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| Book Name: | [**Medical Science: Trends and Innovations**](https://www.bookpi.org/bookstore/product/medical-science-trends-and-innovations-vol-1/) |
| Manuscript Number: | **Ms\_BPR\_4269** |
| Title of the Manuscript:  | **Effects of CD4 count level on patterns of respiratory tract infections of HIV-infected patients in Western India** |
| Type of the Article | **Book Chapter** |

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| PART 1: Comments |
|  | Reviewer’s comment | Author’s Feedback *(Please correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
| **Please write a few sentences regarding the importance of this manuscript for the scientific community. A minimum of 3-4 sentences may be required for this part.** |  |  |
| **Is the title of the article suitable?****(If not please suggest an alternative title)** |  |  |
| Is the abstract of the article comprehensive? Do you suggest the addition (or deletion) of some points in this section? Please write your suggestions here. |  |  |
| **Is the manuscript scientifically, correct? Please write here.**  |  |  |
| **Are the references sufficient and recent? If you have suggestions of additional references, please mention them in the review form.****-** |  |  |
| Is the language/English quality of the article suitable for scholarly communications? |  |  |
| Optional/General comments | 1. The transition between the statistics about HIV/AIDS deaths and the introduction of HAART could be smoother. Consider connecting these two ideas more directly by emphasizing how HAART has both contributed to longer life expectancy and how it has influenced the epidemiology of opportunistic infections, particularly pneumonia.
2. The mention of patients in developing countries being unaware of their HIV status is valuable, but it could benefit from a brief explanation or example of the barriers to HIV testing or healthcare access that contribute to this delay in diagnosis.
3. When discussing the types of opportunistic pneumonias, it might be useful to provide a brief mention of how these infections are diagnosed and the typical treatments used in resource-limited settings. This would help tie the information to practical, real-world applications for physicians working in these areas.
4. The section on intravenous drug users (IDUs) in Malaysia is important and highlights a key population at higher risk. It would be beneficial to expand on this point by discussing how interventions (e.g., needle exchange programs or HIV awareness campaigns) might help reduce the risk of TB and bacterial pneumonias in this group.
5. The discussion on upper respiratory tract infections and the common cold seems slightly disjointed from the rest of the introduction. Consider reframing this section to directly relate to HIV patients, particularly how the immune system's response to respiratory infections may differ in immunocompromised individuals. This would help maintain the focus on HIV-associated pneumonias.
6. It may also be helpful to elaborate on the potential complications of the common cold in HIV-positive individuals, particularly in terms of how viral infections can exacerbate underlying immunodeficiencies.
7. Ensure consistent use of terminology (e.g., “patients whom” should be “patients who”).
8. Clarify whether the statistics on new HIV cases in Malaysia are still relevant.
9. It is noted that the study was approved by the institutional ethical committee. However, it would be helpful to provide more specific information about the ethical considerations, such as informed consent from the participants and whether any patient confidentiality protocols were followed.
10. The phrase “The present prospective study was conducted in between 9th August 2009 to 23rd January, 2012” could be rephrased for clarity. Consider: "This prospective study was conducted from August 9, 2009, to January 23, 2012."
11. The description of HIV testing is clear, but the use of “FACS count” could be expanded slightly to explain that it refers to fluorescence-activated cell sorting (FACS), especially for readers unfamiliar with the acronym. Additionally, providing the threshold for CD4 count that warrants clinical intervention or monitoring could be beneficial.
12. The description of sputum collection and quality control procedures is detailed and well-explained. However, it would be useful to include how the samples were transported to the laboratory (e.g., temperature control, time of transport) to maintain their integrity for testing.
13. The exclusion of "unsuitable" sputum specimens is mentioned. Clarification could be added about how often such unsuitable specimens were discarded and the impact this had on the overall sample size.
14. The case definition for HIV-positive patients and the control group (C1) is appropriately defined. However, the exclusion of patients with allergic common cold could benefit from a brief explanation about why these patients were excluded, especially in the context of their symptoms overlapping with those of RTIs.
15. Also, it may be helpful to clarify the "one patient only once" statement for the case definition to ensure readers understand the inclusion protocol.
16. The description of sputum smear microscopy and culture techniques is thorough. However, the text could benefit from a clearer comparison of the sensitivity of microscopy versus culture in HIV-infected individuals. Including more detail on why culture was not used in all patients (e.g., resource limitations, clinical judgment) would provide more context to this decision.
17. The term "same-day sputum collection" could be further clarified, especially since it was mentioned in the context of improving sensitivity.
18. The methods for detecting fungal pathogens, including Candida, are well-detailed. However, it might be useful to mention any specific criteria used to differentiate between pathogenic and non-pathogenic Candida, as Candida is a common commensal organism.
19. The description of microbiological identification and antibiotic sensitivity testing is well-structured. Including the rationale for using specific media (e.g., Sabouraud's dextrose agar, Lowenstein Jensen Media) in relation to the pathogens under investigation would add clarity to the methodology. Additionally, if any limitations were encountered in terms of media usage or pathogen growth, it would be helpful to mention them.
20. Ensure that all terms, such as "trophozoites and cysts of P. carinii," are clearly defined or referenced. In this case, it would be useful to specify that P. carinii is now known as *Pneumocystis jirovecii*, to align with current terminology.
21. Consider providing a list of abbreviations used in the section, such as "AFB" (Acid-Fast Bacilli) and "NACO" (National AIDS Control Organization), for the benefit of readers unfamiliar with these acronyms.
22. The phrase “All Gram stained smears from samples of sputum were even examined for Poly Morpho Nuclear Leucocytes (PMNL) cells to co relate pathogenicity and avoid contamination” could be rephrased for better clarity. Consider: “All Gram-stained sputum smears were examined for polymorphonuclear leucocytes (PMNL) to assess pathogenicity and avoid contamination.”
23. The term "even" is unnecessary in this context and can be removed for smoother reading.
24. While the purpose of examining PMNLs to correlate pathogenicity and avoid contamination is clear, it would be helpful to explain why this step is crucial in assessing the quality and potential pathogenicity of the sputum. For example, explaining that a high number of PMNLs suggests infection, while a low number might indicate contamination or poor-quality sputum, would give more context.
25. The method used for CD4 count, "Flow cytometry" followed by "FACS count," is mentioned, but it could benefit from additional details for clarity, especially for readers who may not be familiar with these methods. Consider expanding on the use of flow cytometry (e.g., "Flow cytometry, a technique that uses fluorescently labeled antibodies to count and analyze CD4 cells, was used to determine the CD4 count of patients").
26. Additionally, if there is any reference to the specific threshold of CD4 count used to classify patients or the significance of the results, it would strengthen this section.
27. The term "Poly Morpho Nuclear Leucocytes" is correct, but the more common spelling “Polymorphonuclear Leukocytes” might be more familiar to a broader audience. Additionally, the abbreviation "PMNL" should be introduced at first mention.
28. Since flow cytometry is a central method for measuring CD4 counts, a brief mention of the specific reagents or the process of analysis (e.g., the use of CD4-specific antibodies) would add more depth to this description.
29. The reference to the tables is clear, but the paragraph could be strengthened by providing a brief summary or key finding from each comparison. For example, mention whether there were significant differences between HIV seropositive and seronegative groups in terms of the prevalence of bacterial/fungal isolates, or if the CD4 count varied significantly among the different groups (T and C1).
30. Consider rephrasing to introduce the comparisons more effectively. For example: “The prevalence of pathogenic bacterial and fungal isolates in both HIV seropositive (T) and HIV seronegative (C1) groups is presented in Table 1. Additionally, Table 2 shows the comparison of mean CD4 counts between the various patient groups, while Table 3 illustrates the relationship between mean CD4 values and the types of respiratory tract infections caused by different organisms.”
31. It would be helpful to provide a brief description of what is being compared in each table (e.g., the relationship between CD4 count and infection type, or the specific pathogens identified in each group) to help readers understand the context before they refer to the tables.
32. If statistical analyses (e.g., t-tests, ANOVA) were used to compare CD4 counts or isolate prevalence, it would be beneficial to mention this in the text to demonstrate how the comparisons were made. For example: "Statistical significance was assessed using [method], as shown in Tables 2 and 3."

**Table 1 presents a clear summary of the prevalence of pathogenic bacterial and fungal isolates from both HIV seropositive (T) and HIV seronegative (C1) groups. The table includes useful data, with well-organized categories of pathogens, and provides the statistical significance of the comparisons. However, some minor adjustments could improve clarity and ensure the table is presented in the most informative manner.**1. The pathogen names are provided in a concise format, but some additional clarification could be beneficial. For example, "M. tuberculosis- infecs." could be rephrased to "M. tuberculosis infections" to ensure full clarity. Similarly, "Other bacteria" could be further clarified to include specific examples of the bacterial pathogens, if possible. In table 1
2. The column headings could be improved for better readability. For example:

"HIV +VE RTI +VE (T) Patients (n=961)" could be shortened to "HIV+ RTI+ (T) Patients" to avoid redundancy. In table 11. Similarly, "HIV -VE RTI +VE (C1) patients (n=300)" could be written as "HIV- RTI+ (C1) Patients" for consistency and brevity. In table 1
2. It would be helpful to provide a brief explanation of the statistical tests used (e.g., Chi-square test) in the table's legend or in the results section to help readers interpret the p-values. While the p-values are provided, a note explaining the threshold for significance (e.g., p < 0.05) would add clarity. In table 1
3. The “X2 Values” column provides statistical values, but the corresponding p-values are shown in a separate column. To improve clarity, it may be helpful to include both values in a single column, or at least clearly distinguish the Chi-square test results and the p-values for each comparison. In table 1
4. The category “Poly-Microbial” could benefit from more detail. It is important to clarify whether this refers to co-infection with multiple bacterial species, or if it includes any combination of bacterial, fungal, or other pathogens. Providing further clarification or expanding the category description would be helpful. In table 1
5. The percentages are provided for each pathogen group, which is great for understanding the relative prevalence. However, ensure that the number of patients represented by these percentages is clearly explained in the table's legend, especially if the numbers differ significantly between groups (e.g., T and C1 groups). In table 1
6. The category "PMNLs seen but no isolate" could use some clarification. It’s not immediately clear whether this represents cases where PMNLs were observed but no pathogens were identified, or if it refers to cases where no pathogen was successfully cultured despite PMNL presence. Including a more detailed description in the legend would be helpful. In table 1
7. The "No Patients with Viral RTI" row is interesting but somewhat unclear. It would be helpful to clarify that this represents patients who did not present with viral RTIs, and that this is being compared across the HIV-positive and HIV-negative groups. The p-value of <0.001 suggests a strong significance, but additional clarification of what this means in terms of patient demographics or clinical outcomes would strengthen this finding. In table 1
8. Consider adjusting the alignment of the text and values for better readability, especially in the statistical columns (e.g., X2 and p-values). Consistent decimal places should also be applied to all p-values for uniformity.
9. The title “Prevalence of pathogenic bacterial and fungal isolates from both HIV seropositive (T) and HIV seronegative (C1) groups” is accurate but could be made slightly more concise. Consider: "Prevalence of Pathogenic Bacterial and Fungal Isolates in HIV+ and HIV- RTI Patients."

**Table 2 provides valuable data on the comparison of mean CD4 counts among patients with different organisms or types of respiratory tract infections (RTIs). The table is well-organized and clear in presenting the mean CD4 counts, standard deviations, and the percentage of cases for each category. However, there are some areas that could be improved to enhance clarity and interpretation of the data.**Some of the category names could be clarified for better understanding. For example:1. The title “Comparison of mean CD4 of patients of various groups” is appropriate but could be slightly revised for clarity, such as: “Comparison of Mean CD4 Counts in Patients with Different Pathogens and RTI Types.”
2. The category “Only fungal RTI = Candida albicans + Candida (NCAC) + Aspergillus” could be reworded to something like “Fungal RTI (Candida albicans, NCAC, Aspergillus)” for clarity.
3. The term “Atypical bacterial RTI (No isolates with PMNLs seen)” is unclear and may need further explanation in the table legend or in the results section. It would be helpful to explain what is meant by “atypical” and how the absence of isolates affects the interpretation of these cases.
4. The table lists the mean CD4 counts and standard deviations, but there is no mention of the statistical significance of the differences between the groups. Including p-values for the comparisons would be useful, especially if differences between groups (such as pulmonary TB vs. Candida albicans) are being assessed. If these comparisons have been tested statistically, consider adding the results.
5. The wide range in standard deviations (e.g., 268.29 for fungal RTIs) may suggest significant variability in CD4 counts within some groups. It might be helpful to briefly discuss in the text why these variations exist (e.g., could it be due to the severity of infection, adherence to ART, or other factors?).
6. The category “All RTI patients without identified pathogens (Probable Viral RTI)” shows a relatively high mean CD4 count compared to other groups. This may suggest a less severe disease or early-stage infection in these patients. It would be helpful to explain this finding further, particularly in terms of patient management and diagnosis.
7. Ensure consistency in how the groups are labeled. For instance, “Patients excluding only pulmonary TB” is a bit ambiguous. It could be clearer to state “All patients except those with pulmonary TB.”
8. The term “Candida (NCAC)” might need further explanation or a note on what NCAC stands for to avoid confusion among readers who may not be familiar with the abbreviation.
9. The percentages in the “%” column provide useful context for the distribution of cases, but it would be beneficial to clarify whether these percentages represent the proportion of total patients (961) or the proportion within each organism group. It would be clearer if it were stated that these percentages are relative to the total number of patients.
10. Ensure that the table formatting is consistent. For example, the use of "=" in the fungal RTI category could be replaced with “+” to align with the rest of the table.
11. Consistent decimal places for the mean CD4 counts and standard deviations would enhance the readability of the table.
12. The title “Comparison of mean CD4 values of patients suffering from respiratory tract infections by various organisms” is appropriate but could be more precise, such as: “Mean CD4 Counts in HIV-Infected Patients with Respiratory Tract Infections Caused by Various Pathogens.” (table 3)
13. Consider rounding the numbers for consistency (e.g., for mean CD4 counts, standard deviations, and percentages) to two decimal places across all entries. This would improve readability and maintain consistency. (table3)
14. The manuscript lacks a dedicated section discussing limitations, which is a critical component for transparency and contextualizing the findings. Factors such as the small sample size of certain subgroups (e.g., rare pathogens), the limited use of advanced diagnostic tools like culture for tuberculosis, and the study's timeframe (2009–2012) may impact the relevance of the results in the context of current HIV treatment and diagnostics. Additionally, the findings may not be generalizable to populations outside the studied region or to non-resource-limited settings. Including a limitations section would enhance the credibility of the study by addressing these constraints and guiding future research to validate and build upon the presented findings.
15. The reference section of this manuscript includes a broad range of sources relevant to HIV-related respiratory infections and opportunistic pathogens, but it could benefit from several improvements. Many references are outdated, such as the WHO/UNAIDS report from 2008 and studies from the 1980s and 1990s, and should be complemented with more recent findings to reflect current advances. Inconsistencies in citation formatting, including variations in journal name abbreviations, capitalization, and spacing, should be standardized according to a recognized style guide for better readability. Online references, such as those for the Malaysian AIDS Council and NACO, need complete and verified access dates with functional URLs. Additionally, while foundational studies are valuable, there is an over-reliance on older sources, which could be balanced with more contemporary research. Streamlining overlapping references on similar topics would further improve the section's clarity and conciseness. These changes would enhance the section's relevance, accessibility, and scholarly quality.
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| **PART 2:**  |
|  | **Reviewer’s comment** | **Author’s comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
| **Are there ethical issues in this manuscript?**  | *(If yes, Kindly please write down the ethical issues here in details)* |  |

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