induced systemic proinflammatory cytokine/chemokine response
(Chetty et al., 2014)	HIV/TB co-infection patients	82 patients	Increased IL-10	Have potential immunotherapeutic strategy
(Narendran et al., 2013)	HIV/TB co-infection patients	57 patients	Increased IL-6 and CRP	Serve as potential target for the immune interventions and IRIS detection

Serum IL-6 levels: A different pattern in the level of IL-6 cytokine was observed. The patients with HIV-TB co-infection had higher level of IL-6 cytokine than HIV infected patients. At baseline, the level of IL-6 in HIV-TB co-infected patients was 1.7 times higher compared to HIV infected patients (figure 1.3).

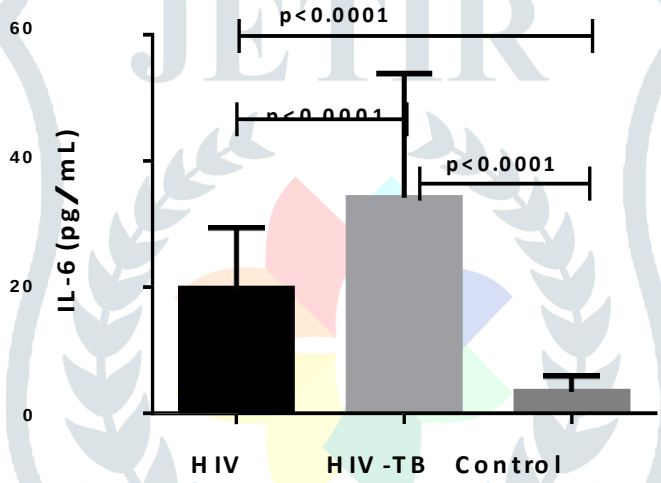


Figure 1.3: Serum IL-6 levels in HIV infected patients, HIV-TB co-infected patients and healthy controls at baseline visit.

Serum IL-4 levels: At baseline visit, the HIV infected patients had marginally higher level of IL-4 cytokine compared to HIV-TB co-infected patients although the difference was not statistically significant. Both the groups had significantly higher levels of IL-6 than healthy controls (Figure 1.4).

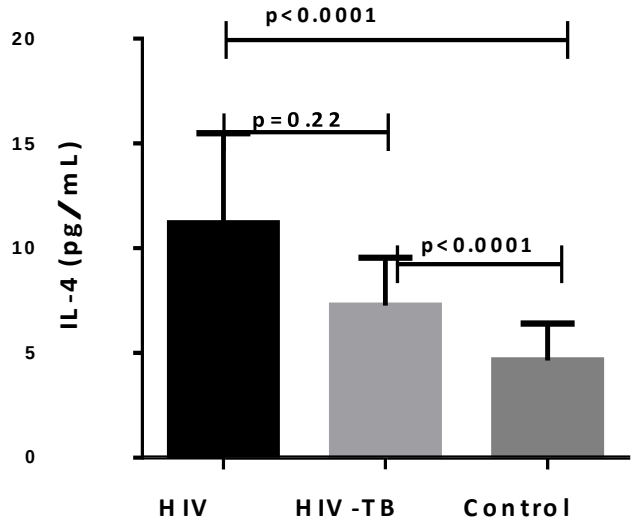


Figure 1.4: Serum IL-4 levels in HIV infected patients, HIV-TB co-infected patients and healthy controls at baseline visit.

Serum IL-1 levels: when compared to HIV infected patients, the patients in HIV-TB co-infected group had 3.3 times lower level of IL-1 cytokine. However, the level of IL-1 cytokine was higher in both groups than healthy controls (Figure 1.5).

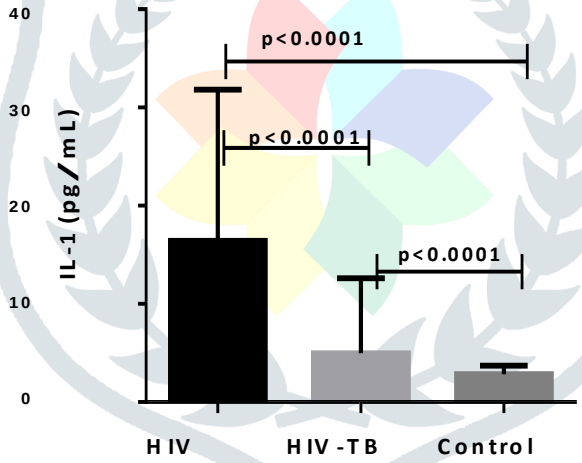


Figure 1.5: Serum IL-1 levels in HIV infected patients, HIV-TB co-infected patients and healthy controls at baseline visit. **Effect of antiretroviral therapy (ART) and dual therapy (ant tubercular and antiretroviral therapy)**

B. Status of Vitamin D in HIV and HIV/TB infection

Vitamin D recognized as a total regulator of calcium and bone homoeostasis. Vitamin D also has varied parameters of physiological activity, such as cellular divergence, expansion, activation, and death of the cell. Alteration of Vitamin D with variant vitamins is due to its major active metabolite, 1α, 25-dihydroxyvitamin D (1, 25 [OH] 2D), which is a steroid hormone. Deficiency of Vitamin D has now been shown to be usual in individuals with active tuberculosis (Martineau et al., 2011; Wilkinson et al., 2000) and is further pervasive in individuals with latent tuberculosis which develops into active disease (Talat et

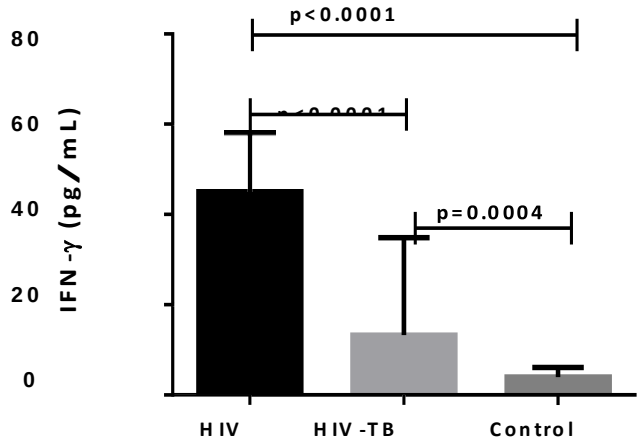
al., 2010). The factor in Vitamin D deficiency is the variation in UV B levels depending upon season and geographical impacts Vitamin D quantity (Webb et al., 1988). Besides higher tuberculosis chances, deficiency of vitamin D has also been recognized to be relatable with high chances of death and acquired immune deficiency syndrome (AIDS) cases in those individuals with HIV-1, from a more extensive diversity of populations (Haug et al., 1998; Viard et al., 2010). Vitamin D consists of anti-inflammatory and antimicrobial properties, and possess the capability to be employed for both therapeutics and prevention of tuberculosis. Supplementation of Vitamin D can overcome the TB morbidity and can inhibit the HIV/TB disease progression (by reducing IRIS incidence) (Coussens et al., 2014).

C. Interplay between Vitamin D and cytokines in HIV and HIV/TB infection

Vitamin D plays a vital role in innate and acquired immunity(Kamen and Tangpricha, 2010; van Etten et al., 2008), and may suppress HIV replication through up-regulation of the antimicrobial peptide, known as cathelicidin (Bergman et al., 2007). Furthermore, studies suggest that hypovitaminosis D accelerates HIV infection (Mehta et al., 2010; Viard et al., 2010), although higher plasma 25-hydroxyvitamin D (25(OH) D) amount provides a more promising immune rehabilitation after antiretroviral therapy (ART) (Ross et al., 2011). Despite having knowledge that many HIV-1 infected patients affected by hypovitaminosis D, neither the foremost and secure amount of vitamin D dosage has yet been developed. Therefore, recognizing associated risk factors for vitamin D deficiency and analyzing the association with HIV-related complications is difficult, especially in HIV-infected adults. Among the high frequency of acquired HIV in children and young adults have a high risk of Vitamin D deficiency in the winter season. Optimum supplementation of Vitamin D determines the level of the active metabolite of Vitamin D - 25-OHD concentrations. It confirms the link between Vitamin D and CD 4 cell counts among the individuals of HIV (Rutstein et al., 2011).

Another evidence is severe hypercalcemia condition in tuberculosis varies broadly between some countries. Doubtless due to the variation in the intake of calcium and vitamin D, the exposure amount of sunlight and the level of disease conclude the measurement for hypercalcemia (Dosumu and Momoh, 2006; Liam et al., 1998). Another evidence is severe hypercalcemia condition in tuberculosis varies widely due to the dissimilarities in the levels of vitamin D and intake of calcium by the individuals, and, the amount of sunlight. A study concludes that tuberculosis looks not to be solely accountable for hypercalcemia; conversely, the amount of hypercalcemia is greater in tuberculosis and HIV co-infected individuals in the tropical regions of Northwest Ethiopia. This concludes that anti-tuberculosis chemotherapy does not improve the condition of hypercalcemia in groups with/without HIV co-infection (Amare et al., 2012).

Serum IFN-γ levels: The HIV infected patients had higher levels of IFN-γ compared to HIV-TB co-infected and healthy controls. The HIV-TB co-infected group had 3.4 times lower level of IFN-γ compared to HIV infected patients (Figure 1.6).



Serum IFN-γ levels in HIV infected patients, HIV-TB co-infected patients and healthy controls at baseline visit.

Vitamin D influences innate immune system by modulating the expression of the immune cells such as monocytes and lymphocytes (Kongsbak et al., 2013; Korf et al., 2012; Morán-Auth et al., 2013). Vitamin D regulates the immune cells by modulating the various transcription factors (NF-AT and NF-kB), which ultimately enhances the phagocytotic and cell activity after the supplementation of Vitamin D. In contrast, in adaptive immunity, Vitamin D helps in reducing maturation of dendritic cells, MHC class II expression levels along with their co-stimulatory molecules (CD40, CD80, and CD86). Vitamin D enhances the tolerance by decreasing the inflammation (Baeke et al., 2010). It has also been reported that Vitamin D decreases the production of IL-12 and IFN-gamma, while increasing IL-10, and enhances the development of Th2 and Treg cells over Th1 and Th17 which promotes tolerance to immune responses (Adams and Hewison, 2010; Smolders et al., 2009).

Tuberculosis immune reconstitution inflammatory syndrome (TB -IRIS) individuals with co-infection of the human immunodeficiency virus (HIV) /tuberculosis initiating antiretroviral therapy (ART) is linked with hypercytokinemia. As corticosteroid therapy and vitamin D has immune modulator characteristics such as (cytokine, chemokine, corticosteroid usage, and vitamin D) (Conesa-Botella et al., 2012).

CTC (corticosteroid) usually changes the inflammatory profile of individuals who evolves TB-IRIS by lowering tumour necrosis factor (TNF), IP -10, interferon γ (IFN -γ), IL -18 and interleukin IL-12p40, IL-6, IL-8, IL-10. The relationship connecting severe deficiency of vitamin D and elevated pro-inflammatory cytokines requires supplementation of vitamin D in HIV/TB co-infected individuals initiating antiretroviral therapy (Conesa-Botella et al., 2012).

The primary active metabolite, 1α, 25-dihydroxyvitamin D (1, 25 [OH] 2D) of vitamin D has anti-inflammatory characteristic, and higher levels of vitamin D are connected to lesser chances of immune-related diseases, sclerosis and depression (Salzer et al., 2012; von Bahr et al., 2015). Also, in an unsystematic experiment of supplementing VitD in tuberculosis infected individuals, a portion of individuals showed improved infection evacuation with a polymorphism in the vitamin D receptor (Martineau et al., 2011). In many cases, Vitamin D deficiency is found to be related to the immune-suppression in the HIV infected patients (Aziz et al., 2013). A recent research of supplementing vitamin D in HIV infection showed a lowered

risk of activating the immune system, which implies an anti-inflammatory function (Fabre-Mersseman et al., 2014). Low levels of Vitamin D represent inflammation markers in TB –IRIS/HIV cases, irrespective of IRIS status (Conesa-Botella et al., 2012).

Patients with a deficiency of Vitamin D has a higher concentration of specific cytokines such as IL -6, TNF -α, D -dimer, higher proportions of CD14dimCD16+ and CX3CR1+ monocytes. Vitamin D deficiency is related to higher inflammation and activated monocyte phenotypes during chronic HIV disease (Manion et al., 2017).In between the active tuberculosis patients and latent tuberculosis infection patients, the concentrations of the Vit-D associated cytokines IL-15 and IL-32 differs. But, IL-15 and IL-32 contributes essential parts in Vitamin D intervened tuberculosis (TB) resistance system. The Vit-D levels triggers IL -1β and that provides resistance to TB and the mycobactericidal activity (Hong et al., 2019).

Recent observations have fascinated the function of vitamin D in tuberculosis (de Haan et al., 2014) and in autoimmune disorders (Yang et al., 2013).*M. tuberculosis* are the most typical opportunistic pathogen plays a part in the progression of IRIS and advanced HIV disease (Conesa-Botella et al., 2009). Deficiency of Vitamin D is prevailing and related to HIV disease (Van Den Bout-Van Den Beukel et al., 2008). A study conducted a medication-controlled experiment of supplementation of vitamin D in individuals with pulmonary tuberculosis (PTB) shown faster clinical recovery compared to other individuals (Salahuddin et al., 2013). Indeed more research on vitamin D for the control of TB infection is required.

A significant role of vitamin D is its involvement in the modulation of the human immune system reaction (Modlin, 2007) and resoluteness of tuberculosis-influenced inflammation (Conesa-Botella et al., 2009) is observed. Various experiments have confirmed that the level of vitamin D inhibits the regulation of cell-mediated immunity (Coussens et al., 2012). Additionally, an essential function of monocyte to trigger TB-IRIS was underlined (Andrade et al., 2014)Furthermore, biomarkers which shows monocytes and myeloid cell trigger activation can provide better forecasting of IRIS and propose novel mechanisms of investigation for precautionary and medication approaches (Musselwhite et al., 2016).

IRIS risk factors are associated with pro-inflammatory cytokine markers such as activation of myeloid cell, coagulation and fibrosis markers before initiating antiretroviral therapy. Other factors such as activation of T-cell and monocyte, inflammatory response and lower vitamin D concentrations are solitarily linked with IRIS chances. Vitamin D acts as a potential target in IRIS pathogenesis (Musselwhite et al., 2016).

Conclusion:

HIV/TB co-infection is a well-recognized global and public health issue. IL-6, IL-12, IL-22, IL-17 appears to be the responsible cytokines elaborated by HIV/TB co-infection. Specific cytokines plays a role in infections and as well as function as biomarkers of the disease. An approach of treating tuberculosis before cART decreases the risk of TB-IRIS. Supplementation of Vitamin D increases the immunity by suppressing the pro-inflammatory cytokines and inhibiting HIV viral replication. However, the effect of vitamin D on viral load needs to be more evaluated. Presently, the data proposes that there is a possible function of supplementation of Vitamin D in the HIV/TB co-infected patients. Still, more studies are required to confirm its position with the proper protocol.

References

Adams, J.S., Hewison, M., 2010. Update in Vitamin D. The Journal of Clinical Endocrinology & Metabolism 95, 471–478. https://doi.org/10.1210/jc.2009-1773

Amare, B., Meseret, S., Yabutani, T., Moges, B., Kassu, A., 2012. Hypercalcemia in patients with tuberculosis and HIV infections in Northwest Ethiopia. Asian Pacific Journal of Tropical Disease 2, S629–S634. https://doi.org/10.1016/S2222-1808(12)60234-5

Amelio, P., Portevin, D., Hella, J., Reither, K., Kamwela, L., Lweno, O., Tumbo, A., Geoffrey, L., Ohmiti, K., Ding, S., Pantaleo, G., Daubenberger, C., Perreau, M., 2019. HIV Infection Functionally Impairs Mycobacterium tuberculosis-Specific CD4 and CD8 T-Cell Responses. J Virol 93. https://doi.org/10.1128/JVI.01728-18

Andrade, B.B., Singh, A., Narendran, G., Schechter, M.E., Nayak, K., Subramanian, S., Anbalagan, S., Jensen, S.M.R., Porter, B.O., Antonelli, L.R., Wilkinson, K.A., Wilkinson, R.J., Meintjes, G., van der Plas, H., Follmann, D., Barber, D.L., Swaminathan, S., Sher, A., Sereti, I., 2014. Mycobacterial Antigen Driven Activation of CD14++CD16− Monocytes Is a Predictor of Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome. PLoS Pathog 10, e1004433. https://doi.org/10.1371/journal.ppat.1004433

Ayelign, B., Workneh, M., Molla, M.D., Dessie, G., 2020. Role Of Vitamin-D Supplementation In TB/HIV Co-Infected Patients. Infect Drug Resist 13, 111–118. https://doi.org/10.2147/IDR.S228336

Aziz, M., Livak, B., Burke-Miller, J., French, A.L., Glesby, M.J., Sharma, A., Young, M., Villacres, M.C., Tien, P.C., Golub, E.T., Cohen, M.H., Adeyemi, O.M., 2013. Vitamin D insufficiency may impair CD4 recovery among Women's Interagency HIV Study participants with advanced disease on HAART. AIDS 27, 573–578. https://doi.org/10.1097/QAD.0b013e32835b9ba1

Baeke, F., Takiishi, T., Korf, H., Gysemans, C., Mathieu, C., 2010. Vitamin D: modulator of the immune system. Current Opinion in Pharmacology, Cancer/Immunomodulation 10, 482–496. https://doi.org/10.1016/j.coph.2010.04.001

Bartley, J., 2010. Vitamin D: emerging roles in infection and immunity. Expert Rev Anti Infect Ther 8, 1359–1369. https://doi.org/10.1586/eri.10.102

Bergman, P., Walter-Jallow, L., Broliden, K., Agerberth, B., Söderlund, J., 2007. The antimicrobial peptide LL-37 inhibits HIV-1 replication. Curr. HIV Res. 5, 410–415. https://doi.org/10.2174/157016207781023947

Bordón, J., Plankey, M.W., Young, M., Greenblatt, R.M., Villacres, M.C., French, A.L., Zhang, J., Brock, G., Appana, S., Herold, B., Durkin, H., Golub, J.E., Fernandez-Botran, R., 2011. LOWER LEVELS OF INTERLEUKIN-12 PRECEDE THE DEVELOPMENT OF TUBERCULOSIS AMONG HIV-INFECTED WOMEN. Cytokine 56, 325–331. https://doi.org/10.1016/j.cyto.2011.08.018

Chetty, S., Porichis, F., Govender, P., Zupkosky, J., Ghebremichael, M., Pillay, M., Walker, B.D., Ndung'u, T., Kaufmann, D.E., Kasprowicz, V.O., 2014. Tuberculosis distorts the inhibitory impact of interleukin-10 in HIV infection. AIDS 28, 2671–2676. https://doi.org/10.1097/QAD.0000000000000437

Conesa-Botella, A., Mathieu, C., Colebunders, R., Moreno-Reyes, R., van Etten, E., Lynen, L., Kestens, L., 2009. Is vitamin D deficiency involved in the immune reconstitution inflammatory syndrome? AIDS Res Ther 6, 4. https://doi.org/10.1186/1742-6405-6-4

Conesa-Botella, A., Meintjes, G., Coussens, A.K., van der Plas, H., Goliath, R., Schutz, C., Moreno-Reyes, R., Mehta, M., Martineau, A.R., Wilkinson, R.J., Colebunders, R., Wilkinson, K.A., 2012. Corticosteroid Therapy, Vitamin D Status, and Inflammatory Cytokine Profile in the HIV-Tuberculosis Immune Reconstitution Inflammatory Syndrome. Clin Infect Dis 55, 1004–1011. https://doi.org/10.1093/cid/cis577

Coussens, A.K., Martineau, A.R., Wilkinson, R.J., 2014. Anti-Inflammatory and Antimicrobial Actions of Vitamin D in Combating TB/HIV. Scientifica (Cairo) 2014. https://doi.org/10.1155/2014/903680

Coussens, A.K., Wilkinson, R.J., Hanifa, Y., Nikolayevskyy, V., Elkington, P.T., Islam, K., Timms, P.M., Venton, T.R., Bothamley, G.H., Packe, G.E., Darmalingam, M., Davidson, R.N., Milburn, H.J., Baker, L.V., Barker, R.D., Mein, C.A., Bhaw-Rosun, L., Nuamah, R., Young, D.B., Drobniewski, F.A., Griffiths, C.J., Martineau, A.R., 2012. Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment. Proc Natl Acad Sci U S A 109, 15449–15454. https://doi.org/10.1073/pnas.1200072109

de Haan, K., Groeneveld, A.J., de Geus, H.R., Egal, M., Struijs, A., 2014. Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. Crit Care 18. https://doi.org/10.1186/s13054-014-0660-4

de Medeiros, R.M., Valverde-Villegas, J.M., Junqueira, D.M., Gräf, T., Lindenau, J.D., de Mello, M.G., Vianna, P., Almeida, S.E.M., Chies, J.A.B., 2016. Rapid and Slow Progressors Show Increased IL-6 and IL-10 Levels in the Pre-AIDS Stage of HIV Infection. PLoS One 11. https://doi.org/10.1371/journal.pone.0156163

Devalraju, K.P., Neela, V.S.K., Ramaseri, S.S., Chaudhury, A., Van, A., Krovvidi, S.S., Vankayalapati, R., Valluri, V.L., 2018. IL-17 and IL-22 production in HIV+ individuals with latent and active tuberculosis. BMC Infect. Dis. 18, 321. https://doi.org/10.1186/s12879-018-3236-0

Dosumu, E., Momoh, J., 2006. Hypercalcemia in patients with newly diagnosed tuberculosis in Abuja, Nigeria. Can Respir J 13, 83–88.

Douek, D.C., Picker, L.J., Koup, R.A., 2003. T Cell Dynamics in HIV-1 Infection. Annual Review of Immunology 21, 265–304. https://doi.org/10.1146/annurev.immunol.21.120601.141053

Egger, M., May, M., Chêne, G., Phillips, A.N., Ledergerber, B., Dabis, F., Costagliola, D., Monforte, A.D., de Wolf, F., Reiss, P., Lundgren, J.D., Justice, A.C., Staszewski, S., Leport, C., Hogg, R.S., Sabin, C.A., Gill, M.J., Salzberger, B., Sterne, J.A., 2002. Prognosis of HIV-1-infected patients starting highly

active antiretroviral therapy: a collaborative analysis of prospective studies. The Lancet 360, 119–129. https://doi.org/10.1016/S0140-6736(02)09411-4

Esser, R., Glienke, W., Andreesen, R., Unger, R., Kreutz, M., Rübsamen-Waigmann, H., v. Briesen, H., 1998. Individual Cell Analysis of the Cytokine Repertoire in Human Immunodeficiency Virus-1–Infected Monocytes/Macrophages by a Combination of Immunocytochemistry and In Situ Hybridization. Blood 91, 4752–60. https://doi.org/10.1182/blood.V91.12.4752.412k06_4752_4760

Fabre-Mersseman, V., Tubiana, R., Papagno, L., Bayard, C., Briceno, O., Fastenackels, S., Dudoit, Y., Rostane, H., Salmon, D., Costagliola, D., Caby, F., Sauce, D., Viard, J.-P., Appay, V., 2014. Vitamin D supplementation is associated with reduced immune activation levels in HIV-1-infected patients on suppressive antiretroviral therapy. AIDS 28, 2677–2682. https://doi.org/10.1097/QAD.0000000000000472

Freeman, M.L., Shive, C.L., Nguyen, T.P., Younes, S.-A., Panigrahi, S., Lederman, M.M., 2016. Cytokines and T-Cell Homeostasis in HIV Infection. J Infect Dis 214, S51–S57. https://doi.org/10.1093/infdis/jiw287

Funderburg, N.T., Andrade, A., Chan, E.S., Rosenkranz, S.L., Lu, D., Clagett, B., Pilch-Cooper, H.A., Rodriguez, B., Feinberg, J., Daar, E., Mellors, J., Kuritzkes, D., Jacobson, J.M., Lederman, M.M., 2013. Dynamics of Immune Reconstitution and Activation Markers in HIV+ Treatment-Naïve Patients Treated with Raltegravir, Tenofovir Disoproxil Fumarate and Emtricitabine. PLoS One 8. https://doi.org/10.1371/journal.pone.0083514

Haug, C.J., Aukrust, P., Haug, E., Mørkrid, L., Ller, F.M., Frøland, S.S., 1998. Severe Deficiency of 1,25-Dihydroxyvitamin D3 in Human Immunodeficiency Virus Infection: Association with Immunological Hyperactivity and Only Minor Changes in Calcium Homeostasis 83, 7.

Hong, Y., Kim, Youngmi, Lee, J.J., Lee, M.G., Lee, C.Y., Kim, Youlim, Heo, J., Han, S.-S., Lee, S.-J., Kim, W.J., Hong, J.Y., 2019. Levels of vitamin D-associated cytokines distinguish between active and latent tuberculosis following a tuberculosis outbreak. BMC Infect Dis 19. https://doi.org/10.1186/s12879-019-3798-5

Kamen, D.L., Tangpricha, V., 2010. Vitamin D and molecular actions on the immune system: modulation of innate and autoimmunity. J Mol Med (Berl) 88, 441–450. https://doi.org/10.1007/s00109-010-0590-9

Kedzierska, K., Crowe, S.M., 2001. Cytokines and HIV-1: Interactions and Clinical Implications. Antivir Chem Chemother 12, 133–150. https://doi.org/10.1177/095632020101200301

Kisuya, J., Chemtai, A., Raballah, E., Keter, A., Ouma, C., 2019. The diagnostic accuracy of Th1 (IFN-γ, TNF-α, and IL-2) and Th2 (IL-4, IL-6 and IL-10) cytokines response in AFB microscopy smear negative PTB- HIV co-infected patients. Sci Rep 9. https://doi.org/10.1038/s41598-019-39048-x

Kongsbak, M., Levring, T.B., Geisler, C., von Essen, M.R., 2013. The vitamin d receptor and T cell function. Front Immunol 4, 148. https://doi.org/10.3389/fimmu.2013.00148

Korf, H., Wenes, M., Stijlemans, B., Takiishi, T., Robert, S., Miani, M., Eizirik, D.L., Gysemans, C., Mathieu, C., 2012. 1,25-Dihydroxyvitamin D3 curtails the inflammatory and T cell stimulatory capacity of

macrophages through an IL-10-dependent mechanism. Immunobiology 217, 1292–1300. https://doi.org/10.1016/j.imbio.2012.07.018

Lakmesari, S.H., Mahmoodabadi, M.J., Hadipour, S., 2020. HIV–TB co-infection treatment control using multi-objective optimized sliding mode. Informatics in Medicine Unlocked 19, 100316. https://doi.org/10.1016/j.imu.2020.100316

Liam, C.K., Lim, K.H., Srinivas, P., Poi, P.J., 1998. Hypercalcaemia in patients with newly diagnosed tuberculosis in Malaysia. Int. J. Tuberc. Lung Dis. 2, 818–823.

Manabe, Y.C., Bishai, W.R., 2000. Latent Mycobacterium tuberculosis-persistence, patience, and winning by waiting. Nat. Med. 6, 1327–1329. https://doi.org/10.1038/82139

Manion, M., Hullsiek, K.H., Wilson, E.M.P., Rhame, F., Kojic, E., Gibson, D., Hammer, J., Patel, P., Brooks, J.T., Baker, J.V., Sereti, I., Study to Understand the Natural History of HIV/AIDS in the Era of Effective Antiretroviral Therapy (the 'SUN Study') Investigators, 2017. Vitamin D deficiency is associated with IL-6 levels and monocyte activation in HIV-infected persons. PLoS ONE 12, e0175517. https://doi.org/10.1371/journal.pone.0175517

Martineau, A.R., Nhamoyebonde, S., Oni, T., Rangaka, M.X., Marais, S., Bangani, N., Tsekela, R., Bashe, L., de Azevedo, V., Caldwell, J., Venton, T.R., Timms, P.M., Wilkinson, K.A., Wilkinson, R.J., 2011. Reciprocal seasonal variation in vitamin D status and tuberculosis notifications in Cape Town, South Africa. Proc. Natl. Acad. Sci. U.S.A. 108, 19013–19017. https://doi.org/10.1073/pnas.1111825108

Mayer, K.H., Hamilton, C.D., 2010. Synergistic Pandemics: Confronting the Global HIV and Tuberculosis Epidemics. Clin Infect Dis 50, S67–S70. https://doi.org/10.1086/651475

Mehta, S., Giovannucci, E., Mugusi, F.M., Spiegelman, D., Aboud, S., Hertzmark, E., Msamanga, G.I., Hunter, D., Fawzi, W.W., 2010. Vitamin D Status of HIV-Infected Women and Its Association with HIV Disease Progression, Anemia, and Mortality. PLoS One 5. https://doi.org/10.1371/journal.pone.0008770

Modlin, R., 2007. The vitamin D receptor and its role in inflammation and host defence: interview with Dr Robert Modlin by Emma Quigley. Expert Opin. Ther. Targets 11, 431–433. https://doi.org/10.1517/14728222.11.4.431

Morán-Auth, Y., Penna-Martinez, M., Shoghi, F., Ramos-Lopez, E., Badenhoop, K., 2013. Vitamin D status and gene transcription in immune cells. The Journal of Steroid Biochemistry and Molecular Biology, SI on Vitamin D workshop 136, 83–85. https://doi.org/10.1016/j.jsbmb.2013.02.005

Musselwhite, L.W., Andrade, B.B., Ellenberg, S.S., Tierney, A., Belaunzaran-Zamudio, P.F., Rupert, A., Lederman, M.M., Sanne, I., Sierra Madero, J.G., Sereti, I., 2016. Vitamin D, d-dimer, Interferon γ, and sCD14 Levels are Independently Associated with Immune Reconstitution Inflammatory Syndrome: A Prospective, International Study. EBioMedicine 4, 115–123. https://doi.org/10.1016/j.ebiom.2016.01.016

Narendran, G., Andrade, B.B., Porter, B.O., Chandrasekhar, C., Venkatesan, P., Menon, P.A., Subramanian, S., Anbalagan, S., Bhavani, K.P., Sekar, S., Padmapriyadarshini, C., Kumar, S., Ravichandran, N., Raja, K., Bhanu, K., Mahilmaran, A., Sekar, L., Sher, A., Sereti, I., Swaminathan, S., 2013. Paradoxical

tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) in HIV patients with culture confirmed pulmonary tuberculosis in India and the potential role of IL-6 in prediction. PLoS ONE 8, e63541. https://doi.org/10.1371/journal.pone.0063541

Riou, C., Perez Peixoto, B., Roberts, L., Ronacher, K., Walzl, G., Manca, C., Rustomjee, R., Mthiyane, T., Fallows, D., Gray, C.M., Kaplan, G., 2012. Effect of Standard Tuberculosis Treatment on Plasma Cytokine Levels in Patients with Active Pulmonary Tuberculosis. PLoS One 7. https://doi.org/10.1371/journal.pone.0036886

Ross, A.C., Judd, S., Kumari, M., Hileman, C., Storer, N., Labbato, D., Tangpricha, V., McComsey, G.A., 2011. Vitamin D is linked to carotid intima-media thickness and immune reconstitution in HIV-positive individuals. Antivir Ther 16, 555–563. https://doi.org/10.3851/IMP1784

Rutstein, R., Downes, A., Zemel, B., Schall, J., Stallings, V., 2011. Vitamin D status in children and young adults with perinatally acquired HIV infection. Clinical Nutrition 30, 624–628. https://doi.org/10.1016/j.clnu.2011.02.005

Salahuddin, N., Ali, F., Hasan, Z., Rao, N., Aqeel, M., Mahmood, F., 2013. Vitamin D accelerates clinical recovery from tuberculosis: results of the SUCCINCT Study [Supplementary Cholecalciferol in recovery from tuberculosis]. A randomized, placebo-controlled, clinical trial of vitamin D supplementation in patients with pulmonary tuberculosis'. BMC Infect Dis 13, 22. https://doi.org/10.1186/1471-2334-13-22

Salzer, J., Hallmans, G., Nyström, M., Stenlund, H., Wadell, G., Sundström, P., 2012. Vitamin D as a protective factor in multiple sclerosis. Neurology 79, 2140–2145. https://doi.org/10.1212/WNL.0b013e3182752ea8

Smolders, J., Thewissen, M., Peelen, E., Menheere, P., Cohen Tervaert, J.W., Damoiseaux, J., Hupperts, R., 2009. Vitamin D Status Is Positively Correlated with Regulatory T Cell Function in Patients with Multiple Sclerosis. PLoS ONE 4, e6635. https://doi.org/10.1371/journal.pone.0006635

Tan, H.Y., Yong, Y.K., Shankar, E.M., Paukovics, G., Ellegård, R., Larsson, M., Kamarulzaman, A., French, M.A., Crowe, S.M., 2016. Aberrant Inflammasome Activation Characterizes Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome. J. Immunol. 196, 4052–4063. https://doi.org/10.4049/jimmunol.1502203

Van Den Bout-Van Den Beukel, C.J.P., Fievez, L., Michels, M., Sweep, F.C.G.J., Hermus, A.R.M.M., Bosch, M.E.W., Burger, D.M., Bravenboer, B., Koopmans, P.P., Van Der Ven, A.J.A.M., 2008. Vitamin D deficiency among HIV type 1-infected individuals in the Netherlands: effects of antiretroviral therapy. AIDS Res. Hum. Retroviruses 24, 1375–1382. https://doi.org/10.1089/aid.2008.0058

van Etten, E., Stoffels, K., Gysemans, C., Mathieu, C., Overbergh, L., 2008. Regulation of vitamin D homeostasis: implications for the immune system. Nutr. Rev. 66, S125-134. https://doi.org/10.1111/j.1753-4887.2008.00096.x

Viard, J., Souberbielle, J., Kirk, O., Knysz, B., Losso, M., Gatell, J., Pedersen, C., Bogner, J., Mocroft, A., Lundgren, J., 2010. Vitamin D and clinical disease progression in HIV infection: results from the EuroSIDA study. J Int AIDS Soc 13, O43. https://doi.org/10.1186/1758-2652-13-S4-O43

von Bahr, L., Blennow, O., Alm, J., Björklund, A., Malmberg, K.-J., Mougiakakos, D., Le Blanc, A., Oefner, P.J., Labopin, M., Ljungman, P., Le Blanc, K., 2015. Increased incidence of chronic GvHD and CMV disease in patients with vitamin D deficiency before allogeneic stem cell transplantation. Bone Marrow Transplant 50, 1217–1223. https://doi.org/10.1038/bmt.2015.123

Webb, A.R., Kline, L., Holick, M.F., 1988. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J. Clin. Endocrinol. Metab. 67, 373–378. https://doi.org/10.1210/jcem-67-2-373

WHO | Global tuberculosis report 2019 [WWW Document], n.d. . WHO. URL http://www.who.int/tb/publications/global_report/en/ (accessed 7.7.20).

Wilkinson, R.J., Llewelyn, M., Toossi, Z., Patel, P., Pasvol, G., Lalvani, A., Wright, D., Latif, M., Davidson, R.N., 2000. Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study. The Lancet 355, 618–621. https://doi.org/10.1016/S0140-6736(99)02301-6

Yang, C.-Y., Leung, P.S.C., Adamopoulos, I.E., Gershwin, M.E., 2013. The Implication of Vitamin D and Autoimmunity: a Comprehensive Review. Clin Rev Allergy Immunol 45, 217–226. https://doi.org/10.1007/s12016-013-8361-3

.