

# Status of Tuberculosis Infection and the Progression of HIV: Literature Study

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**Abstract**—There are several factors that affect the development of HIV, one of which is TB co-infection. HIV and TB both play a role in reducing the function of the immune system. The aim of this study was to examine the relationship between the status of TB infection in HIV+ patients with the development/progression of HIV to AIDS and to observe the variation in the development/progression of HIV to AIDS in HIV+ patients who were co-infected with TB. Research articles were identified from the four databases Pub Med, BMC Public Health, Science Direct and Pro Quest. The review was undertaken to synthesize the findings in articles published between January 2010-October 2020 with the protocol and evaluation of the study using PRISMA. A total of 6 articles met the inclusion and exclusion criteria, consisting of 4 retrospective cohort studies and 2 prospective cohorts. The results of the analysis found that 4 articles discussed about TB/HIV with CD4 cells and all were significant. Two articles noted a decrease in CD4 cell count in the TB/HIV group and the other two found an increase in CD4 cell count. Although there was an increase, compared to the non-TB group, the total of CD4 in TB/HIV co-infected individuals tended to be lower. In viral load, two articles noted a decrease, but only one article mentioned a significant difference but did not compare it with the non-TB group. The progression of HIV to AIDS was noted in two articles and it was found that the risk of progression in the TB/HIV group was higher than in the non-TB group. TB infection in HIV patients affects the development of HIV through the interaction of the immune system. Further research on tuberculosis infection progressing from HIV to AIDS needs to examine the type or location of tuberculosis.

**Keywords**—Tuberculosis infection status; HIV; disease progression

## I. INTRODUCTION

Human Immunodeficiency Virus (HIV) has become a global health problem which since the beginning of the epidemic has caused 35.4 million deaths related to acquired immunodeficiency

syndrome (AIDS) [1]. In 2018, it was found that there were 770,000 HIV-related deaths and 1.7 million new infections with an estimated number of HIV cases at the end of 2018 of 37.9 million people [2]. Tuberculosis (TB) is the main opportunistic infection associated with HIV [3]. TB is prone to occur in people with HIV where people with HIV are at risk of 15-22 times experiencing reactivation of latent TB [2], [4]. TB cases estimated worldwide in 2018, it was estimated at 10 million, with 8.6% of them being HIV sufferers with an estimated death from TB in HIV patients of 251,000 deaths [2], [5]. Data from the Global tuberculosis report 2019 stated that of 1.2 million people who had just registered for HIV treatment in 2018, 8% of them were diagnosed with TB in the same year and globally there were 477,461 HIV sufferers who had TB [6].

TB infection can occur at any stage of immune deficiency [7]. Most of the TB bacterial infections in HIV-negative people do not progress to active TB, while HIV-positive people are prone to developing active TB [4], [8]. Death from TB in HIV patients is caused by changes in cytokines levels by opportunistic infections [1]. So far, the best single predictor and commonly used to predict the development of HIV/AIDS is CD4 cell count [9], [10]. Another biomarker recommended by WHO for monitoring HIV sufferers is viral load [11]. Viral load is defined as the number of copies of the HIV virus (HIV RNA) in the blood expressed in mL [9], [11]. HIV and TB both have a role in reducing immune system function, although the mechanism of modification of the immune system by infection that increases susceptibility to TB is not fully understood, HIV infection is known to be one of the strongest risk factors for the development of TB infection into active disease [4], [8]. Dealing with the above explanation, the aim of this study was to provide an overview of the relationship between TB infection

and HIV progression to AIDS as information to improve effective disease management and control.

## II. METHOD

### A. Search Strategy

This study was a literature study and it used Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) as a protocol and evaluation and is registered with PROSPERO with registration number CRD42021250877. Articles were identified through electronic databases namely Pub-med, BMC Public Health, Science direct and Pro-quest and were limited to Scholarly Journal articles and published between January 2010 to October 2020. The article search strategy used Boolean operators OR and AND with additional quotation marks for keywords in the form of phrases. Keywords used to identify articles include keywords TB ("Tuberculosis infection status"; "Latent Tuberculosis Infection"; LTBI; "Active Tuberculosis"; "TB Disease"; Tuberculosis; TB; "Pulmonary Tuberculosis"; PTB; "Extra-pulmonary tuberculosis" "; EPTB) and HIV progression ("HIV Progression"; "HIV disease progression"; "Viral load change"; "CD4"; "Acquired Immunodeficiency Syndrome"; AIDS).

Several inclusion criteria were created to screen relevant articles. These criteria included (1) research respondents were HIV positive patients aged 15, (2) include tuberculosis infection variables, (3) described the influence of TB on changes in HIV clinical status to AIDS/changes in viral load/changes in total of CD4 cell (4 ) study design used a cohort or case-control, (5) English language and (6) full text articles.

### B. Data Extraction

Data extraction used PRISMA flow diagrams and was carried out by recording the number of articles and the reasons for excluding articles at each selection stage [12]. A total of 621 articles were identified from the 4 previously mentioned electronic databases. The selection results issued 615 articles with details of 30 duplicate articles, 87 articles were not available in full text, and 498 articles did not meet the inclusion and exclusion criteria. The remaining 6 articles consisting of 4 retrospective cohort studies and 2 prospective cohorts met the inclusion criteria and entered the feasibility assessment stage. To assess the quality of articles, a critical appraisal was carried out using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies from the National Heart, Lung, and Blood Institute (NHLBI) [13], while for bias assessment used the Tool to Assess Risk of Bias in Cohort Studies for articles with a cohort study design [14].

## III. FINDING AND DISCUSSION

### A. Finding

After releasing the articles that did not meet the requirements, 6 articles that met the inclusion criteria with a range of articles published between 2013 and 2020 entered the analysis stage. Articles A1-A6 are a type of Scholarly Journal article with the research locations mostly on the African continent. Articles A1 was done in Brazil, A2 and A3 were done in South Africa, A4 was done in Nigeria, A5 was done in 9 countries including South Africa, and A6 was done in Kenya. The study design of the six articles was a detailed cohort, two articles used a prospective cohort study design and four articles used a retrospective cohort. The length of follow-up for each article is different, the shortest duration is 180 days and the longest duration is 10 years. The results of the critical appraisal of the six articles have good quality (average score of 74.5%) with a low bias tendency. Details of the study characteristics for each article can be seen in table 1.

In general, the participants in the study in all analyzed articles were HIV patients aged 18 years with a median age of 25-37.7 years. There are three out of six articles with research respondents dominated by women. Three of the six articles discussed the respondent's level of education where two articles mentioned a median length of education of >8 years and one article mentioned a median of 2 years of education. For the characteristics of respondents based on clinical information there are several criteria that were collected including baseline CD4 and Viral Load, and Body Mass Index (BMI). The characteristics of study respondents for each article can be seen in table 2.

There are different data collection methods in each article. In A1 and A3 data collection was carried out directly, where to obtain CD4 and VL data, blood samples were taken. For A2 and A5 all respondent data comes from other studies. While A4 and A6 respondent data is collected from patient medical record data contained in health facilities. Variations also appear in the timing of TB diagnosis. In A1, a TB diagnosis was made prior to follow-up indicated by the inclusion criteria requiring the respondent to have a TB diagnosis at the time of recruitment. For A2 there is no mention of the time of diagnosis and the basis for the diagnosis of TB. In A3 TB diagnosis was made at the time of recruitment or before the follow-up period where the respondent's diagnosis was based on the Tuberculin Skin Test (TST) and excluded respondents who had active TB. The timing of the TB diagnosis on A4 was made during the follow-up period, this was indicated by the exclusion criteria whereby the investigator excluded respondents who had TB at the time of recruitment. For A5 and A6, the timing of TB diagnosis was at

recruitment or before follow-up, judging by the investigator's grouping of respondents at the time of ART initiation.

Article A1 found a statistically significant difference in baseline CD4 cells ( $p=0.000$ ) between group 1 TB-HIV CD4  $>200$  cells/mm<sup>3</sup> and group 2 TB-HIV  $<200$  cells/mm<sup>3</sup>. In group 1 with total of CD4  $<200$  cells/mm<sup>3</sup> (CDC laboratory criteria for AIDS) the median baseline CD4 total was lower than in group 2. Regarding HIV progression, the two groups both experienced a significant increase in CD4 cell count and a decrease in viral load at 30 the first day after ART initiation.

Article A2 *did not* mention the extent of CD4 and VL changes during follow-up and only mentioned *initial amount of* CD4 and VL. However, A2 found that respondents with TB co-infection had a 2 times higher risk of changing their condition from normal to mild (aHR = 2.08; 95% CI: 1.02–4.71) and 1.8 times higher from advanced to severe (aHR = 1.86; 95% CI: 1.05–4.61) compared to respondents without TB co-infection.

Article A3 found a decrease in CD4 cell count by 3.3 cells/mm<sup>3</sup> per month (95% CI: 3.0–3.5). In addition, A3 also found a relationship between episodes of active TB and a decrease in CD4 cells of 56.4 cells/mm<sup>3</sup> per month ( $p=0.049$ ). Regarding viral load, A3 reported a decrease in VL per year of 0.03 log 10 copies/ml but this was not significant.

TABLE 1. Study Characteristics

Article Code	Author, Published Year	Title	Publisher, Journal	Study Design	Study Period	Location	Sample
A1	da Silva et. al., 2013	T Cell Activation and Cytokine Profile of Tuberculosis and HIV-Positive Individuals during Antituberculous Treatment and Efavirenz-Based Regimens	Public Library of Science; PLoS One	Cohort perspective	2006-2011 (Follow up duration 180 days after ART initiation)	Brazil	54
A2	Dessie et. al., 2020	Modelling immune deterioration, immune recovery and state-specific duration of HIV-infected women with <i>viral load</i> adjustment: using parametric multistate model	BioMed Central; BMC Public Health	Cohort perspective	2004-2017 (Follow up duration is conducted until ART is initiated)	South Africa	219
A3	Martinson et. al., 2014	CD4 and Viral Load Dynamics in Antiretroviral-Naïve HIV-Infected Adults from Soweto, South Africa: A Prospective Cohort	Public Library of Science; PLoS One	Cohort perspective	2003-2005 (Follow up duration is median 44 months/until ART is initiated)	South Africa	1106
A4	Musa et. al., 2015	Incidence of tuberculosis and immunological profile of TB/HIV co-infected patients in Nigeria	Medknow Publications; Annals of Thoracic Medicine	Cohort perspective	2004-2007 (Follow up duration is 10 years until April 2017)	Nigeria	345
A5	Périsse et. al., 2013	Outcomes among HIV-1 Infected Individuals First Starting Antiretroviral Therapy with Concurrent Active TB or Other AIDS-Defining Disease	Public Library of Science; PLoS One	Cohort perspective	2005-2007 (The follow up duration is until April/May 2010)	Brazil; Haiti; India; Malawi; Peru; South Africa; Thailand; United States of America; Zimbabwe	1571
A6	Silka et. al., 2013	Active Tuberculosis Is Associated with Worse Clinical Outcomes in HIV-Infected African Patients on Antiretroviral Therapy	Public Library of Science; PLoS One	Cohort perspective	2004-2007 (The follow up duration is 1 year)	Kenya	21.242

TABLE2. Respondent Characteristics

Article Code	Gender	Educational Level	Baseline CD4	Baseline Viral Load (VL)	Body Mass Index (BMI)
A1	Male: 42 (77,8%) Female: 12 (22,2%)	-	112 cells/mm <sup>3</sup> median	VL HIV-1 5,02 log <sub>10</sub> copies/ml median	-
A2	Male: 0 (0%) Female: 219 (100%)	69,9% (±153) finish education grade 11/12	519 cells/mm <sup>3</sup> median	4,23 log <sub>10</sub> copies/ml median	-
A3	Male: 184 (17%) Female: 922 (84%)	Median of education year 2 (2-3)	490 cells/mm <sup>3</sup> median	16,050 copies/ml median (4,2 log <sub>10</sub> copies/ml)	24,8 Kg/m <sup>2</sup> median
A4	Male: 140 (40,58%) Female: 205 (59,42%)	-	- <200 cells/mm <sup>3</sup> : 106 patients (30,72%) - 200-349 cells/mm <sup>3</sup> : 101 patients (29,28%) - ≥350 cells/mm <sup>3</sup> : 138 patients (40%)	- - -	- <18 Kg/m <sup>2</sup> : 23 patients (7,12%) - 18-24,9 Kg/m <sup>2</sup> : 173 patients (53,56%) - 25-29,9 Kg/m <sup>2</sup> : 85 patients (24,64%) ≥30 Kg/m <sup>2</sup> : 42 patients (12,17%)
A5	Male: 831 (52,9%) Female: 740 (47,1%)	-	Kelompok TB (PTB+EPTB) - <50 cells/mm <sup>3</sup> : 12 participants (11,8%) - 50-99 cells/mm <sup>3</sup> : 27 participants (26,4%) - 100-199 cells/mm <sup>3</sup> : 41 participants (40,2%) - 200-299 cells/mm <sup>3</sup> : 22 participants (21,6%)	VL HIV-1 Kelompok TB (PTB+EPTB) - <100.000 c/mL: 26 participants (25,5%) - ≥100.000: 76 participants (74,5%)	-
A6	-TB/ HIV: Male: 2.406 (46,4%) Female: 2780 (53,6%) - HIV: Male: 5600 (34,9%) Female: 10.456 (65,1%)	Education >8 years -TB/ HIV: 2.035 (43,9%) - HIV: 5.677 (40,4%)	Kelompok TB/ HIV - 0-49 cells/mm <sup>3</sup> : 1.330 patients (37,1%) - 50-199 cells/mm <sup>3</sup> : 1.810 patients (50,5%) - ≥200 cells/mm <sup>3</sup> : 446 patients (12,4%) Kelompok HIV - 0-49 cells/mm <sup>3</sup> : 3.292 patients (26%) - 50-199 cells/mm <sup>3</sup> : 7.284 patients (57,5%) - ≥200 cells/mm <sup>3</sup> : 2.097 patients (16,6%)	TB/ HIV: Male: 2.406 (46,4%) Female: 2780 (53,6%) HIV: Male: 5600 (34,9%) Female: 10.456 (65,1%)	-TB/ HIV: 18,7 median - HIV: 19,8 median

Article A4 found a statistically significant difference at 5 ( $p = 0.0201$ ) and 6 ( $p = 0.005$ ) between TB-HIV and HIV-only patients. A4 also found a large decrease in CD4 cell counts in TB-HIV patients in the 5th year of follow-up by 19.47 L while for the 6th year it was 3.87 L. Analysis of CD4 trends on A4 showed that HIV-TB patients had lower CD4 counts than HIV-only patients.

The results of the statistical test article A5 found that the TB group experienced worse primary outcomes than the other groups and this was statistically significant ( $p=0.042$ ). Primary outcome on A5 was defined as virological failure/HIV progression to AIDS/new infection or OI reinfection/death.

Besides, A5 also found that there was no significant difference between the three study groups regarding the progression of HIV to AIDS ( $p=0.37$ ). Regarding viral load, A5 stated that 75% of the TB/HIV group had a VL 100,000 copies/mL and that respondents experienced virological failure ( $\geq 1000$  copies/mL on two consecutive measurements) as many as 21 (20.6%) patients. The incidence of AIDS was relatively low in all study groups, specifically for the TB group, there were 5 (5%) patients who developed AIDS.

Article A6 found that the TB/HIV group's overall CD4 count was lower than the non-TB HIV group. The study also noted an increase in CD4 cell count in both groups, this was due to ART/treatment received. Regarding the AIDS Defining Event (ADE), A6 found that patients had a 31% risk of developing an AIDS Defining Event (ADE) ( $aHR = 1.313$ ; 95% CI: 1.187–1.453).

Two articles noted a decrease in CD4 cell count in the TB/HIV group and the other two found an increase in CD4 cell count. Although there was an increase, compared to the non-TB group, the CD4 count in TB/HIV coinfecting individuals tended to be lower. Regarding viral load parameters, two articles noted a decrease, but only one article mentioned a significant difference but did not compare it with the non-TB group. The progression of HIV to AIDS was noted in two articles and it was found that the risk of progression in the TB/HIV group was higher than that in the non-TB group (Table 3).

Four of the six articles included in the analysis compared the outcomes between the TB/HIV group and the HIV-free group, namely A2, A4, A5, and A6. These four articles stated that the CD4 cell count in the TB/HIV group was lower than in other groups in the study. Except for A5, all articles noted a change in CD4.

TABLE 3. The Study Findings

Article Code	Sample	Data Collection	Tuberculosis Variables	HIV Disease Progression Variables	Finding
A1	54 HIV-TB positive patients	- Diagnosis of TB is based on signs and symptoms and culture. Blood sampling to measure CD4 and VL	54 TB-HIV patients; patients getting TB and HIV treatment	Changes in the total of CD4 during follow-up: - 30 days: 245 cells/mm <sup>3</sup> - 60 days: 264 cells/mm <sup>3</sup> - 90 days: 287 cells/mm <sup>3</sup> - 180 days: 291 cells/mm <sup>3</sup> VL changes during follow-up: - 30 days: 2.2 log10 copies/ml - 60 days: 1.7 log10 copies/ml - 90 days: 1.7 log10 copies/ml - 180 days: 1.7 log10 copies/ml	- There is an increase in CD4 and decrease in VL after 30 days of HAART  - Statistically, there was a significant difference in baseline parameters CD4 (p=0.000) and VL (p=0.006) between the TB-HIV CD4 group >200 cells/mm <sup>3</sup> and TB-HIV <200 cells/mm <sup>3</sup>
A2	219 HIV positive women	- Data taken from a prospective (on-going) cohort study by the Center for the AIDS Program of Research in South Africa (CAPRISA)  - Measurement of CD4 and VL performed at each visit	9.2% of the total 219 patients were co-infected with TB	There is no detail description of the CD4 cell count and VL development of TB-HIV patients during the follow-up period. The severity of the disease was defined as: normal (CD4 500), mild (350≤CD4<499), advanced (200≤CD4<349), severe (CD4<200).	TB coinfection accelerated the change in the condition of HIV patients from normal to mild (aHR = 2.08; 95% CI: 1.02-4.71) and from advanced to severe (aHR = 1.86; 95% CI: 1.05-4.61)
A3	1106 HIV positive patient with latent TB	- Data were taken from a randomized trial of TB preventive treatment. TB diagnosis based on TST (≥5 mm)  - CD4 measurements were carried out annually until 2004 and every 6 months thereafter.  - Measurement of VL was only performed at initial screening/90 days post-randomization.	1,106 HIV positive participants with positive TST results and not active TB.	- Median CD4 decline per month 3.3 cells/mm <sup>3</sup> (95% CI: 3.0-3.5)  - The median CD4 decline in men was 2.6 cells/mm <sup>3</sup> per month  - The median CD4 decline in women is 3.3 cells/mm <sup>3</sup> per month  - VL decrease per year 0.03 log 10 copies/ml	Estimated median CD4 change in active TB per month in cells/mm <sup>3</sup> using the Random effects model  - Univariate analysis: -3.2 (p<0.001)  Multivariate analysis: -3.3 (p=0.049)
A4	345 HIV positive patients	- Diagnosis of TB is based on screening for signs and symptoms, sputum smear testing, and chest X-ray and tissue biopsy	47 HIV-TB patients.	Changes in the total of CD4 cell of TB-HIV patients during follow-up at year 1:- 5: 19.47 μL - 6: 3.87 μL	- The results of the 10-year CD4 trend analysis of TB-HIV patients had lower CD4 cell counts than

	if necessary - The data is taken from the patient's medical record		patients with HIV alone.
A5	<p>1571 HIV positive patients</p> <p>- Data taken from the Prospective Evaluation of Anti-retroviral Combination for Treatment Naïve, HIV Infected Person in Resourced-limited Setting (PEARLS) study by AIDS Clinical Trials Group (ACTG)</p> <p>- Blood sampling is done at the initial screening and at the visit</p>	<p>102 HIV-TB participants</p> <p>78% of TB group participants had CD4 &lt;200 cells/mm<sup>3</sup></p> <p>75% of participants in the TB group had a VL 100,000 copies/mL</p>	<p>- There was a statistically significant difference in CD4 cell count at 5 (p = 0.0201) and 6 (p = 0.005) between TB-HIV and HIV-only patients.</p> <p>- The TB group had worse primary outcome than the group without disease and the group with AIDS-defining illness, statistically significant with p=0.042</p> <p>- 5 participants in the TB group developed AIDS with a median follow-up time of 184 weeks (5% of the total 102 participants).</p> <p>- 40 participants in the no-disease group developed AIDS with a median follow-up time of 184 weeks (3% of the total 1413 participants).</p>
A6	<p>21,242 HIV positive patients</p> <p>- Data is taken from electronic medical records</p> <p>- Diagnosis of TB is based on clinical signs, radiological findings, and laboratory results</p>	<p>5,186 TB/HIV patients</p> <p>Differences in the total of CD4 cell in the TB/HIV and HIV non-TB groups at 6 weeks after ART initiation</p> <p>- TB/HIV: 200 cells/mm<sup>3</sup></p> <p>- HIV: 221 cells/mm<sup>3</sup></p> <p>Differences in CD4 cell counts in the TB/HIV and HIV non-TB groups one year after ART initiation</p> <p>- TB/HIV: 251 cells/mm<sup>3</sup></p> <p>- HIV: 269 cells/mm<sup>3</sup></p>	<p>- The total CD4 cell in the TB/HIV group was lower than in the non-TB HIV group.</p> <p>- TB/HIV patients were 31% more likely to develop a new AIDS Defining Event (ADE) (aHR = 1.313; 95% CI: 1.187–1.453).</p> <p>- Kaplan-Meier curve showed the TB/HIV group has a higher probability of experiencing ADE.</p>



## B. Discussion

In this study, it found a relationship between tuberculosis and the development of HIV. The four articles analyzed reported that the TB/HIV group had lower CD4 cell counts than the non-TB HIV group. Tuberculosis is known to affect the regulation of the immune system and HIV prognosis [21], [22]. A previous study found that the monthly average decrease in CD4 cell counts in HIV positive patients with opportunistic infections (IO) was twofold greater than in patients without OIs [23]. In line with this, another study found differences in immune activation where HIV positive people with active TB had a higher level of T cell activation compared to those with latent TB or without TB [24]. When infection by microbes occurs then the stimulus activates T cells, at the same time there is damage to the immune system by HIV because the stimulus triggers HIV gene transcription [25]. There were different findings regarding changes in total of CD4 cell.

Two articles reported a decrease in the total of CD4 cell while 3 articles reported an increase in the total of CD4 cell. This difference in findings was due to differences in the treatment of research respondents where 3 articles that reported an increase in the total of CD4 cell mentioned the use of ART among their respondents. An increase in the total of CD4 cell after ARV therapy was also found in another study where after the initiation of ART there was an increase in the total of CD4 cell at 6, 12 and 24 months [26]. On the viral load (VL) parameter, two articles reported a decrease in VL levels. One article found a significant decrease and one article found a non-significant decrease. This difference in significance level may be related to differences in respondent characteristics and differences in ART use. Articles that found a significant reduction in VL reported use of ART whereas articles that did not find a significant reduction excluded those currently or have been on ART and only included respondents with latent TB at the time of recruitment. ART suppresses the replication of the HIV virus and increases CD4 cells which will have an impact on reducing morbidity and mortality [27].

The prevalence of change in status to AIDS in the TB/HIV group was higher than in other groups in the study with a 31% risk of developing ADE. The low prevalence of status changes and the risk of developing AIDS may be related to the presence of ART received by study respondents. A London study comparing HIV/TB patients receiving pre- and post-HAART TB treatment found that in the first year the cumulative risk of developing AIDS in the post-

HAART group was lower (34%) compared to the pre-HAART group [28].

## IV. CONCLUSION

Dealing with the results of the analysis above, it can be concluded that TB infection in HIV patients affected the development of HIV through the interaction of the immune system. The existence of active TB infection results in T cell activation which then triggered HIV virus transcription and it will have an impact on increasing viral load and decreasing CD4 cells because HIV destroys CD4 T lymphocytes. lower than the non-TB group. Further research on the impact of tuberculosis infection on the progression of HIV to AIDS was needed, especially on the type or location of tuberculosis.

## REFERENCES

- [1] K. Lagat, "Factors Leading to Faster Progression of HIV to AIDS," p. 69, 2018.
- [2] WHO, "HIV/AIDS," Nov. 15, 2019. <https://www.who.int/news-room/fact-sheets/detail/hiv-aids> (accessed Mar. 07, 2020).
- [3] M. Roser and H. Ritchie, "HIV / AIDS," *Our World in Data*, Apr. 2018, Accessed: Oct. 06, 2020. [Online]. Available: <https://ourworldindata.org/hiv-aids>
- [4] A. Pawlowski, M. Jansson, M. Sköld, M. E. Rottenberg, and G. Källénus, "Tuberculosis and HIV Co-Infection," *PLOS Pathogens*, vol. 8, no. 2, p. e1002464, Feb. 2012, doi: 10.1371/journal.ppat.1002464.
- [5] A. MacNeil, "Global Epidemiology of Tuberculosis and Progress Toward Meeting Global Targets — Worldwide, 2018," *MMWR Morb Mortal Wkly Rep*, vol. 69, 2020, doi: 10.15585/mmwr.mm6911a2.
- [6] World Health Organization, *Global tuberculosis report 2019*. 2019. [Online]. Available: <http://apps.who.int/iris>
- [7] Z. Toossi *et al.*, "Impact of tuberculosis (TB) on HIV-1 activity in dually infected patients: Impact of pulmonary TB on HIV-1 disease," *Clinical & Experimental Immunology*, vol. 123, no. 2, pp. 233–238, Feb. 2001, doi: 10.1046/j.1365-2249.2001.01401.x.
- [8] J. Bruchfeld, M. Correia-Neves, and G. Källénus, "Tuberculosis and HIV Coinfection," *Cold Spring Harb Perspect Med*, vol. 5, no. 7, p. a017871, Jul. 2015, doi: 10.1101/cshperspect.a017871.
- [9] L. Astari and Y. E. Safitri, "Viral Load pada Infeksi HIV (Viral Load in HIV Infection)," vol. 21, no. 1, p. 9, 2009.
- [10] V. Gupta and S. Gupta, "Laboratory markers associated with progression of HIV infection," *Indian Journal of Medical Microbiology*, vol. 22, no. 1, p. 7, Jan. 2004.
- [11] M. Sanou *et al.*, "Study of Viral Load as A Predictive Marker of the Evolution of HIV Type 2 Infection in Burkina Faso," *Act Scie Micro*, vol. 2, no. 10, pp. 91–95, Sep. 2019, doi: 10.31080/ASMI.2019.02.0378.
- [12] M. K. Swartz, "The PRISMA Statement: A Guideline for Systematic Reviews and Meta-Analyses," *Journal of Pediatric Health Care*, vol. 25, no. 1, pp. 1–2, Jan. 2011, doi: 10.1016/j.pedhc.2010.09.006.
- [13] National Heart, Lung, and Blood Institute, "Study Quality Assessment Tools | NHLBI, NIH," 2020.

- <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools> (accessed Nov. 09, 2020).
- [14] D. Benford *et al.*, "The principles and methods behind EFSA's Guidance on Uncertainty Analysis in Scientific Assessment," *EFSA J*, vol. 16, no. 1, Jan. 2018, doi: 10.2903/j.efsa.2018.5122.
  - [15] T. P. da Silva, C. B. W. Giacoia-Gripp, C. A. Schmaltz, F. M. S. Anna, V. Rolla, and M. G. Morgado, "T Cell Activation and Cytokine Profile of Tuberculosis and HIV-Positive Individuals during Antituberculous Treatment and Efavirenz-Based Regimens," p. e66095, Jun. 2013, doi: 10.1371/journal.pone.0066095.
  - [16] Z. G. Dessie, T. Zewotir, H. Mwambi, and D. North, "Modelling HIV disease process and progression in seroconversion among South Africa women: using transition-specific parametric multi-state model," *Theor Biol Med Model*, vol. 17, no. 1, p. 10, Jun. 2020, doi: 10.1186/s12976-020-00128-5.
  - [17] N. A. Martinson *et al.*, "CD4 and Viral Load Dynamics in Antiretroviral-Naïve HIV-Infected Adults from Soweto, South Africa: A Prospective Cohort," *PLoS One*, vol. 9, no. 5, May 2014, doi: 10.1371/journal.pone.0096369.
  - [18] B. M. Musa, B. Musa, H. Muhammed, N. Ibrahim, and A. G. Musa, "Incidence of tuberculosis and immunological profile of TB/HIV co-infected patients in Nigeria," *Ann Thorac Med*, vol. 10, no. 3, pp. 185–192, 2015, doi: 10.4103/1817-1737.160838.
  - [19] A. R. S. Périssé *et al.*, "Outcomes among HIV-1 Infected Individuals First Starting Antiretroviral Therapy with Concurrent Active TB or Other AIDS-Defining Disease," *PLoS One*, vol. 8, no. 12, p. e83643, Dec. 2013, doi: <http://dx.doi.org/10.1371/journal.pone.0083643>.
  - [20] A. M. Siika *et al.*, "Active Tuberculosis Is Associated with Worse Clinical Outcomes in HIV-Infected African Patients on Antiretroviral Therapy," *PLOS ONE*, vol. 8, no. 1, p. e53022, Jan. 2013, doi: 10.1371/journal.pone.0053022.
  - [21] L. Aaron *et al.*, "Tuberculosis in HIV-infected patients: a comprehensive review," *Clinical Microbiology and Infection*, vol. 10, no. 5, pp. 388–398, May 2004, doi: 10.1111/j.1469-0691.2004.00758.x.
  - [22] C. Affusim, V. Abah, E. B. Kesieme, K. Anyanwu, T. A. T. Salami, and R. Eifediyi, "The Effect of Low CD4+ Lymphocyte Count on the Radiographic Patterns of HIV Patients with Pulmonary Tuberculosis among Nigerians," *Tuberculosis Research and Treatment*, vol. 2013, p. e535769, Jan. 2013, doi: 10.1155/2013/535769.
  - [23] R. E. Chaisson, J. E. Gallant, J. C. Keruly, and R. D. Moore, "Impact of opportunistic disease on survival in patients with HIV infection," *AIDS*, vol. 12, no. 1, pp. 29–33, Jan. 1998.
  - [24] Z. A. Sullivan, E. B. Wong, T. Ndung'u, V. O. Kasproicz, and W. R. Bishai, "Latent and Active Tuberculosis Infection Increase Immune Activation in Individuals Co-Infected with HIV," *EBioMedicine*, vol. 2, no. 4, pp. 334–340, 2015, doi: <https://doi.org/10.1016/j.ebiom.2015.03.005>.
  - [25] R. Budiarti, "HIV Infection: Immunopathogenesis and Risk Factor to Fishermen," *Oceana Biomedicina Journal*, vol. 1, no. 1, Art. no. 1, Jan. 2018, doi: 10.30649/obj.v1i1.4.
  - [26] N. M. Yasin, H. Maranty, and W. R. Ningsih, "Response to antiretroviral therapy undergone by HIV/AIDS patients," *Indonesian Journal of Pharmacy*, vol. 0, no. 0, Art. no. 0, Jul. 2011, doi: 10.14499/indonesianjpharm0iss0pp212-222.
  - [27] I. E. Ajmala and L. Wulandari, "Terapi ARV pada Penderita Ko-Infeksi TB-HIV," *Jurnal Respirasi*, vol. 1, no. 1, Art. no. 1, 2015, doi: 10.20473/jr.v1-i.1.2015.22-28.
  - [28] K. Dheda, F. C. Lampe, M. A. Johnson, and M. C. Lipman, "Outcome of HIV-Associated Tuberculosis in the Era of Highly Active Antiretroviral Therapy," *The Journal of Infectious Diseases*, vol. 190, no. 9, pp. 1670–1676, Nov. 2004, doi: 10.1086/424676.